Abstracts

Hormone Research in Paediatrics

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Presenting authors are underlined

Plenary Lectures

PL1

A Kiss before Sex

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Infertility affects one in six couples in the UK. Identification of novel factors which are critical to reproductive function could lead to improved therapies for infertility.

Kisspeptin has been identified as a key regulator of the reproductive system. Defective kisspeptin signalling causes a failure of reproductive hormone release (hypogonadotrophic hypogonadism) in rodents and man leading to a failure to go through puberty.

My group have determined the effects of kisspeptin on stimulation of reproductive hormone release in humans. Kisspeptin infusion to male volunteers significantly increased plasma LH, FSH and testosterone. Administration of kisspeptin to female volunteers increased plasma LH in all phases of the menstrual cycle with the greatest effect in the preovulatory phase.

We have recently determined the therapeutic potential of kisspeptin in patients with infertility:

- i) Hypothalamic amenorrhea is defined as the cessation of menstruation due to abnormal signalling between the hypothalamus and the pituitary gland. It accounts for over 30% of cases of amenorrhea in women of reproductive age. We have shown that kisspeptin administration stimulates reproductive hormone release and can restore LH pulsatility in with hypothalamic amenorrhea.
- ii) IVF treatment is now widely and successfully used to enable infertile couples to conceive. However, IVF treatment can result in the potentially life threatening condition, ovarian hyperstimulation syndrome (OHSS) due to the pharmacological use of human chorionic gonadotrophin (hCG) to stimulate oocyte maturation in current IVF protocols. A more physiological stimulus for oocyte maturation, such as kisspeptin, may avoid this dangerous side effect and improve the safety and efficacy of IVF treatment. We have shown that kisspeptin can effectively and safely trigger oocyte maturation resulting in the birth of healthy children without OHSS.
- iii) Hypogonadotropic hypogonadism is hypogonadism due to either hypothalamic or pituitary dysfunction. Whilst gonadotropin releasing hormone (GnRH) can directly test pituitary function, no specific test of hypothalamic function exists. Kisspeptin-54 (KP54) is a neuropeptide that directly stimulates hypothalamic GnRH-release and thus could be used to

specifically interrogate hypothalamic function. Our work shows that KP54 fully discriminated men with CHH from healthy men. Thus, KP54 could be used to specifically interrogate hypothalamic GnRH neuronal function in patients with congenital hypogonadotropic hypogonadism.

Our future work aims to deliver novel kisspeptin based therapies into the clinic to improve the outcomes of patients with reproductive disorders.

PL2

New Drugs for Youth with Type 2 Diabetes

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Metformin was the first and only drug approved in 1999 for use in youth with type 2 diabetes (T2D) based on a small, randomized clinical trial. Insulin was also approved but this was based only on the effective use of insulin in children with T1D. For more than 20 years, no new drugs had been approved for use in pediatric T2D based on a randomized study.

A major reason why many of the new drugs have not been approved in pediatrics is that adolescents with T2D are difficult to recruit for these studies. For example, adolescents with T2D often miss clinic visits and are lost to follow-up and compliance with taking meds and carrying out other diabetes-related tasks is poor. Many patients are also excluded due to behavioral problems, depression and other psychiatric disorders.

However, formation of the Pediatric Diabetes Consortium (PDC) of leading pediatric diabetes treatment centers in the US was an important turning point, since a primary aim of the PDC is to improve the care of adolescents with T2D by making drugs with proven effectiveness in adults available to youth with T2D. The PDC has already accomplished its current primary goal by participation in the following studies:

- Exenatide by once weekly injection (approved)
- Oral dapagliflozin (in analysis of study outcomes)
- Phase III dapagliflozin and saxagliptin vs placebo study (nearing completion of randomization)
- Dinamo Phase III empagliflozin and linagliptin vs placebo (nearing completion of enrollment)
- Dinamo Mono study (in early recruitment phase)
- Liraglutide by daily injection (approved)
- Oral Semaglutide (in early recruitment phase)
- Phase III Alogliptin versus Placebo Study (nearing completion)

We strongly believe that the results of these and future randomized clinical trials will transform the care of youth with type 2 diabetes in the future.

PL3

Abstract Unavailable

PL4

Abstract Unavailable

PL5**Advances and Challenges in the Care of Transgender/
Gender Diverse Youth**

Stephen Rosenthal

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In many parts of the world, increasing numbers of transgender/gender diverse (TGD) youth are seeking medical care to bring their physical sex characteristics into alignment with their gender identity—their inner sense of self as male, female, or somewhere on the gender spectrum. Compelling studies in the last decade have produced evidence supporting the concept that gender identity is not simply a psychosocial construct but likely reflects a complex interplay of biological, environmental, and cultural factors. In addition, while there are uncertainties in the care of TGD youth and a need for long-term safety and efficacy research, several studies have demonstrated the clear mental health benefits of gender-affirming medical care (including pubertal blockers and gender-affirming sex hormones) first pioneered by the Dutch, which have informed the current Endocrine Society's Clinical Practice Guideline (CPG) for Gender-Dysphoric/ Gender-Incongruent Persons, cosponsored by ESPE and numerous other professional associations.

Despite the above-noted advances in the care of TGD youth, significant barriers have recently emerged that would greatly restrict access to gender-affirming medical care. In the United Kingdom a high court has issued a ruling that would prevent youth under the age of 16 from receiving pubertal blockers without a court order. In the United States, pending legislation in several states would prohibit gender-affirming medical care to those under 18 years of age and would criminalize providers who follow the currently existing Endocrine Society's Clinical Practice Guidelines.

This presentation will review advances in our understanding of the prevalence of TGD youth, the mental health impact of gender-affirming medical care, potential adverse effects of such care, gaps in knowledge, priorities for research, and an overview of ethical dilemmas and barriers to care.

PL6

Abstract Unavailable

PL7

Abstract Unavailable

PL8**The Long term effects of adolescent obesity**

Thomas Reinehr

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Adolescent obesity has an immense burden of disease and results in premature death due to several mechanisms: The classic cardiovascular risk factors associated with obesity, such as hypertension, dyslipidemia and type 2 diabetes mellitus, lead to cardiovascular diseases and consequently to premature death. Furthermore, adolescent obesity is associated with many life-limiting cancer types occurring 10 to 20 years later replacing smoking as the leading modifiable cause for cancer.

However, obesity in adolescence has major implications not only for the affected adolescents but also for society. Obesity in adolescents is associated with a range of social problems, including difficulties securing an apprenticeship or a job or finding a partner. Adolescents with obesity are also at increased risk of having children with obesity later in life.

All these consequences lead to high costs for the health-care system. It is quite clear that obesity in adolescence is associated with increased health-care use (direct cost) as well as indirect costs (productivity losses including sick-leave days, long-term incapacity, early retirement and premature death). Additionally, adolescents with obesity might be less able to contribute to financing our social system when they are adults since they have likely problems to get an employment.

Although efficient treatment options are available that have been proven in randomized controlled trials, such as lifestyle interventions, drugs and bariatric surgery for adolescents with severe obesity, these interventions fail frequently in clinical practice as most adolescents with obesity do not seek medical care. Furthermore, adolescent patients are characterized by low treatment adherence.

In conclusion, since adolescent obesity leads to reduce quality of life, many social problems, premature death, and immense costs not only for our health system, we have to identify and overcome treatment barriers and have to optimize treatment approaches even if our present attempts fail frequently.

Endocrine Hypertension – Aetiology Directed Management

S1.1

Pathogenesis of Familial and Sporadic Hyperaldosteronism: New Concepts Involving Ion Channels

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Endocrine disorders are the most common causes of secondary hypertension. Early diagnosis and treatment is crucial for prevention of cardiovascular complications. Several rare but important entities like Cushing's syndrome and pheochromocytoma/paraganglioma can cause endocrine hypertension, in contrast to primary aldosteronism, which is quite frequent. **Definition, classification and prevalence:** With a prevalence of 6% in unselected patients with hypertension, 5 to 12% of hypertensive patients in specialized outpatient clinics and 23% in therapy-refractory patients, primary hyperaldosteronism (PA) is the most common cause of surgically treatable secondary hypertension. The causes of PA are usually a unilateral aldosterone-producing adrenal adenoma (APA) or bilateral (micronodular) idiopathic adrenal cortex hyperplasia (BAH). The "classic" hypokalemic variant occurs more frequently in the case of APA, whereas the normokalemic form is mostly observed in BAH forms. **Case finding:** PA screening is required in patients with refractory hypertension, younger patients with hypertension, patients with arterial hypertension and hypokalemia, patients with arterial hypertension and obstructive sleep apnoe syndrome, and patients with arterial hypertension and adrenal incidentaloma. Screening is performed using the sensitive, but not very specific, aldosterone to renin ratio (ARR). Subtype differentiation is carried out by means of CT imaging of the adrenal glands in combination with, as a gold standard, adrenal vein catheterization to differentiate between unilateral and bilateral aldosterone production. In the case of a technically unsuccessful catheterization, nuclear medical procedures (e.g. CXCR4-PET / CT, etomidate-PET) are used in individual cases. **Genetics:** Most cases of PA are sporadic but inherited patterns of the disease have been reported in the literature. Four forms of familial

hyperaldosteronism (FH-I- FH-IV) are currently recognized, and the genetic basis has been clarified in recent years. In FH-I patients, aldosterone excess is produced by a *CYP11B1/CYP11B2* fusion gene and it is suppressed by glucocorticoid treatment. FH-II is caused by mutations in the inwardly rectifying chloride channel *CLCN2*. FH-III is caused by mutations in *KCNJ5*, a gene coding for an inward rectifier K⁺ channel and mutations in the T-type calcium channel subunit *CACNA1H* cause FH-IV. A number of somatic mutations have been identified in ion channels and transporters that drive the aldosterone excess in patients with APA. No clinical application has been firmly established although a potential future use may lie in steroid profiling to circumvent AVS in patients with bilateral disease by selection of those patients with a high probability of having an APA or by selecting patients with an APA carrying *KCNJ5* mutations using macrolide antibiotics as selective inhibitors. Genetic testing is recommended in patients with a diagnosis of early-onset PA (< 20 years old) or with a family history of PA or stroke at a young age (< 40 years) for the presence of the hybrid *CYP11B1/CYP11B2* gene that causes FH type I and in very young patients with a diagnosis of PA (for example, < 20 years) for germline mutations in the *KCNJ5* gene that cause FH type III. Genetic testing of patients in these target groups offers the possibility of an early diagnosis of asymptomatic relatives and provides timely treatment when appropriate. **Therapy:** Patients with PA have an increased risk of stroke, myocardial infarction, atrial fibrillation and renal insufficiency compared to patients with essential hypertension. Early diagnosis and the appropriate targeted initiation of therapy seem all the more important. An adrenalectomy is indicated for unilateral PA. In the case of BAH, therapy with spironolactone (25-50mg / d) should be initiated.

Learning Points:

After this lecture, you should:

- Know the prevalence and at risk populations of endocrine hypertension
- Know the target population which should be screened for PA
- Be able to apply appropriate tests to diagnose and subtype PA
- Be able to identify familiar forms of PA
- Be able to initiate individualized treatment depending on subtype of PA

Key Words: primary aldosteronism, aldosterone, cortisol, adrenal vein sampling, endocrine hypertension, secondary hypertension

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S1.2

Abstract Unavailable

Recent Breakthroughs in our Understanding of Calcium and Phosphate Homeostasis

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S2.1

Circadian rhythms of skeletal homeostasis

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Circadian clock system is an evolutionarily conserved system, by which organisms adapt their metabolic activities to environmental inputs including nutrient availability. The master pacemaker of the clock system is located in the suprachiasmatic nucleus (SCN) in the hypothalamus. The neurons in the SCN are entrained by the signals from the light through the retinal-hypothalamic tract and the light-dark cycle of the environment creates the rhythmic patterning of behavioral and physiological rhythmicity. In addition to the central pacemaker, peripheral tissues also possess their own circadian network and synchronize with the central clock system through hormonal and neuronal signals. Organisms utilize this system to maximize the efficiency of time-of-day-dependent utilization of ingested nutrients by optimizing the metabolic processes in peripheral tissues; therefore, the disruption of this system has been pathogenically linked to the disintegration of metabolic homeostasis including skeletal metabolism. These findings point to the important role of circadian clock system as a nodal point to link nutrient availability and metabolism. Calcium is a critical nutrient involved in skeletal metabolism, and circulating calcium levels are known to have daily rhythms in human, indicating that calcium homeostasis is under the regulation of circadian clock system; however, this has not been well studied so far. Based on this background, the speaker has been investigating the role for circadian clock system in calcium homeostasis using a mouse model in which intestinal circadian clock system is disrupted, and found that intestinal clock network regulates calcium absorption in a time dependent manner, which results in the disintegration of skeletal homeostasis. In this talk, the speaker would like to present current findings how calcium homeostasis is regulated by circadian clock system and its influence on skeletal metabolism.

S2.2

Calcitropic and non-calcitropic roles of the calcium sensing receptor

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The calcium-sensing receptor (CaSR) is the master regulator of calcium homeostasis. This class C G-protein coupled receptor

binds extracellular calcium and phosphate, and is the target of calcimimetic and calcilytic drugs. The CaSR is expressed on the cell surface as a homodimer and is most highly expressed in the parathyroid glands and the renal thick ascending limb, where it acts to maintain a near-constancy of plasma calcium concentrations by regulating parathyroid hormone (PTH) secretion and urinary calcium excretion, respectively. The other major calcitropic role of the CaSR involves regulating secretion of parathyroid hormone related peptide (PTHrP) from the mammary gland during lactation. The importance of the CaSR for calcium homeostasis has been demonstrated by the identification of germline loss- and gain-of-function CaSR mutations, which cause familial hypocalciuric hypercalcaemia (FHH) and autosomal dominant hypocalcaemia (ADH), respectively, and also by the efficacy of drugs targeting the CaSR for the treatment of parathyroid disorders. The CaSR also has non-calcitropic physiological roles and is highly expressed in the pancreatic islets, where it regulates insulin secretion and may potentially influence glucose homeostasis. In addition, abnormal expression or function of the CaSR is implicated in the pathogenesis of asthma and also malignancies such as carcinoma of the breast. This has led to CaSR targeted drugs being evaluated for non-calcitropic disorders. Novel strategies such as utilising inhaled calcilytic drugs for asthma may help to minimize adverse effects arising from inappropriate modulation of the CaSR in calcitropic tissues.

Management of Rare Obesity

S3.1

Abstract Unavailable

S3.2

Hypothalamic Obesity in Craniopharyngioma

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Although craniopharyngiomas are of low-grade histological dignity and have good prognosis in terms of overall survival, survivors may suffer from devastating consequences caused by hypothalamic damage. Disease and/or treatment-related hypothalamic damage leads to disturbed hunger-satiety and thirst feelings, decreased energy expenditure, behavioral problems, disturbances of circadian rhythm, temperature dysregulation, and pituitary dysfunction. These patients are at great risk for developing hypothalamic obesity and comorbidities leading to premature mortality. Tumor- and/or treatment-associated lesions of specific posterior

hypothalamic areas (i.e. area of mammillary bodies and beyond) are risk factors for the development of severe obesity and reduced quality of life during long-term follow-up. A combination of hypothalamus-sparing surgical intervention and protonbeam therapy has been shown to be effective in order to control residual craniopharynioma with less hypothalamic morbidity. Reported pharmacotherapeutic interventions for hypothalamic obesity can be compromised in four categories: stimulants, antidiabetic agents, hypothalamic-pituitary substitution therapy and others, such as oxytocin or octreotide. The reported effects are generally modest and often transient. Currently, there is still no consensus regarding the optimal pharmacotherapy. There are multiple forms of bariatric surgery in hypothalamic obese craniopharyngioma patients reported, such as laparoscopic adjustable gastric banding (LAGB), gastric bypass, Roux-en-Y gastric bypass, sleeve gastrectomy, and biliopancreatic diversion. Of these, Roux-en-Y gastric bypass showed the best results, with in total six studies and fourteen patients included, of whom all showed improvement of their BMI. However, the use of irreversible bariatric procedures in pediatric CP patients is invasive and controversially discussed for medical, ethical and legal reasons.

Conclusions: The late sequelae of CP can be severe, mainly caused by the consequences of hypothalamic damage and may lead to decreased quality of life. Prevention of hypothalamic obesity is most effective, thus hypothalamus-sparing therapeutic approaches should have main focus in these patients.

Recent Developments in Congenital Adrenal Hyperplasia

S4.1

Abstract Unavailable

S4.2

Abstract Unavailable

Novel Therapies in Endocrinology

S5.1

Novel Therapies in the Treatment of Congenital Hyperinsulinism

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Congenital hyperinsulinism (HI) is the most common cause of persistent hypoglycemia in infants and children. In the past 20+ years there have been tremendous advances in the understanding of the molecular genetics of HI, including the discovery of the mechanisms responsible for a focal form of the disease that can cured surgically. However, treatment options for non-focal HI continue to be limited, with only one drug currently approved for this indication. As a result of delayed diagnosis and inadequate treatment options, up to 50% of children with HI experience neurodevelopmental deficits, thus, there is an urgent need for new effective and safe therapies. Efforts have been directed at repurposing existing drugs and at identifying new therapeutic targets. We have identified the GLP-1 receptor as a potential therapeutic target for HI. GLP-1 is an incretin hormone secreted by the intestinal L-cells that plays a critical role in the regulation of glucose homeostasis, and GLP-1 mimetic therapies are now broadly use in the treatment of diabetes. We have shown that the GLP-1 receptor is constitutively active in islets isolated from a mouse model of K_{ATP} hyperinsulinism (*Sur1*^{-/-} mouse), the most common type of HI, and that the GLP-1 receptor antagonist, exendin-(9-39), inhibits insulin secretion in mouse and human islets lacking K_{ATP} channels. In preclinical studies, we demonstrated that exendin-(9-39) prevents fasting hypoglycemia in *Sur1*^{-/-} mice. In clinical studies, we have shown that exendin-(9-39) increases fasting glucose in children, adolescents, and adults with K_{ATP} HI and prevents protein-induced hypoglycemia in affected children. In neonates with severe diazoxide-unresponsive HI, exendin-(9-39) reduces the glucose infusion rate required to maintain euglycemia. Other therapies under development include modified glucagon analogues, somatostatin receptor agonists, and inhibitors of the insulin receptor. The ongoing efforts promise to make possible a personalized-approach to treatment of children with HI and to improve their long-term outcomes.

S5.2

Abstract Unavailable

Bone Formation: The Growth Plate and Beyond

S6.1

Epigenetic regulation of the growth plate

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Longitudinal growth is driven by endochondral ossification at the growth plate, where chondrocytes undergo a well-organized cellular differentiation process from stem-like progenitors to rapidly-proliferating transit-amplifying cells and to hypertrophic chondrocytes. Numerous recent studies have demonstrated that epigenetic modifications play a crucial role in human development and childhood growth. For example, Brachydactyly mental retardation syndrome (BDMR) is caused by haploinsufficiency of histone deacetylase HDAC4, while a triad of phenotypically similar human overgrowth syndromes is caused by genetic variants affecting histone and DNA methylation: mutations in H3K27 histone methyltransferase EZH2 cause Weaver syndrome; mutations in H3K36 histone methyltransferase cause Sotos syndrome; and mutations in DNA methyltransferase DNMT3A cause Tatton-Brown-Rahman syndrome. In this paper, we will discuss how these recent advances may provide us with important insights into growth plate biology and their clinical implications in childhood growth disorders.

S6.2

Growth Plate: New insights in the origin and function of the growth plate

Andrei Chagin

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Epiphyseal growth plates, tiny cartilage discs located to the end of long bones, are necessary for longitudinal growth of the skeleton. When and why these structures appeared as individual organs was not very clear until recently. Bringing together an evolutionary approach with comparative analysis, mathematical modelling and both physical and biological experiments allowed to reveal that spatial allocation of the growth plate reduces mechanical stresses within the structure, which are otherwise harmful for hypertrophic chondrocytes. This mechanical protection is executed by bony epiphyses, which separates the growth plate from articular cartilage. This protection comes at the expense of numerous chondroprogenitors. Analysis of clonal dynamics revealed that bony epiphysis creates a stem cell niche within the underlying growth plate, allowing the remaining chondro-progenitors to acquire stem cell properties and maintain longitudinal growth.

Taken together, these observations revealed novel principles underlying linear skeletal growth.

The Molecular Basis of Rare Endocrine Disorders

S7.1

Abstract Unavailable

S7.2

Abstract Unavailable

Management of Childhood Brain Tumours

S8.1

Novel Insights Into the Management of Cranial Diabetes Insipidus

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Central diabetes insipidus (CDI) is the end result of a number of disorders that affect the hypothalamic-neurohypophyseal region (HPR). The diagnosis of the underlying condition despite the use of new biochemical parameters including copeptin is challenging and raises several concerns for patients and parents as it requires long-term follow-up. Thus, a proper etiological diagnosis can be achieved via a series of steps that start with clinical observations and then progress to more sophisticated techniques.

Thickening of the pituitary stalk is the most common finding on MRI scans in several inflammatory conditions and autoimmune diseases affecting the HPR or germinoma, but it is not specific to any single subtype. A progressive increase in the size of the anterior pituitary gland should alert physicians to the possibility that a germinoma is present, whereas a decrease can suggest the presence of an inflammatory or autoimmune process. Tumor-associated CDI is uncommon in children younger than 5 years of age. Most children with acquired CDI and thickened pituitary stalk have anterior pituitary hormone deficiencies during follow-up. Biopsy of enlarged pituitary stalk should be reserved for patients with hypothalamic-pituitary mass and progressive thickening of the pituitary stalk since spontaneous recovery may occur.

Serial MRI and integration with T2-DRIVE images and recent “mismatch imaging pattern” provides an important framework towards a better diagnosis of pituitary lesions and MRI STIR Technology is promising for the early identification of disease specific-dependent CDI. We also underscore the paramount importance of long-term clinical follow-up and reassessment of endocrine function as well as monitoring of signs or symptoms of Langerhans cell histiocytosis reactivation over time.

S8.2

Abstract Unavailable

Surgical Management of Endocrine Disorders

S9.1

Abstract Unavailable

S9.2

Abstract Unavailable

Pathways to Improved Diagnosis and Management of Hypothalamo-Pituitary Disorders

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S10.1

Abstract Unavailable

S10.2

Delayed puberty: A genetic condition?

Sasha Howard

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Young people presenting with delay in pubertal onset or progression may have one of a spectrum of conditions, with different underlying pathological mechanisms. Whilst environmental factors such as nutrition and emotional well-being can influence the timing of puberty, in the majority of patients presenting with significantly delayed puberty there is a clear family history of delayed or arrested puberty. Pubertal timing is known to be a trait with strong heritability, demonstrating that genetic factors play a key role in determining the timing of puberty. The pace of discovery of gene mutations responsible for delayed or absent puberty in human patients has accelerated in recent years due to next generation sequencing techniques.

The identification of causal genetic defects in certain pathways has shed light on the pathogenesis of delayed and disrupted puberty. The development, maturation and function of the gonadotropin releasing hormone (GnRH) system is vital for appropriate timing of pubertal development, and genetic mutations in key regulators of this element of the hypothalamic-pituitary-gonadal (HPG) axis result in a spectrum of conditions ranging from isolated delayed puberty to absent puberty with anosmia. Controlling the activation of this GnRH network, a carefully balanced system of inhibitory and excitatory signals upstream of GnRH secretion are vital for puberty onset and progression, and defects in this system can also lead to delayed puberty. External inputs on the HPG axis, including those linking energy metabolism to the kisspeptin-GnRH system, are also important permissive signals for pubertal development and mutations in genes in these pathways may lead to late onset of puberty associated with changes in body mass.

Recent discoveries include mutations in genes responsible for GnRH neuronal migration leading to both isolated (self-limited) delayed puberty and absent puberty (hypogonadotropic hypogonadism or Kallmann syndrome), genes related to the nitric oxide synthesis pathway, and genes which cause a syndrome of delayed puberty with autistic-spectrum disorder or developmental delay. This talk will also consider the utility of genetic testing for diagnosis of the underlying clinical condition in individuals with delayed puberty.

Calcium and Phosphate Beyond Bone

S11.1

Phosphate toxicity: focus on medial vascular calcification

Jakob Voelkl

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Inorganic phosphate is essential for bone stability and various cellular metabolic pathways. Serum phosphate levels are regulated by an endocrine triangle of calcitriol, parathyroid hormone and fibroblast growth factor 23. In addition, a mineral buffering system is required to prevent mineral stress and ectopic calcification by spontaneous precipitation of calcium and phosphate. Current research indicates a complex interplay of phosphate homeostasis and inflammatory processes, especially in the cardiovascular system. Elevations of serum phosphate levels have been associated with increased cardiovascular mortality, not only in patients with chronic kidney disease but also in the general population. A critical process presumably underlying this association is medial vascular calcification. Especially in vascular smooth muscle cells, exposure to elevated phosphate conditions induces complex signalling events to promote pro-calcific alterations. These cells can foster a pro-calcific environment and augment an active calcification process by various mechanisms, such as cytokine and vesicle release, matrix remodelling and degradation of the calcification inhibitor pyrophosphate. Inflammatory mediators and signalling pathways have recently been connected to vascular smooth muscle cell calcification. Nonetheless, multiple gaps remain in the understanding of the complex role of phosphate and mineral stress on the cardiovascular system and until now, no broadly applicable therapeutic strategy is available to prevent medial vascular calcification.

S11.2

Vitamin D and male reproduction

Martin Blomberg Jensen

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Newer studies have indicated that vitamin D has more widespread effects than the classical effects on bone and calcium-phosphate homeostasis. The presence of the vitamin D receptor (VDR) in the testis and male reproductive tract indicates a role for vitamin D in male reproduction. Indeed, vitamin D deficiency and global knock out models of VDR or CYP27B1 in rodents have shown that vitamin D and calcium are important regulators of male reproductive function. Several groups have in recent years published human data, which is in line with a beneficial role for sperm motility and sex steroid production. However, the clinical importance of vitamin D and calcium in regulating male fertility remains to be explored. To determine the impact of vitamin D and calcium supplementation on male reproductive function

Copenhagen Bone Gonadal study (CBG-Study) was conducted. The CBG-study is a single center, double blinded randomized clinical trial of 330 vitamin D insufficient (≤ 50 nmol/l) infertile men. The primary endpoint is changes in semen after 5 months supplementation with 300.000 IE cholecalciferol day one in addition to 1400 IE + 500 mg calcium or placebo once daily. At end of trial, men receiving vitamin D supplementation had no net change in semen quality or pregnancy rate. However, men with vitamin D deficiency had an increase in serum inhibin B and men with low sperm counts had higher pregnancy rates. Moreover, men treated with vitamin D had 13% lower fasting serum insulin concentrations and 19% lower HOMA-IR compared with the placebo-treated men. In conclusion activation of the vitamin D receptor seems to be important for male reproductive function but high-dose vitamin D supplementation had no significant effect on reproductive function except in men with severe vitamin D deficiency although minor beneficial effects on glucose homeostasis and HDL cholesterol levels were found in all infertile men.

Epigenetics and Genetics in Endocrine Disorders

S12.1

Epigenetics, imprinting and growth

I Karen Temple

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Human imprinting disorders are congenital disorders of growth, development and metabolism, associated with disturbance of gene dosage at imprinted loci across the genome. Causes of disease include point mutations, structural variants, uniparental disomy and 'epimutations' with a parent of origin specific effect. Further complexity underlies the causes of the epigenomic errors that may be the result of genetic and environmental factors at different times during the development of the oocyte, the sperm and the early embryo.

The diagnosis of these disorders is important to optimise growth, prevent long-term metabolic disturbance and childhood cancers. Imprinting disorders are likely underdiagnosed resulting in a group of patients offered suboptimal treatment. Causes include:-

1. many of the clinical features of imprinting disorders are non-specific and change with age making diagnosis difficult
2. heterogeneity and clinical overlap between conditions requires a broad diagnostic approach across many imprinted loci
3. standard diagnostic pathways that focus on genomic sequencing do not identify a significant proportion of molecular mechanisms underlying imprinting disorders
4. multi-locus imprinting disturbance (MLID) may affect the phenotype which can range from early miscarriage to less

classical non-specific developmental delay and yet is not tested for routinely in most labs

5. diagnostic genomic sequencing focuses on the patient and not the mother. Maternal mutations in a key network of oocyte-expressed genes can result in MLID in their offspring who do not share the mutations.

S12.2

The role of genetic analysis in primary ovarian failure

Philippe Touraine

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Primary (premature) ovarian insufficiency (POI) is defined as a loss of ovarian activity before the age of 40, and is characterized by menstrual disturbances (amenorrhea or oligomenorrhea) with elevated gonadotropins (follicle-stimulating hormone [FSH] ≥ 25 IU/L) and low serum estradiol levels. The incidence of POI is around 1 per 100 women overall, and 1 per 1000 women under the age of 30 years. POI leads to infertility and an increased risk of osteoporosis and cardiovascular disease. Different mechanisms are known to be involved in the pathogenesis of POI: decreased primordial follicular pool at birth, accelerated follicular atresia, or a dysfunction of follicular growth. Several causes of POI have been identified, including autoimmunity or iatrogenic causes like chemotherapy or ovarian surgery. Some authors have also suggested environmental causes. Genetic disorders involved include not only Turner syndrome (4-5% of cases of POI) and FMR1 (Fragile X Mental Retardation type 1) gene premutation (3% to 15% of cases of POI), but also monogenic disorders (syndromic or non syndromic). Around 70% of cases remain unexplained, though some of these cases of idiopathic POI may be linked to genetic abnormalities. In recent years, new genetic screening techniques have identified genetic alterations that may be linked to POI. Many familial studies have identified mutations involved in POI, and a few cohort studies have described variants of candidate genes or copy number variants. The conference will be the opportunity to discuss the clinical management of POI patients and the different genetic strategies to be proposed.

Joint ESPE/ISPAD Symposium: Novel Technologies in the Treatment of Diabetes

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S13.1

Latest developments in closed loop technology

Emma Willmot

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Type 1 diabetes is one of the most challenging long-term conditions to manage. On an average day the person with diabetes is expected to check their glucose multiple times, plan their dietary intake so that they are able to administer the calculated dose of insulin, via an insulin pump or injection, 15 minutes before the meal. They need to constantly strive for optimal glucose levels but the inherent variability in insulin requirements means that this often results in debilitating iatrogenic hypoglycaemia. The burden on the individual and/or their carers is substantial. Diabetes technology, in the form of closed loop systems, provide a potential solution to both improve clinical outcomes and simultaneously alleviate some of the burden of living with diabetes. In a closed loop system the continuous glucose monitor communicates with the insulin pump to automate insulin delivery in a gluco-responsive manner. This lecture will explore the commercially available closed loop systems and the published randomised controlled trial data supporting their use. Across the published studies, closed loop systems have been associated with improvements in time in range, time below range and HbA1c. Furthermore, qualitative work has provided insight into the psychosocial benefits associated with use of the systems. Despite these demonstrated benefits, a range of barriers to the uptake of closed loop systems exist. This lecture will explore these and suggest how we tackle each in turn. Finally, consideration will be given to the large number of people who, unable to access funded commercial closed loop systems, have opted to build their own do-it-yourself closed loop system. Despite reassuring outcomes in terms of glycaemic control, the use of these do-it-yourself systems present an ethical and medicolegal conundrum for healthcare professionals. The outcomes of the Diabetes Technology Network UK healthcare professional opinions of do-it-yourself closed loop systems will be shared.

S13.2

Abstract Unavailable

Meet the Expert

MTE1

Abstract Unavailable

MTE2

Diagnosis and management of a child with pituitary adenoma

Marianne Skovsager Andersen

Odense University Hospital, Odense, Denmark

A prolactinoma is the most common pituitary adenoma, but a pituitary adenoma is rarely diagnosed in children. Corticotropinomas and somatotropinomas are observed, whereas clinically non-functioning pituitary adenomas, TSH-adenomas and gonadotroph adenomas are very rare in children; a minor percentage of pituitary tumours are aggressive.

Genetic cause and syndromic disease are more often seen in children and adolescents with a pituitary adenoma compared to adults, and it is necessary to perform genetic screening in most pediatric patients with a pituitary adenoma to optimize therapy and follow-up. Dopamine-D2-receptor-agonist therapy is first-line treatment also in pediatric patients with a prolactinoma, and impaired gonadal function will usually be restored, when prolactin levels are normalized. Surgery is primary therapy in Cushing's disease, gigantism or acromegaly, but a considerable number of patients will need additionally medical therapy and in some cases radiotherapy. Hypopituitarism needs to be considered at the time of diagnosis of a pituitary adenoma, after therapy and during follow-up, especially after radiotherapy.

The 2017 World Health Organization (WHO) classification system on the pituitary is based on tumour cell lineage and transcriptional factor nuclear staining. Sometimes we need no more than a scan of the pituitary region to decide, that the tumour is aggressive, however, in selected cases, it is necessary to assess tumour proliferative potential by mitotic count and Ki-67 index. Experimental medical therapy, e.g. temozolomide, is indicated in few pediatric patients with an aggressive or malignant pituitary tumour, and we need O6-methylguanine-DNA methyl transferase (MGMT) status for the clinical decision making. Close collaboration between the pediatrician and endocrinologist is very fruitful during transition to adulthood.

MTE3

Abstract Unavailable

MTE4

Cystic Fibrosis-related diabetes

Andrea Kelly

Children's Hospital of Philadelphia, Philadelphia, USA. University of Pennsylvania Perelman School of Medicine, Philadelphia, USA

Emerging in childhood and becoming increasingly prevalent to affect 40-50% of adults with cystic fibrosis (CF), CF-related diabetes (CFRD) is a common co-morbidity with the potential to negatively impact nutritional status, pulmonary function, and survival. Stymying interventions to preserve beta-cell function, the mechanisms underlying the progressive insulin secretion defects responsible for CFRD are poorly delineated. This meet-the-professor session will use case-based presentations to review current diagnostic guidelines and recent literature surrounding alternatives to the standard oral glucose tolerance test (OGTT), consider management of abnormal glucose tolerance (AGT) and CFRD in the setting of various nutritional regimens and co-morbidities, and to appraise the potential impact of modulator therapy upon patients with AGT.

MTE5

Management of MEN1 in Children and Adolescents

Maria Luisa Brandi

F.I.R.M.O. Foundation, Florence, Italy

Approximately 12% to 17% of MEN1 patients are diagnosed with the disease in the first two decades of life. Clinical evident disease appears uncommon before adolescence, with consensus guidelines currently recommending phenotype screening of confirmed MEN1 carriers commencing by age 5 years. A recent publication reviewed the recent literature in this area, that demonstrates that mortality is rare in children and young adults, whereas morbidity is not uncommon for various endocrine manifestations.

In this presentation, the considerations in supporting and managing these younger patients will be discussed in detail.

MTE6

Abstract Unavailable

MTE7

Abstract Unavailable

MTE8

Abstract Unavailable

How Do I...

How Do I... Session 1

HDI1.1

Non-Classic congenital adrenal hyperplasia (NCCAH) - From Childhood to Adulthood

Naomi Weintrob

Dana-Dwek Children Hospital, Tel-Aviv, Israel

NCCAH is considered the most common autosomal recessive endocrine disorder, with a carrier frequency of 1:7 to 1:25. The disorder is caused by mild mutations in the *CYP21A2* gene retaining enzymatic activity of 20-50%. The genotype may be either mild/mild or mild/severe mutations. The partial enzymatic deficiency leads to increased production of adrenal androgens. The patients present with different degrees of postnatal virilization: precocious pubarche during childhood and polycystic ovary-like syndrome or infertility in adolescence and young adulthood. If untreated during childhood, they might have premature epiphyseal fusion and compromised adult height.

We have shown that early hydrocortisone therapy initiated before the occurrence of significant bone age advancement improves adult height. We therefore recommend initiation of therapy at the first sign of androgen excess, with careful follow-up to avoid under and over-treatment. We also found that cases with the mild/severe genotype present earlier, and have more frequent central precocious puberty and more compromised adult height. These patients had significantly lower cortisol response to ACTH stimulation: 70% failed the short ACTH test, compared to 48% of the mild/mild genotype and 0% of the controls. We suggest that patients with the mild/severe genotype have a more severe phenotype and may need continuation of therapy and stress coverage during adulthood.

As for fertility, we showed that the pregnancy and birth rates of women with NCCAH are similar to the general population and that glucocorticoid therapy does not affect pregnancy outcome, although it might shorten the time to conceive in a subgroup of patients who failed to conceive spontaneously.

We also demonstrated that phenotypic variability is partially explained by the length of the CAG repeats within the androgen receptor, and that the addition of anti-androgen might therefore be beneficial for females with hirsutism.

HDI1.2

Abstract Unavailable

HDI1.3

Abstract Unavailable

How Do I... Session 2

HDI2.1

Abstract Unavailable

HDI2.2

Abstract Unavailable

HDI2.3

Advise patients on insulin dosing for real meals

Ewa Pankowska

Instytut Diabetologii, Warsaw, Poland

In Functional Intensive insulin therapy (FIIT), despite the using injection or continuous subcutaneous insulin infusion (CSII), the golden standard in meal insulin programming is

carbohydrate food counting. On the other hand more and more study have shown how fat and protein meals raise postprandial glycaemia for long time than 3 hours. It was also observed that prolonged insulin delivery in normal and square-wave bolus for a mixed meal helps to normalize glycaemia profile if compared with a regular bolus setting.

There for I want to present the complex food counting considering the total caloric values of meal in prandial insulin programming and a new concept was introduced for these purposes called fat-protein exchange factor (FPU) defined as 100 kcal of fat or/and protein foods. Finally, it was established that the dose of insulin should be calculated based on the number of carb unit (exchanges 10 gram or 40 kcal) and the number of fat-protein units multiplied by insulin ratios. Total dose of insulin calculated for a meal was counted as the sum of insulin dose for carb U and FP U. People with diabetes make decisions about the dose of insulin for meals every day. For this it is essential to strengthen their competences and help in choosing the type of bolus and its dose. It is also important to adjust the type and dose of bolus to the time of the meal.

Controversies

Should CGM be Used in Every Child with Diabetes?

CON1.1

Abstract Unavailable

CON1.2

Abstract Unavailable

Should Children with Isolated Idiopathic GHD be Retested in Early/Mid-Puberty, rather than Wait until Adult Height is Achieved?

CON2.1

Should children with isolated idiopathic GHD (IIGHD) be retested in early/mid-puberty, rather than wait until adult height is achieved? (PRO)

Sandro Loche

Pediatric Endocrine Unit, Pediatric Hospital Microcitemico
"A. Cao", ARNAS G. Brotzu, Cagliari, Italy

More than 60% of patients with IIGHD have normal GH responses to stimulation when retested at the end of growth, and more than 40 % when retested between one year from the start of treatment and mid puberty. This is probably due to the poor diagnostic accuracy of GH stimulation tests and IGF-I measurement. These are strong arguments in favour of early retesting to avoid the burden, cost and potential side effects of unnecessary treatment. There should be no risk of early termination of GH therapy since the available data indicate that patients who stop treatment after retesting do not end up shorter than those who continue treatment. We suggest to perform retesting after one year in patients with a non satisfactory response to treatment and at mid puberty in the remaining. Priming with sex steroids at retesting may be used in prepubertal patients in pubertal age (>11 for boys and >10 for girls). We suggest to use the same GH stimulation test used at diagnosis with a peak cut-off of 7 µg/L. In selected cases when the diagnosis is particularly uncertain retesting could be performed after 3-6 months before starting treatment. Patients and family should be aware from the beginning that the diagnosis is uncertain and that retesting will be performed at some point and treatment could be eventually stopped. This would minimize the risk of losing physician credibility and would encourage patients' and families' empowerment. We suggest long-term follow-up for all patients who stop treatment after retesting. Improvement of the diagnostic phase with revision of current guidelines is needed.

CON2.2

Should children with isolated idiopathic GHD (IIGHD) be retested in early/mid-puberty, rather than wait until adult height is achieved? (AGAINST)

Jan-Maarten Wit

Leiden University Medical Centre, Leiden, Netherlands

The many false-positive diagnoses of IIGHD do not automatically imply that re-testing is needed. Instead, the diagnostic procedure should be improved. Still, re-testing of children can be useful.

Regarding the timing, re-testing within 1-2 months would only extend the diagnostic procedure. Re-testing after one year may be a useful option if the growth response appears insufficient. The current approach of re-testing at near-adult height (NAH) is associated with highest GH waste and patient burden. Testing at mid-puberty has the benefit of long-term physiological exposure to sex steroids, and a lower GH waste and patient burden than current practice. However, decisions are needed about which GHST should be used, whether sex hormone priming is indicated, the optimal cut-off for the GH peak, and possible adjustment for BMI SDS.

The effect of discontinuation of rhGH treatment on adult height in an adolescent with a normal GH peak at re-testing in mid-puberty is uncertain. Two small uncontrolled (and potentially biased) studies showed a 0.4-0.5 SD lower NAH adjusted for target height. The reported positive effect by doubling the rhGH dose in puberty on NAH suggests that pubertal growth is GH dependent.

The benefit of re-testing is a reduction of GH waste and patient burden. Risks include uncertainty about the effect on adult height and potential patient anxiety. Further, the physician's credibility may be at stake and a repeat test will be necessary at NAH if the GH peak in mid-puberty is low.

I propose a stricter diagnostic phase associated with full explanation of the re-testing schedule; re-testing after 1 year if the growth response insufficient; re-testing at mid-puberty in all; discontinuation of rhGH treatment if the GH peak is sufficient; and careful long-term follow-up.

GPED

The Use of Long-Acting Insulin Analogues in Low and Middle Income Countries

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GPED1.1

For the use of long acting insulin analogues in low and middle income countries

Suzanne Sap

The University of Yaounde I, Yaounde, Cameroon

Quality of care of children living with diabetes varies widely around the world. Since discovering of insulin a hundred years ago, it's still unavailable for a large part of children living with diabetes in developing world. According to World Health Organisation (2019), less than 13% of people living with diabetes in these countries have access to long acting insulin analogues. Thus, primary challenges of management of type I diabetes is reduction of mortality especially at diagnosis, but rapidly, the question of metabolic control and reduction of acute and chronic complications appears as secondary challenges of management for many teams around the world.

Research of appropriate solutions for better care leads to discovery of new insulin, new technologies etc. The WHO selects essential medicines on the basis of their role in solving a public health issue, their innocuity, their efficacy and the cost/efficacy. Is long acting insulin responding to this criteria? We will therefore showed that diabetes care obey today to a "double standard". We also state that, long acting insulin are benefit for children, adolescent and young adults living with type I diabetes in developing countries regarding to their nutrition challenges, prevention of acute and chronic conditions. Finally, we will review literature showing advantages of long acting insulin in type I diabetes compared to intermediate insulin, and its cost effectiveness.

Conclusion: Long acting insulin are important in better management of children with type I diabetes in low and middle income countries

Keys words: long acting insulin, developing countries, type I diabetes

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GPED1.2

Abstract Unavailable

Young Investigators

Young Investigators

YI1.1

Identification of novel genetic causes of familial central precocious puberty

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*Rade Vuković*⁹, *Slađana Todorović*⁹, *Aleksandra Jančevska*¹⁰,
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Introduction: The major genetic cause of CPP is the paternally inherited Makorin RING-finger protein 3 (MKRN3) deficiency. Rare patients carry variants in kisspeptin and its receptor and *DLK1*.

Objectives: To identify genetic causes of CPP.

Population and Methods: *MKRN3* Sanger sequencing was performed in 56 unrelated subjects (12 familial non-maternal, 44 sporadic (6 boys)), whole-genome sequencing (WGS) in 15 family trios (10 maternal), and whole-exome sequencing (WES) in 38 probands (13 familial maternally, 5 sporadic boys, 20 sporadic girls - CPP before 7 years).

Results: Pathogenic *MKRN3* variants were identified 5/12 familial subjects (42%), including a novel missense variant, none in sporadic patients. In the coding regions of 398 genes associated with age at menarche on average 25 rare (MAF<0.2%) variants/person were identified; however, genetic landscape varied greatly between patients. No *DLK1* variants were detected. In genes

associated with hypogonadotropic hypogonadism (HH) 17 rare and predicted pathogenic coding missense or nonsense variants were found heterozygous. Some of them were previously associated with HH, including p.Q106R in *GNRHR*, p.H83R in *TAC3*, p.A194D and p.C389X in *KISS1R* and p.L173R in *PROKR2* gene. Rare (MAF<0.025%) predicted pathogenic variants in axon guiding pathway *SEMA3/NRP/PLXNA*, which is relevant for GnRH neuron migration, were more frequent in our cohort as compared to a general population, yet evenly distributed across genes.

Conclusions: *MKRN3* variants were common in non-maternal familial CPP. Certain HH variants tolerated CPP. Potentially pathogenic variants in axon guiding pathway seem to be overrepresented in the CPP cohort as compared to the general population, which should be verified by testing a larger cohort and addressing the mechanisms.

YI1.2

Early life events and postnatal effects from infancy to childhood

Valentina Chiavaroli

University of G. d'Annunzio Chieti and Pescara, Chieti, Italy

Early life events can profoundly affect an individual's metabolic phenotype, inducing adaptive responses that may be protective *in utero* but potentially disadvantageous for long-term health. Indeed, environmental cues during sensitive windows of development may result in altered growth and lead to an increased risk of cardiovascular and metabolic alterations later in life. In this talk, I will discuss several models of exposure to early life events, which were the topic of my Long-term Research Fellowship granted in 2015 by the European Society for Paediatric Endocrinology (ESPE).

YI1.3

Genetics and endocrine phenotypes of the MEHMO syndrome

Juraj Staník

Department of Pediatrics, Medical Faculty of the Comenius University, Bratislava, Slovakia; DIABGENE, Institute of Experimental Endocrinology, Biomedical Research Center, Slovak Academy of Sciences, Bratislava, Slovakia

Introduction: Monogenic obesity is a heterogeneous group of rare conditions involving less than 5% of the children with obesity. The most common subtypes of monogenic obesity are mutations of the genes *MC4R*, *SIM1*, and *PCSK1*. Rare monogenic obesity forms include also MEHMO syndrome. MEHMO is an X-linked condition characterized by Mental retardation, Epilepsy, Hypogonadism/hypogonitalism, Microcephaly, and Obesity. In our studies we have described the genetics, and endocrine phenotypes of 2 boys with MEHMO syndrome.

Results: Both boys were carrying a frame-shift mutation (1465fs) in the *EIF2S3* gene inherited from their healthy

mothers. EIF2S3 encodes the γ subunit of the eukaryotic translation initiation factor 2 (eIF2), which is involved in protein synthesis. Both probands had microcephaly, hypogonadism, severe psychomotor retardation and seizures. After a short period of failure to thrive, both of them had rapid weight-gain and developed obesity. Neonatal hypoglycemia switched to insulin-dependent non-autoimmune diabetes during the first year of life accompanied by development of panhypopituitarism. These conditions were due to dysregulation and gradual decline of peptide hormone secretion. However, only proteins secreted on demand were affected, as concentration of albumin and IgG immunoglobulins were in normal range. On the other hand one proband had frequent respiratory infections responding well to therapy with immunoglobulins. One of the boys died at the age of 4 years, the second is still alive currently age 11 years.

Conclusions: X-linked MEHMO syndrome is a severe condition caused by a mutation in EIF2S3 encoding the γ subunit of the eukaryotic translation initiation factor 2. The clinical picture results from the damaged protein synthesis. Particularly dysregulation and gradual decline of concentrations of peptide hormones secreted on demand are responsible for the complex endocrine phenotype. Such conditions as MEHMO syndrome help us to understand regulation mechanisms of the endocrine system in children.

Y11.4

Abstract Unavailable

Y11.5

Vegf-A mRNA transfection to improve islet graft revascularization

Willem Staels

Beta Cell Neogenesis (BENE) Research Group, Vrije Universiteit Brussel (VUB), Brussels, Belgium. Service of Pediatric Endocrinology, Department of Pediatrics, KidZ Health Castle, Universitair Ziekenhuis Brussel (UZ Brussel), Brussels, Belgium

Diabetes mellitus is a pandemic metabolic disorder characterized by chronic hyperglycemia. The pathogenic process is the result of insulin insufficiency. Insulin is a peptide hormone produced in the beta cells of the pancreatic islets. Current diabetes treatments strive for glycemic control but fail to solve the underlying beta cell defect. This approach has increased the life expectancy and quality of most patients with diabetes but has turned diabetes into a chronic disease. Curative strategies should aim at restoring and protecting the functional beta cell mass which in turn would self-regulate a fine-tuned glucose homeostasis. Beta cell transplantation has already proven its therapeutic value and is clinically applied in a selected group of patients with diabetes. However, the procedure suffers from a large islet cell loss immediately following

transplantation. This cellular loss is at least partly due to insufficient graft revascularization. To tackle this hurdle, we devised a novel approach based on the transfection of islet cells with mRNA encoding the proangiogenic factor VEGF-A immediately before transplantation. Such an approach using in vitro transcribed mRNA for gene delivery has important advantages over classic gene therapy: (i) the overexpression is transient thus avoiding side effects of chronic VEGF-A overexpression such as increased vascular permeability and inflammation, and (ii) the inherent risks of viral-vector-based methods, such as insertional mutagenesis or vigorous immune reaction are absent. We provide proof-of-concept for the ability of VEGF-A mRNA-therapy to enhance the vascularization of both mouse and human beta cell grafts.

Key Learning Points

- Beta cell transplantation has provided proof of concept of its potential to cure diabetes.
- Beta cell transplantation suffers from a major cell loss post-transplantation due to insufficient graft revascularization
- *Vegf-A* mRNA transfection of beta cells before transplantation improves graft revascularization and is a promising strategy to improve engraftment success in clinical islet transplantation protocols.

Working Group Symposia

ESPE Working Group on Bone and Growth Plate (BGP) Symposium

WG1.1

Abstract Unavailable

WG1.2

Craniosynostoses - genes and bone biology

Steve Twigg

University of Oxford, Oxford, United Kingdom

Expansion of the skull vault to accommodate the growing brain is driven primarily by growth at cranial sutures. These are fibrous joints between the flat bones of the skull that translate growth pressure from the brain into a balanced proliferation and differentiation of cells of the osteoblast lineage. This process is sensitive to environmental and genetic insults and premature fusion of one or more sutures, termed craniosynostosis is a common (~1 in 2000), and serious craniofacial malformation. In about a quarter of all

cases a monogenic cause can be identified with mutations in over 100 genes associated with craniosynostosis. Analysis of mouse models for some of these genes highlights the role of abnormalities in both developmental patterning and in proliferation-differentiation balance in craniosynostosis. Better delineation of these mechanisms requires a clearer understanding of the cell populations that make up a cranial suture. In recent work we generated single-cell transcriptomes from murine coronal sutures and performed extensive expression validation. We found distinct pre-osteoblast signatures between the bone fronts and periosteum, a ligament-like population above the suture that persists into adulthood, and a chondrogenic-like population in the dura mater underlying the suture. Lineage tracing revealed an embryonic *Six2*⁺ osteoprogenitor population that contributes to the postnatal suture mesenchyme, with these progenitors being preferentially affected in a *Twist1*^{+/-}; *Tcf12*^{+/-} mouse model of Saethre-Chotzen Syndrome.

WG1.3

Abstract Unavailable

ESPE Working Group on Obesity (OWG) Symposium

WG2.1

Environmental obesogens

Leonardo Trasande

Department of Pediatrics, Division of Environmental Pediatrics, NYU Langone Medical Center, New York, USA. Departments of Population Health and Environmental Medicine, NYU Langone Medical Center, New York, USA. NYU Wagner School of Public Service, New York, USA. NYU College of Global Public Health, New York, USA

Rapidly accumulating evidence supports the role of synthetic chemicals as obesogens and cardiometabolic risks. This presentation provides an overview of the latest evidence, safe and simple steps for prevention, and business case for policy intervention.

WG2.2

Maternal obesity and offspring health

Rebecca Reynolds

University of Edinburgh, Edinburgh, United Kingdom

Maternal obesity is the most common metabolic disturbance in pregnancy affecting more than 1 in 5 women in some regions. Obesity has short term risks during pregnancy for both mother and child, with increasing evidence demonstrating that there are also longer term risks of these exposures in pregnancy impacting on health of the offspring across the lifespan. Consistent and increasing evidence demonstrates a range of adverse health outcomes for offspring born to mothers who are obese in pregnancy. This includes increased risk of obesity, metabolic syndrome, cardiovascular risk factors in childhood and death from cardiovascular disease in adulthood, as well as neurodevelopmental and neuro-psychiatric outcomes in childhood. Potential mechanisms will be discussed including the role of glucose/insulin resistance and dysregulation of the hypothalamic-pituitary-adrenal axis. Evidence from the literature reporting links between maternal obesity and diabetes and offspring outcomes will be reviewed including from data-linkage studies, experimental studies and mechanistic studies as well as our own data from follow up of children born to severely obese women (BMI>40) who were characterised in detail in pregnancy. Data from follow-up studies of offspring born to mothers who participated in intervention trials in pregnancy (diet/lifestyle, pharmacological and bariatric surgery) will also be presented. Disentangling the 'in utero' exposure from the 'postnatal' environment is challenging in human studies and further studies are needed to understand underlying mechanisms. With limited evidence that intervention trials in pregnancy lead to improved outcomes for the child, consideration needs to be given to pre-conception interventions. Ensuring women are healthy prior to pregnancy offers a major opportunity to optimise the health of the next and future generations.

ESPE Working Group on Diabetes Technology (DT) Symposium

WG3.1

Abstract Unavailable

WG3.2

Decision Support System for the diabetologists - practical experience

Klemen Dovc

UMC Ljubljana University Children's Hospital, Ljubljana, Slovenia. University of Ljubljana Faculty of Medicine, Ljubljana, Slovenia

Optimal management of type 1 diabetes requires precise insulin administration to maintain glucose within optimal glucose ranges. Insulin dosage regimens are complicated by day-to-day variability in insulin requirements to maintain near-normoglycemia, which can cause considerable excursions in glucose levels.

Digital decision support systems have been developed to help healthcare professionals facilitate timely, more frequent and adequate insulin dose adjustments, either in person or remotely, and thus improve glycemic control for individuals with diabetes. This field includes a wide range of algorithms to guide diverse aspects of diabetes management and insulin dosing adjustments, including tools to use in times of physical activity and eating, various insulin bolus calculators for meal-time dosing; and advanced algorithms to guide insulin dosing adjustments for individuals using insulin pumps, multiple daily injections, and automated insulin delivery. Decision support systems for healthcare providers and also individuals living with diabetes are becoming a subject for intensive research, development, and adoption in routine clinical practice. Several decision support systems have been introduced in the past years, some using advanced data science methods, including machine learning and artificial intelligence.

In this presentation, we will present contemporary data on decision support systems used to optimize glycemic control in individuals living with diabetes.

WG3.3

The impact of fear of hyperglycemia in parents of children with type 1 diabetes mellitus on overall glycemic control

Alon Liberman, Michal Nevo-Schenker, Iris Sachar-Lavie, Moshe Phillip

Schneider Children's Medical Center, Petah Tikva, Israel

Background: Achieving proper glycemic control is the major goal in the management of type 1 diabetes. The Diabetes Control and Complication Trial showed that optimal glycemic control can decrease micro- and macrovascular complications in adolescents and adults with type 1 diabetes. Both hypo and hyperglycemia affect crucial regions in the developing brain.

In children and young adolescents, most of the work towards achieving optimal glycemic control is led by the parents. Many studies have been published exploring parental fear of hypoglycemia and accompanying behaviors. Our clinical experience shows that similar behaviors are also relevant to hyperglycemia; however,

the topic of fear of hyperglycemia has not received adequate attention in the published literature, especially among children with T1D.

Aim: To design and test the reliability and validity of a new fear of hyperglycemia fear survey parent version and to assess the correlation between parental fear of hyperglycemia and the child's overall glycemic control as reflected by HbA1C, time in range and hypoglycemic events.

Methods: 50 parents of type 1 diabetic patients aged 6-14 years old to validate the Hyperglycemia Fear Survey – Parent version. The same parents completed the validated Hypoglycemia Fear Survey – Parent version and the validated Diabetes Treatment Satisfaction Questionnaire (DTSQ) – Parent version. The correlation between parental fear of hyperglycemia and the child's overall glycemic control was assessed.

Results: The Hyperglycemia Fear Survey was found to be valid and reliable. Significant correlations between parental fear of hyperglycemia and glycemic control were found.

Conclusion: The hyperglycemia fear survey – parent version can be considered a valid tool for the measuring fear of hyperglycemia among parents and caregivers of children with type 1 diabetes. It can also be associated with the child's overall glycemic control.

ESPE Working Group on Disorders of Sex Development (DSD) Symposium

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WG4.1

New insights into sex differentiation and their relevance to disorders of sex development

Barbara Nicol

NIEHS/NIH, Durham, USA

Embryos initially form undifferentiated gonads, reproductive tracts and external genitalia that will progressively acquire female or male characteristics. This fate decision is initiated in the undifferentiated gonads and depends on sex chromosomes and fine-tuned expression of complex networks of molecular pathways. Defects at different levels of this cascade of events can trigger a large spectrum of Disorders of sex development (DSDs), defined as "congenital conditions within which the development of chromosomal, gonadal, and anatomic sex is atypical". For a majority of DSD cases, the genetic etiology remains unfortunately unknown.

Our lab uses the mouse as a model to understand the molecular events that control sex differentiation during fetal development. Supporting cells dictate the fate of the gonads by differentiating into either Sertoli cells or granulosa cells. We recently identified the transcription factor RUNX1 as a supporting cell marker that becomes granulosa cell specific during gonad differentiation. RUNX1 plays complementary/redundant roles with FOXL2 to maintain fetal granulosa cell identity and combined loss of RUNX1

and FOXL2 results in masculinization of fetal ovaries. Genome-wide binding of RUNX1 overlaps with FOXL2 occupancy in the fetal ovary, suggesting that RUNX1 and FOXL2 directly target common sets of genes. This result also highlights the interest of identifying the genomic regions bound by transcription factors involved in gonad differentiation as potential regions of interest for DSDs, beyond the genes themselves. Finally, new technologies like single-cell RNA-seq are revolutionizing the field by creating a detailed roadmap of dynamic changes happening in each cell population composing the reproductive organs, which could be a steppingstone in better understanding of the molecular origins of DSDs.

WG4.2

Advances in the Measurement of Steroid Hormones

Stefan A. Wudy

Justus Liebig University, Giessen, Germany

While steroid hormones as universal signals of intercellular communication arose very early in the evolution of life, it was only recently that their isolation and structural elucidation has been achieved. Steroid hormones are small, structurally closely related molecules sharing the typical 4-cyclic sterane basic structure. However, there is a big diversity of functionally different steroid hormones and their metabolism is complex. Thus, their analysis is highly challenging. Due to the multiplicity of enzymes involved, there is a huge variety of steroid related disorders, which often share clinical signs and symptoms. From a clinical perspective, reliable hormonal determination presents a most reasonable initial diagnostic approach as well as a backbone of monitoring these highly complex patients. From a scientific view, reliable steroid hormone determination is a prerequisite when characterizing new steroid hormone actions.

This lecture is aimed at clinicians and scientists alike. After a brief historical review, the principles as well as the pros and cons of the currently most important methods in the analysis of unconjugated and conjugated steroid hormones, such as immunoassay and mass spectrometry based methods will be discussed. The focus of the latter will lie on the currently prevailing hyphenated techniques gas chromatography-mass spectrometry and liquid chromatography-tandem mass spectrometry. Their application will be illustrated by examples from clinical and scientific practice. Additionally, quality assurance will present another important point. Furthermore, an outlook on future analytical developments will also be given.

Hormone analysis is a main pillar of endocrinology. Every clinician or scientist should be familiar with the principles of the methods used. Since reliable steroid hormone analysis requires extremely high expertise both in analytics as well as in steroid biochemistry, collaboration and networking between hormone analysts, clinicians, and scientists are highly advantageous.

ESPE Working Group on Paediatric and Adolescent Gynaecology (PAG) Symposium

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WG5.1

Deciphering the genetics of central precocious puberty

Ana Claudia Latronico

Sao Paulo University, Sao Paulo, Brazil

Puberty is a crucial biological process normally occurring at a specific time during the lifespan, during which sexual and somatic maturation are completed, and reproductive capacity is reached. Pubertal timing is not only determined by genetics, but also by endogenous and environmental cues, including nutritional and metabolic signals. During the last decade, we have learned much regarding the essential roles of kisspeptins and the neuropeptide pathways that converge on these neurones to modulate kisspeptin signalling, as well as neurokinin B and dynorphin, the co-transmitters of Kiss1 neurones in the arcuate nucleus, and the effects of melanocortins on puberty. Central precocious puberty (CPP) is diagnosed when premature activation of the hypothalamic-pituitary axis occurs. Its causes are heterogeneous, with alterations of the central nervous system being of special interest, and with environmental factors also playing a role in some cases. During the last decade, several mutations in different genes (including *KISS1*, *KISS1R*, *MKRN3* and *DLK1*) that cause CPP have been discovered. Loss-of-function mutations in *MKRN3* are the most common monogenic cause of CPP known to date.

WG5.2

Abstract Unavailable

ESPE Working Group on Gender Incongruence (GI) Symposium

WG6.1

Abstract Unavailable

WG6.2

Abstract Unavailable

ESPE Working Group for Paediatric Endocrine Nurses (ESPEN) Symposium

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WG7.1

Abstract Unavailable

WG7.2

Abstract Unavailable

WG7.3**Nursing care for the child with gender dysphoria**

Paul Carruthers

Leeds Children's Hospital, Leeds, United Kingdom

This presentation will provide an insight into the Gender identity Development service (GIDS) endocrine pathway. The service has experienced a difficult year with well documented legal challenges; these will be briefly presented highlighting the impact this has had on patient care.

It is important when working with gender incongruent young people to be aware of the use of appropriate pronouns, co-occurring difficulties and the importance of advocacy in our nursing practice. The presentation will provide the listeners with an introductory toolkit to working with gender diverse young people.

ESPE Working Group on Turner Syndrome Symposium

WG8.1

Abstract Unavailable

WG8.2**Turner syndrome and hormone replacement therapy**

Claus H. Gravholt

Aarhus University Hospital, Aarhus, Denmark

Turner syndrome is a condition in females missing a sex chromosome (45,X) or parts of the second sex chromosome. It is considered a rare condition and associated with a range of characteristics, such as short stature, ovarian dysgenesis, delayed puberty and infertility, congenital malformations of the heart, endocrine disorders, including a range of autoimmune conditions and type 2 diabetes. Morbidity and mortality is clearly increased compared with the background population and the average age at diagnosis is quite delayed. During recent years it has become clear that a multidisciplinary approach to the patient with Turner syndrome is necessary. Hypergonadotropic hypogonadism is seen in most females with Turner syndrome, and puberty has to be induced in most cases. In addition to estrogen and progesterone deficiency, TS is also accompanied by low testosterone levels. According to TS guidelines, hormone replacement therapy (HRT) should be initiated in TS women with primary or secondary amenorrhea, preferably starting between 11 and 12 years of age, continuing until the normal age of natural menopause. HRT is necessary to induce puberty, to maintain secondary sex characteristics, and to facilitate uterine growth, appropriate peak bone mass, and possibly neuro-cognitive function, and it improves the metabolic profile via a positive influence on body composition. However, empiric data on the long-term effects of HRT in women with TS is limited, especially concerning the impact on endocrine conditions, cardiovascular diseases and mortality. Some have raised concerns that HRT in TS women may induce the development of deep venous thrombosis and pulmonary embolism. The proper dose of HRT with female sex steroids has not been established, and, likewise, benefits and/or drawbacks from HRT have not been thoroughly evaluated. Likewise, no framework is in place for continuous follow-up during adult years in many countries. Recent data from the Netherlands and Denmark show that a sizable proportion (13-15%) of females with TS do not receive proper HRT, despite guideline recommendations. New long term data on HRT underscores the importance of securing optimal treatment and reducing morbidity and perhaps mortality. Here, the optimal sex hormone replacement therapy will be discussed.

WG8.3

Blood Pressure in Turner Syndrome - a practical approach

Debbie Matthews

Great North Children's Hospital, Newcastle upon Tyne, United Kingdom

Females with Turner syndrome (TS) have a reduced life expectancy of about 13 years and a substantial excess mortality; about 50% of this is the result of cardiovascular pathology. Hypertension affects 20–60% of females with TS and is the single most modifiable risk factor for cardiovascular disease. However, hypertension in TS is both under-diagnosed and under-treated.

The presentation details a practical approach to monitoring blood pressure and managing hypertension in TS. The prevalence of hypertension, the causes and end-organ effects are explored. Methods for monitoring blood pressure in children and adolescents are described. Finally, making a diagnosis of hypertension is discussed together with management, remaining uncertainties and ideas for future research.

Endo-ERN Symposium

Endo-ERN Symposium

EE1.1

Update on the consensus on Congenital Hypothyroidism: a patient-centered approach

Michel Polak

Pediatric Endocrinology, Gynecology and Diabetology,
Ile de France Regional Newborn Screening Program,
University Hospital Necker Enfants Malades, INSERM U1016
and 1163, Université de Paris, Paris, France

Background: An ENDO-ERN initiative was launched which was endorsed by the European Society for Pediatric Endocrinology and the European Society for Endocrinology with 22 participants from the ENDO-ERN and the two societies. The aim was to update the practice guidelines for the diagnosis and management of congenital hypothyroidism (CH). A systematic literature search was conducted to identify key articles on neonatal screening, diagnosis and management of primary and central congenital hypothyroidism. The evidence-based guidelines were graded with the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system, describing both the strength of recommendations and the quality of evidence. In the absence of sufficient evidence, conclusions were based on expert opinion.

Summary: The recommendations include the various neonatal screening approaches for CH as well as the etiology (also genetics), diagnostics, treatment and prognosis of both primary and central CH. When CH is diagnosed, the expert panel recommends the immediate start of correctly dosed levothyroxine treatment and frequent follow-up including laboratory testing to keep thyroid hormone levels in their target ranges, timely assessment of the need to continue treatment, attention for neurodevelopment and neurosensory functions and, if necessary, consulting other health professionals, and education of the child and family about CH. Harmonisation of diagnostics, treatment and follow-up will optimise patient outcomes. Lastly, all individuals with CH are entitled to a well-planned transition of care from pediatrics to adult medicine.

Conclusions: This consensus guidelines update should be used to further optimize detection, diagnosis, treatment and follow-up of children with all forms of CH in the light of the most recent evidence. It should be helpful in convincing health authorities of the benefits of neonatal screening for CH. Further epidemiological and experimental studies are needed to understand the increased incidence of this condition.

EE1.2

Patient expectation and unmet needs in XLH

Martha Kirchhoff

Phosphatdiabetes e.V., Lippstadt, Germany

The aim of the lecture is to show the expectations and unmet needs of people affected by X-linked hypophosphatemia. As XLH is a rare disease, these patients face the same problems as most of other rare disease causes, but there are additional burdens in XLH, related to the specifics of the disorder.

X-linked hypophosphatemia is a rare inherited metabolic bone disease, which can also be caused by a spontaneous mutation. There is an alteration in the PheX gene what leads to renal phosphate wasting, reduced intestinal phosphate absorption and a deficient Vitamin D activation.

The list of symptoms and clinical manifestations of this complex disorder is long. They may change and get worse during life. The course of the illness, as well as appearance and severity of the symptoms differ extremely, even within one family.

XLH is a chronic, progressive, and lifelong disorder. It affects all areas and all stages of life. It does not only have an impact on the individual, but on the families, society, and health care system. For XLH is not fully understood, it demands not only the patients, but also the clinicians.

XLH is a disabling and challenging disease, leading to a reduced quality of life. As main topics, expectations and needs change during a life time, treatment and therapy management have continuously to be adapted.

There is a lack of knowledge on both sides, patients, and clinicians.

To understand the expectation and needs of people suffering from XLH, it is essential to look at the totality of influence factors of this disease on life.

The knowledge of expectations and unmet needs of patients with XLH could help to improve their therapy management and care.

EE1.3

Abstract Unavailable

ESPE Yearbook Sessions

Year of Paediatric Endocrinology 1

YB1.1

Abstract Unavailable

YB1.2

Antenatal and Neonatal Endocrinology

Khalid Hussain

Sidra Medicine, Doha, Qatar

I have chosen 3 manuscripts for my year book presentation on antenatal and neonatal endocrinology. The first manuscript describes the use of induced pluripotent stem cells (iPSCs) to study the genetic mechanisms of congenital hyperinsulinism (CHI). The derivation of iPSCs and their subsequent conversion to islet like clusters from a patient with diffuse CHI due to a homozygous mutation in the *ABCC8* provides a unique opportunity to study the molecular basis of CHI and to develop potential novel treatment options by screening for new drug targets in-vitro. The second manuscript describes a novel disorder due to homozygous mutations in the *YIPF5* gene which cause a complex syndrome of neonatal/early onset diabetes mellitus, epilepsy and microcephaly. The underlying mechanism of the diabetes involves the accumulation of proinsulin (unable to be transported to the Golgi) in the beta-cells with increased ER stress markers and a tendency to apoptosis. Finally, the third manuscript reviews the evidence for the use of probiotics for preventing gestational diabetes mellitus (GDM). In summary this review did not find any evidence of certainty that supports the use of probiotics for reducing the risk of developing GDM. Only 2 studies conducted in women with GDM

and atopic disease suggested a possible reduction in the risk of GDM with probiotics. More importantly and of concern, the review found with a high degree of certainty that the use of probiotics increases the risk of developing pre-eclampsia. This observation suggests that great care needs to be taken in all future studies involving the use of probiotics in pregnancy.

YB1.3

Abstract Unavailable

YB1.4

Growth and Growth Factors

Stefano Cianfarani^{1,2,3}, *Elena Inzaghi*², *Valentina Pampanini*², *Daniilo Fintini*²

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Long-term safety of rhGH therapy in childhood has been object of intense investigation in the last decade. Two recent observational studies have focused on the risk of cardiovascular diseases in young adults treated with rhGH during childhood. After subdividing the large cohorts of patients in different risk groups they found that both mortality and morbidity from cardiovascular diseases were higher than the general population in the low risk group including patients with isolated GH deficiency, idiopathic short stature and small for gestational age.

Genetic control of height has been widely explored using genome-wide association studies (GWAS). Although familial short stature (FSS) is the most common type of short stature, its genetic profile remains largely unknown. Two recent studies have highlighted the genetics underlying FSS. Ten novel genetic single nucleotide polymorphisms (SNPs) and ten pathogenic variants in collagen genes (*COL2A1*, *COL11A1*, and *COL11A2*) were identified in children diagnosed as having FSS.

YB1.5

Bone, Growth Plate and Mineral Metabolism

Marta Baroncelli¹, Adalbert Raimann², Raja Padidela³,
Ola Nilsson^{1,4}

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The skeletal research field develops rapidly and has produced several exciting findings in the last year and includes advances in the treatment of rare skeletal disorders and an ever deeper understanding into the fundamental molecular mechanisms that control skeletal development, metabolism, growth, and mineralization.

The targeting of the C-type natriuretic peptide (CNP) pathway and options to directly antagonize the overactivity of the FGFR3 pathway in achondroplasia continues to be a subject of high interest and excitement and in the 2021 yearbook we highlight the double-blind, randomized placebo-controlled phase 3 study of a CNP analogue (vosoritide) in children with achondroplasia. We also highlight the identification of a novel gene for autosomal dominant hypophosphatemic rickets, publication of new growth charts for X-linked hypophosphatemia and two large well-designed paediatric vitamin D trials for the prevention of tuberculosis and asthma exacerbation, respectively.

Translational highlights include review on the recent advances of mineral metabolism and biomineralization, *in vivo* data suggesting that modification of the synovial microenvironment may allow endogenous skeletal stem cells to form hyalin cartilage and thereby heal articular cartilage injuries, as well as a study using gene targeting in zebra fish to reveal the pathogenic mechanism by which mutations in CRTAP and P3H1 causes osteogenesis imperfecta type VII and VIII, respectively.

Advances in the understanding of skeletal biology a study by McDonald *et al.* that challenges the current dogma on the origin and fate of osteoclasts as they show evidence that multinucleated osteoclasts can fission into daughter cells, a.k.a. osteomorphs, that subsequently are recycled into bone resorbing osteoclasts via a RANKL-dependent process. Additional articles in this section directly and indirectly highlight the critical role of loading and mechanical stress on the growing skeleton. Several of these exciting findings will be highlighted in the presentation.

Year of Paediatric Endocrinology 2

YB2.1

DSD and Transgender - Updates 2021

Christa Flueck¹, Martine Cools², Anna Nordenström³

¹University of Bern, Bern, Switzerland. ²University of Gent, Gent, Belgium. ³University of Stockholm, Stockholm, Sweden

In the past year, basic and genetic studies revealed again novel genes and mechanisms implicated in 46,XX and 46,XY DSD. The *Fgf9*^{-/-} mouse model of human synostosis syndromes revealed an unexpected male-to-female sex reversal phenotype, so far not observed in humans. Specific heterozygous human *WT1* gene variants located in the 4th zinc finger were found to cause 46,XX virilization due to (ovo-)testicular DSD, and the transcription factor FKBP4 was reported as novel candidate gene for androgen insensitivity syndrome. Furthermore, several 46,XY patients suffering from complex syndromes owing to congenital disorders of glycosylation were recognized with a DSD phenotype likely due to early disruption of sexual development. Single-cell sequencing has been introduced as a promising method to elucidate the complex mechanisms of gonadal and sexual developmental, and is predicted to help understanding the pathomechanisms of DSDs.

Several clinical studies on patient reported outcomes have been published informing on topics such as sex assignment, needs in adolescents and during transition for sexual health as well as on long-term outcome after genital surgery.

In transgender medicine, the largest body of literature was in topic (long-term) effects of hormonal treatments and their current controversies. Studies reported on possible behavioral and neurobiological effects of GnRH agonist treatment, and on increased risk of intracranial meningioma in trans women using high dose cyproterone acetate. In addition, studies addressed thrombosis risk and bone health related to GnRH agonist and gender affirming hormone therapy. However, many of these studies suffer from limitations including small numbers, retrospective and/or single center design, non-uniform study protocols and short observation period.

YB2.2

Puberty

Anne-Simone Parent^{1,2}, Sara Moline², Delphine Franssen¹

¹University of Liège, Liège, Belgium. ²University Hospital of Liège, Liège, Belgium

This presentation will focus on last year's main discoveries regarding puberty. Some of these studies help us further understand the role of MKRN3 in puberty and better define the phenotype associated with MKRN3 mutations. Large cohort studies bring more information regarding secular trends in central precocious puberty, premature thelarche or adrenarche but also

gynecomastia. This presentation will also address new discoveries regarding the effect of prenatal stress on pubertal timing and the results of the first phase 3 study of a subcutaneous 6-month leuprolide acetate.

YB2.3

Abstract Unavailable

YB2.4

Oncology and Chronic Disease

Carla Bizzarri

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As in previous years, most of the studies concern the medium and long-term complications of cancer therapy. Issues related to long-term surveillance strategies represent an emerging topic of discussion. In comparison with previous years, this year we have found few truly original and innovative studies. Rather, the attention of the researchers seems to be focused on confirming and consolidating acquired data, in particular:- The development of subsequent neoplasms in childhood cancer survivors does not correlate with the use of substitutive therapy with growth hormone, but seems to be primarily associated with the use of radiotherapy.- The hormone deficiencies resulting from cancer treatment are predominantly secondary to radiotherapy. Chemotherapeutic drugs cause a minor long-term endocrine damage, although some of them (particularly alkylating agents) have a significant gonadotoxic effect.- Novel genetic markers influencing detrimental effects of chemotherapy on long-term ovarian function have been reported. The identification of these markers can improve the development of risk prediction models. Fertility preservation programs, including ovarian tissue cryopreservation, would benefit from personalized counselling directed to adolescent and young adults at higher risk of gonadotoxicity.

YB2.5

Abstract Unavailable

Year of Paediatric Endocrinology 3

YB3.1

Abstract Unavailable

YB3.2

Abstract Unavailable

YB3.3

Abstract Unavailable

YB3.4

Abstract Unavailable

YB3.5

Abstract Unavailable

Henning Andersen Prize Winners

HA1

A Global Natural History Study of Fibrodysplasia Ossificans Progressiva (FOP): 36-Month Outcomes in Participants Aged <25 Years

Robert J. Pignolo¹, Geneviève Baujat², Matthew A. Brown³, Carmen L. De Cunto⁴, Edward C. Hsiao⁵, Richard Keen⁶, Mona Al Mukaddam⁷, Kim-Hanh Le Quan Sang⁸, Rose Marino⁹, Aude Houchard¹⁰, Frederick S. Kaplan⁷

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Background: FOP is an ultra-rare, severely disabling genetic disorder characterised by progressive heterotopic ossification (HO) following flare-ups. The median age at diagnosis is 5 years, and patients are managed by multiple specialties. No study to date has provided a longitudinal evaluation of FOP. Final data are presented for participants, aged <25 years, enrolled in the first 36-month, prospective, global natural history study of FOP (NCT02322255).

Methods: Individuals with FOP aged ≤65 years with a documented *ACVR1*^{R206H} mutation were enrolled in the study; this analysis includes participants aged <25 years at Baseline. HO volume was evaluated by low-dose whole-body computed tomography (WBCT), excluding the head. Physical function was assessed using the Cumulative Analogue Joint Involvement Scale (CAJIS; total score 0-30 represents degree of ankylosis across joints) and the FOP Physical Function Questionnaire (FOP-PFQ; % total score); in both measures higher scores indicate more severe limitations. Change from Baseline (CfB) at Month 36 in HO volume, CAJIS and FOP-PFQ are presented.

Results: Of 87 participants aged <25 years at Baseline, 32 had evaluable WBCT HO data at Baseline and Month 36. At Month 36, 87.5% of participants had new HO. CfB in mean [SD] total WBCT

HO volume over 36-months was highest in those aged 8-<15 years (88.28×10^3 [109.77×10^3] mm³; n=13) and 15-<25 years (92.48×10^3 [164.12×10^3] mm³; n=12) versus those 2-<8 years (52.54×10^3 [39.98×10^3] mm³; n=7). Mean (SD) number of body regions with new HO at Month 36 were: 2-<8 years, 3.6 (2.6); 8-<15 years, 2.9 (1.7); 15-<25 years, 2.5 (2.0). Across median follow-up durations of 34.0 months, 30.1 months and 24.0 months for those aged 2-<8 years, 8-<15 years and 15-<25 years, mean (SD) number of clinical visit/telephone contact flare-ups by participant were 3.2 (3.2), 2.1 (2.1) and 1.7 (1.8), respectively. Mean (SD) number of flare-ups per participant-month were 0.1 (0.1), 0.1 (0.2) and 0.1 (0.1), respectively. Mean CfB to Month 36 in CAJIS and FOP-PFQ were small across age groups (CAJIS: 0.9-1.6 [n=34]; FOP-PFQ: 2.4%-10.3% [n=29]).

Conclusions: Total WBCT HO volume increased over 36-months confirming the progressive nature of FOP. Participants aged 2-<8 years reported the highest mean number of flare-ups and had more body regions with new HO versus participants 8-<25 years, despite lower new HO volumes. Measurement of new HO by WBCT is a viable method to monitor disease progression. CAJIS and FOP-PFQ were not sufficiently sensitive to assess progression over 36-months.

HA2

Biphasic Pattern of Circulating Reproductive Hormones in Female Infants – The Longitudinal COPENHAGEN Minipuberty Study

Marie Lindhardt Ljubicic^{1,2}, Alexander Siegfried Busch^{1,2}, Emmie Upners^{1,2}, Margit Bistrup Fischer^{1,2}, Jørgen Holm Petersen^{1,2}, Lars Lau Raket³, Hanne Frederiksen^{1,2}, Trine Holm Johannsen^{1,2}, Anders Juul^{1,2,4}, Casper P. Hagen^{1,2}

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Background: Minipuberty denotes a transient activation of the hypothalamic-pituitary-gonadal (HPG) hormone axis in infancy. This activation provides an opportunity to examine the gonadal function in infants suspected of hypogonadism before the axis is silenced during childhood. However, female minipuberty remains poorly elucidated.

Objective: The study aimed to evaluate dynamic changes in luteinizing hormone (LH), follicle-stimulating hormone (FSH), inhibin B, anti-Müllerian hormone (AMH), estrone (E1), estradiol (E2), and sex hormone-binding globulin (SHBG) in infant girls during first year of life and to establish sex- and age-related reference ranges for these hormones.

Method: The COPENHAGEN Minipuberty Study (ClinicalTrials.gov #NCT02784184) is a prospective, longitudinal cohort study of 233 healthy infants (98 girls) born AGA to healthy

mothers between 2016 and 2019. Each child was examined 6 times including repeated blood sampling during the first years of life. Random-coefficient spline models were fitted to each hormone using maximum-likelihood estimation procedures for linear mixed models, which allowed for prediction of the individual hormone level trajectories as well as estimation of population-level local peak times of hormones. Generalized Additive Model for Location, Scale and Shape was used to establish reference ranges.

Results: In total, data from 98 infant girls with 266 available serum samples were included in this study. A biphasic hormone pattern with two peaks was observed in raw data as well as normalized mean curves for all hormones. The first peak for all hormones was timed around postnatal days 16–27, while the second peaks occurred day 107–125 for inhibin B, AMH, E1, E2, and SHBG. For LH and FSH, the second peaks occurred slightly later (day 165 and 171, respectively). For all hormones, nadir between peaks was observed between postnatal days 58 to 78. In addition, reference curves were established for LH, FSH, inhibin B, AMH, E1, E2, and SHBG. The average within-child variation was up to ± 1.2 standard deviation scores for all hormones, except for E1 (± 1.4).

Conclusion: In this study of minipuberty in healthy, infant girls with repeated blood sampling during the first year of life, we found a hitherto undescribed biphasic secretory pattern of reproductive hormones, which appeared more prolonged than previously anticipated. Thus, the window of opportunity for endocrine diagnostics in female infants may be wider than previously assumed.

serum 17-hydroxyprogesterone (17OHP), androstenedione (A4) and testosterone (T) and their metabolites in urine. Several studies have also described 11-oxygenated 19-carbon (11oxC19) steroids as a clinically relevant androgenetic source and highlighted their potential as markers for evaluation of adrenal androgen excess in patients with 21-hydroxylase deficiency (21OHD).

Methods: Cross-sectional single center study including 34 patients with classic 21OHD (men=14; women=20) and 32 BMI- and age-matched controls (men=15; women=17). Saliva was collected at five different timepoints throughout the day adjusted to intake of glucocorticoid medication. Salivary concentrations of the following steroids were analyzed by LC-MS/MS: 17OHP, A4, T, 11 β -hydroxyandrostenedione (11OHA4) and 11-ketotestosterone (11KT).

Results: Similar to the previously described rhythmicity of 17OHP, 11OHA4 and 11KT concentrations followed a distinct diurnal rhythm in both patients and controls with highest concentrations in the early morning and declining throughout the day (**11-OHA4:** male patients $\Delta_{\text{mean}} = 79\%$; male controls $\Delta_{\text{mean}} = 81\%$; female patients $\Delta_{\text{mean}} = 33\%$; female controls $\Delta_{\text{mean}} = 91\%$; **11KT:** male patients $\Delta_{\text{mean}} = 64\%$; male controls $\Delta_{\text{mean}} = 60\%$; female patients $\Delta_{\text{mean}} = 49\%$; female controls $\Delta_{\text{mean}} = 81\%$). Significant correlations between the area under the curve (AUC) for 17OHP and 11KT ($r(p)_{\text{male}} = 0.741^{**}$; $r(p)_{\text{female}} = 0.842^{****}$), and 11OHA4 ($r(p)_{\text{male}} = 0.385^{\text{n.s.}}$; $r(p)_{\text{female}} = 0.527^*$) were observed in patients but not in controls. P-value ≤ 0.05 (*), ≤ 0.01 (**), ≤ 0.001 (***), ≤ 0.0001 (****).

Conclusions: This study is the first to describe the diurnal rhythm of 11oxC19 steroids in salivary profiles in both healthy controls as well as patients with CAH due to 21OHD. Adrenal 11oxC19 androgens are clearly secreted following a diurnal pattern. This should be considered when evaluating their utility for monitoring treatment control.

Free Communications

Adrenal

FC1.1

Salivary profiles of 11-oxygenated androgens follow a diurnal rhythm in patients with congenital adrenal hyperplasia

Hanna F. Nowotny¹, Matthias K. Auer¹, Christian Lottspeich¹, Heinrich Schmidt², Ilja Dubinski², Martin Bidlingmaier¹, Jo Adaway³, James Hawley³, Brian Keevil³, Nicole Reisch¹

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Background: Routine biochemical assessment in patients with congenital adrenal hyperplasia (CAH) includes measurement of

FC1.2

Variation of glucocorticoid dose and biomarkers in children with congenital adrenal hyperplasia – longitudinal analysis of real world data from the I-CAH registry

Neil Lawrence^{1,2}, Irina Bacila¹, Jeremy Dawson³, Jillian Bryce⁴, Erica LT van den Akker⁵, Tânia Aparecida Sartori Sanchez Bachega⁶, Federico Baronio⁷, Niels Holtum Birkebæk⁸, Walter Bonfig^{9,10}, Hedi Claahsen¹¹, Eduardo Correa Costa¹², Liat Devries¹³, Heba Elsedfy¹⁴, Ayla Guvan¹⁵, Sabine Hannema¹⁶, Violeta Iotova¹⁷, Hetty J van der Kamp¹⁸, Maria Clemente Leon¹⁹, Corina Raducanu Lichiardopol²⁰, Tatjana Milenkovic²¹, Uta Neumann²², Anna Nordenström^{23,24}, Sukran Poyrazoglu²⁵, Ursina Probst-Scheidegger²⁶, Luisa De Sanctis²⁷, Ajay Thankamony^{28,29}, Ana Vieites³⁰, Zehra Yavas³¹, Faisal Ahmed⁴, Nils Krone^{1,2}

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Aim: Recommendations for replacement glucocorticoids in CAH suggest a dose per body surface area (BSA) of glucocorticoids of 10-15mg/m²/day to maintain a 17-OH Progesterone (17OHP) level of 12-36 nmol/l across all ages. We used longitudinal analysis to assess whether biomarkers and dose of hydrocortisone varied with age in children within the I-CAH registry.

Method: This retrospective multi-centre study, including 21 centres (14 countries), analysed data from the International-CAH Registry. We analysed repeated measures using linear mixed-effects modelling (LMEM) (*lme4*, *Rstudio*) to obtain insight into the within patients and between centres variability of dose and biomarkers.

Results: A total of 308 patients (50% female) from 21 centres on hydrocortisone replacement with 2707 visits between 2000-2020 were available for modelling, with 1813 visits with biomarker data available. Median age at visit was 3.2 years (Interquartile Range (IQR) 1.7, 6.1), maximum age at visit was 18.7 years, and median number of visits available per patient was 7 (IQR 5,10.5). Androstenedione increased with age in a univariate LMEM (0.86+0.56*age, $p<0.001$) whereas 17OHP did not correlate with age within patients ($p>0.05$). Weight z-scores increased with age within patients (fixed effects: $-2.1+0.35*age$). A random intercept multivariate LMEM showed that weight z-score had a significant impact upon dose, increasing weight correlating with a decrease in dose (mg/m²/day) ($12.4-1.02*weight+0.085*age$, $p<0.001$). This equates to a child having a dose decrease of 1.02mg/m²/day with each 1 point increase in their weight z-score. Random effects of this model showed that the patient's treating centre had a larger effect on dose than the individual patient effect (Centre Intraclass Correlation Coefficient=0.68).

Conclusions: Repeated measures analysis of real world data shows relative dose of glucocorticoid replacement per body surface area decreases as they experience an increase in weight z-score. The main contributor to dose variability is a difference in practice between centres, with notable interindividual variability in dose between patients within centres, an average increase in Androstenedione with age, but no change in 17OHP with age. Further use of appropriate multivariate and longitudinal analysis, accounting for puberty, will improve our understanding of how the dosing of glucocorticoids should be informed by patient biomarkers and biomarkers, and help standardise the management of CAH across centres.

FC1.3

Re-appraising the use of urinary steroid profiles for assessing therapy control in children with 21-hydroxylase deficiency – results from the CAH-UK cohort study

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Introduction: Patients with congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21OHD) have specific plasma and urinary steroid patterns, with 11-oxygenated C19 steroids established as key adrenal-specific androgens. Monitoring glucocorticoid (GC) replacement remains a challenge in the absence of reliable biomarkers.

Aim: To reassess the urinary steroid profile of children with CAH in relation to plasma steroids.

Methods: We analysed 24-hour urinary steroid profiles in relation to morning plasma steroid panels and clinical data from 91 patients with 21OHD on hydrocortisone therapy (ages 8–18 years, 53% females), from 14 UK centres. Urinary steroid concentrations (GC-MS) were adjusted for body area and log₁₀-transformed. We analysed urinary metabolites individually and grouped together as cortisol sum, 17-hydroxyprogesterone (17OHP) sum and androgen sum. The 11 β -hydroxysteroid dehydrogenase (HSD11B) activity was calculated using the formula (5 α -tetrahydrocortisol + tetrahydrocortisol)/ tetrahydrocortisone.

Results: Cortisol sum adjusted for HSD11B activity increased with GC dose (multivariate linear regression, $R^2=0.288$, $p<0.001$); this relationship did not change with age or sex. Male patients had higher cortisol metabolites than females ($p=0.02$), likely due to

higher hydrocortisone doses ($p=0.03$). 17OHP sum and androgen sum correlated well with plasma 17OHP, androstenedione, testosterone, 11-hydroxyandrostenedione and 11-ketotestosterone. The strongest correlation for plasma 17OHP was with the 21-deoxycortisol metabolite, pregnanetriolone ($r_s=0.767$, $p<0.001$), while 11-hydroxyandrostenedione and 11-ketotestosterone correlated best with urinary 11-hydroxyandrostosterone ($r_s=0.829$, $p<0.001$ and $r_s=0.736$, $p<0.001$). Pregnanetriolone, 11-hydroxyandrostosterone, 17OHP and androgen sums varied significantly (Kruskal-Wallis, $p<0.001$) among patient subgroups of control based on plasma 17OHP (normal range 12–36 mmol/l), but not in relation to GC doses. For urinary pregnanetriolone, setting a range of lg 0 – 2 $\mu\text{g}/\text{m}^2/\text{day}$ identified 81% cases with suppressed and 65% cases with high plasma 17OHP. Linear regressions indicated that urinary pregnanetriolone correlates with plasma 17OHP (Intercept=0.63, $R^2=0.271$, $p<0.001$), while androstosterone correlates with plasma androstenedione (Intercept=2.1, $R^2=0.358$, $p<0.001$). Urinary aetiocholanolone correlated with plasma testosterone, more significantly in females (Intercept=1.8, $R^2=0.336$, $p<0.001$) compared to males (Intercept=1.8, $R^2=0.145$, $p=0.024$). Plasma 11-hydroxyandrostenedione and 11-ketotestosterone correlated with urinary 11-hydroxyandrostosterone (Intercept=2.4, $R^2=0.466$, $p<0.001$) and 11-oxo-aetiocholanolone (Intercept=2.0, $R^2=0.187$, $p<0.001$), respectively.

Conclusions: Urinary cortisol metabolites correlate with the GC dose, having the potential to be used for monitoring compliance to treatment and GC toxicity. 17OHP and androgen metabolites closely correlate with plasma biomarkers of disease control, including the adrenal-specific 11-oxygenated C19 androgens. Our findings support the use of urinary steroid profiles as a non-invasive monitoring test in managing challenging cases of CAH.

FC1.4

Acute Illness and Death in Children with Adrenal Insufficiency

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Background: Adrenal Insufficiency (AI) is a heterogeneous diagnosis comprising multiple central and peripheral causes. The unifying feature is the requirement for glucocorticoid replacement and subsequent risk of life-threatening Adrenal Crisis (AC) and Adrenal Death (AD). Very few studies have investigated rates of AD in children. Multiple studies have reported symptoms of children with AC as interpreted by medical staff but no studies have looked at parentally reported symptoms prior to hospital admission. We investigated preceding symptoms and parental management of AC and incidence of AD and associated factors.

Methods: Data from children and young people with AC and AD over a 13-year period, were reviewed. Medical notes and coroner's reports were reviewed for those with AD. Separately, data

were collected through interview-aided questionnaires from children with AI who had AC in the previous eight years. A final study investigated parent perceptions of parenteral hydrocortisone.

Results: Thirteen patients died (median age 10 years) over a thirteen-year period resulting in an estimated incidence of one AD per 300 patient years and one AD per year in our patient cohort. Those with unspecified adrenal insufficiency were overrepresented ($P = 0.004$).

Thirty-eight patients were identified with hospital attendance with AC. Responses from twenty patients (median age 7.5 years) with AC reported nausea/vomiting (75%) and drowsiness (70%) as common symptoms preceding AC. All patients received an increase in oral hydrocortisone prior to admission but only two received intramuscular hydrocortisone from parents.

Questionnaires revealed that 79% of parents reported confidence in the administration of intramuscular hydrocortisone and only 20% identified a missed opportunity for injection.

Conclusions: The rate of AD in our cohort was higher than published figures for children with T1DM, a figure already significantly elevated from the population mean. This highlights the importance of medical professionals understanding the severity of this disease.

In children experiencing AC, parents followed 'sick day' guidance for oral hydrocortisone in all cases. However, these same patients rarely administered intramuscular hydrocortisone. This is a contrasting finding from the 79% of parents who reported confidence in this exact task, highlighting a significant discrepancy between perceived confidence with a task and performance of that at the time of greatest clinical need. Local training programmes for management of AC are comprehensive, but apparently insufficient to prevent the most serious crises and deaths. New strategies to encourage use of parenteral hydrocortisone must be devised.

FC1.5

Outcome of COVID-19 infections in patients with adrenal insufficiency

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Background: Clinical outcome data of patients with adrenal insufficiency, who were affected by COVID-19, have been collected as a common initiative by the ESE Rare Disease Committee and ENDO-ERN via the European Registries for Rare Endocrine Conditions (EuRRECa) project.

Methods: This Webropol-based questionnaire included a total of 32 questions collecting quantitative and qualitative data. Of the 19 medical centres out of ten European countries that signed up to report on e-REC, 15 reported a total of 50 cases using the online registry and 11 centres completed the questionnaire. In total, 34 cases of adrenal insufficiency (AI) were reported.

Results: Of the 34 cases of AI reported, 28 cases (82 %) were affected by primary adrenal insufficiency (46 % Addison's disease (n = 13), 39 % congenital adrenal hyperplasia (n = 11)). Affected AI patients had a mean age of 41 (SD 21) years at the timepoint of diagnosis and were male in 44% (15 male, 19 female). Of those 13 patients with Addison's disease, 85 % suffered from additional autoimmune endocrine disorders. Most relevant comorbidities were hypertension (n = 6, 18 %), obesity (n = 6, 18 %) and diabetes mellitus (n = 3, 9 %). Most frequent symptoms of COVID-19 infected patients included fever (n = 20, 59 %), cough (n = 20, 59 %), tiredness or exhaustion (n = 20, 56 %), muscle pain (n = 18, 53 %), headaches (n = 14, 42 %) and loss of taste and smell (n = 11, 32 %). Two thirds of patients increased their daily glucocorticoid dose from a mean of 24 mg/d (SD 14 mg/d) to a mean of 44 mg/d (SD 25 mg/d). Only one of the surveyed patients administered i.m. injection of 100 mg hydrocortisone at home. Three patients (9 %) had to be admitted to hospital due to adrenal crisis and two patients (6 %) due to the severity of infection with a mean hospitalization time of 12.2 days. One of the patients had to be transferred to the intensive care unit. One patient reported persistent disease, all other patients reported complete remission.

Conclusion: This European multicentric questionnaire is the first to collect data on the outcome of COVID-19 infection in patients with adrenal insufficiency with or without any concomitant disease. Although numbers of collected cases are relatively low, it suggests good clinical outcome in case of duly dose adjustments and emphasizes the importance of patient education on sick day rules.

FC1.6

Tumor DNA methylation profiling as a prognostic marker for pediatric patients with adrenocortical tumors

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Abnormal DNA methylation contributes to tumor progression and is emerging as a prognostic marker in several types of cancers. To investigate whether DNA methylation is associated with pediatric adrenocortical tumor (pACT) presentation and patient prognosis, we analyzed the methylation profile of 57 tumors (MethylationEPIC BeadChip Array-Illumina) and patients' clinicopathological features and outcome. The study comprehended 40 girls and 17 boys, with median age at diagnosis of 2.1 years (0.2-16.6). Reduced overall survival was observed in patients older than 4 years of age (n=43, p<0.0001, 5-year survival [5ys]=43%), in

those presenting with Cushing's syndrome (n=7, p<0.0001, 5ys=28%), advanced/non localized disease (IPACTR stages III and IV; n=11, p<0.0001, 5ys=33%) or carcinomas (n=10, p=0.04, 5ys=56%). Unsupervised analysis of methylation data (M-values; Euclidean distance and Ward's D method; *Pvclust*, R, version 4.0.3) included all 766,031 probes filtered in after quality control, and revealed two groups with distinct methylation signatures with a bootstrap support of 99%, namely pACT-1 and pACT-2. The overall variance of differentially methylated probes (DMPs; Wilcoxon rank-sum test FDR p-values <10⁻⁶ and, simultaneously, median M-value difference >2) between the groups was 0.084% (n=642 probes). Further ranking of DMPs excluded those with sample individual M-value invasion (*I*>0, n=561; 0.074%) between groups, and identified the DMPs that most distinguished them (*I*=0, n=81; 0.01%). pACT-1 presented 51 hypomethylated and 30 hypermethylated DMPs, being enriched for hypomethylation in genes' body region and for hypermethylation in promoter regions (p=0.0006). pACT-1 was significantly hypermethylated in CpG islands (p=0.007) and hypomethylated in non-CpG islands (p=0.0008) than pACT-2. DMPs analysis yielded 23 hypomethylated and 15 hypermethylated genes in pACT-1. Patients in pACT-1 were older at diagnosis (p=0.0004) and were more likely to be diagnosed after 4 years of age (80 vs 13%; p<0.0001), to present with Cushing syndrome (40 vs. 4%; p=0.01), non-localized/advanced disease (70 vs 8%; p=0.0001) or carcinomas (71 vs 17%; p=0.009), to require adjuvant chemotherapy (90 vs. 9%; p<0.0001), and to experience post-surgery recurrence/metastasis (90 vs 6%; p<0.0001). Hence, patients in pACT-1 had reduced disease-free (p<0.0001, 5ys: 11 vs 91%) and overall survival from the disease (p=0.0001, 5ys: 20 vs 98%) than those in pACT-2, even after stratifying for the aforementioned prognostic features. Tumor methylation profiles were not associated with P53 p.R337H (p=0.57) or *CTNNB1* (p=0.6) activating mutations. Our data supports tumor methylation profile as a robust and independent prognostic biomarker for pACT and suggests a feasible list of candidate genes for further validation.

Fat Metabolism and Obesity

FC2.1

Efficacy and Safety Results of a Phase 2 Trial of Setmelanotide in Obesity Due to *SH2B1* Variants and 16p11.2 Deletion Syndrome

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Background: Variants in *SH2B1* or a 220-kilobase pair distal deletion of chromosome 16p11.2, including *SH2B1*, are associated with severe, early-onset obesity and hyperphagia. The melanocortin-4 receptor (MC4R) agonist setmelanotide is being investigated in individuals with rare variants in genes in the MC4R pathway.

Methods: This ongoing, Phase 2 study (NCT03013543) enrolled individuals aged ≥ 6 years with obesity due to *SH2B1* variants or distal deletion of chromosome 16p11.2. Obesity was defined as body mass index (BMI) ≥ 30 kg/m² in those aged ≥ 16 years or BMI ≥ 95 th percentile in those aged 6–15 years. Following dose titration of setmelanotide, patients received open-label treatment for 3 months. The proportion of patients who were responders (defined as $\geq 5\%$ weight loss in those ≥ 18 years old or ≥ 0.15 reduction in BMI Z score in those < 18 years old), mean percent changes in body weight and changes in BMI Z score by age, and adverse events (AEs) were assessed at month 3.

Results: Thirty-five patients, 22 with *SH2B1* variants and 13 with 16p11.2 deletion, were enrolled. At baseline, for the 22 patients ≥ 18 years old, mean (standard deviation [SD]) body weight was 139.7 (35.4) kg, and for the 13 patients < 18 years old, mean (SD) BMI Z score was 3.6 (0.6). Fifteen patients (42.9%) experienced $\geq 5\%$ weight loss (≥ 18 years old; n=8) or ≥ 0.15 reduction in BMI Z score (< 18 years old; n=7) at month 3. For patients ≥ 18 years old, mean (SD) percent weight change from baseline was -7.2% (2.1%; n=8 [*SH2B1* variants, n=5; 16p11.2 deletion, n=3]) for responders, -0.8% (2.3%; n=14) for nonresponders, and -3.1% (3.9%) overall. For patients < 18 years old, mean (SD) change in BMI Z score was -0.25 (0.06; n=7 [*SH2B1* variants, n=5; 16p11.2 deletion, n=2]) for responders, -0.03 (0.06; n=6) for nonresponders, and -0.15 (0.13) overall. One serious AE of melanocytic nevus occurred in an adult patient, for which melanoma was excluded, which was considered not treatment related. Common

AEs included skin hyperpigmentation (71.4%), nausea (48.6%), and headache (37.1%). AEs led 9 patients (25.7%) to discontinue the study.

Conclusions: Patients with *SH2B1* variants or 16p11.2 deletion syndrome had early-onset severe obesity. In 3 months, 43% achieved $\geq 5\%$ weight loss or ≥ 0.15 reduction in BMI Z score, with similar response rates in those with *SH2B1* variants (46%) and 16p11.2 deletion (38%). A 3-month trial may be useful to identify those with setmelanotide-responsive variants involving *SH2B1* affecting the MC4R pathway.

FC2.2

Phase 3 Trial of Setmelanotide in Participants With Bardet-Biedl Syndrome: Placebo-Controlled Results

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Background: In a Phase 3 trial in participants with obesity due to Bardet-Biedl syndrome (BBS) and Alström syndrome, setmelanotide was associated with significant reduction from baseline in body weight and hunger at Week 52 (primary endpoint), with outcomes driven by responses in individuals with BBS.

Methods: In the same trial (NCT03746522), individuals with BBS or Alström syndrome were randomized and received setmelanotide or placebo for 14 weeks. Obesity was defined as weight > 97 th percentile in those aged 6–15 years and body mass index ≥ 30 kg/m² in those aged ≥ 16 years. Body weight, hunger, and adverse events (AEs) were assessed. Because all primary endpoint responders were participants with BBS, preliminary data are reported for those participants.

Results: 32 participants with BBS were enrolled, 29 with age ≥ 12 years. Relative to placebo (negligible weight loss of -0.2 kg), there were significant reductions in body weight (Table 1) and hunger (Table 2) with setmelanotide. There was 1 serious treatment-related AE of anaphylactic reaction that occurred in a participant during placebo treatment. In all participants, including

those with Alström syndrome, the most common AE was injection site erythema (setmelanotide, 42.1%; placebo, 36.8%). AEs were generally similar between treatment groups; however, 11 participants (57.9%) receiving setmelanotide experienced skin hyperpigmentation compared with 0 participants receiving placebo.

Conclusions: Participants with BBS who received setmelanotide experienced significantly greater weight loss and hunger reduction versus those who received placebo. Of note, participants with BBS who received placebo had negligible weight loss. Setmelanotide may be a promising treatment for obesity in individuals with BBS.

Table 1. Change in Body Weight From Baseline at Week 14 in Participants With BBS

	Treatment group		
	Setmelanotide, mean (SD) (n=14)	Placebo, mean (SD) (n=15)	Mean difference (95% CI)
Change, kg	−4.0 (5.3)	−0.2 (2.9)	−3.8 (−7.0, −0.6) P=0.0113
Percent change	−3.2% (4.5)	−0.2% (2.4)	−3.0% (−5.6, −0.3) P=0.0164

BBS, Bardet-Biedl syndrome; CI, confidence interval; SD, standard deviation.

Table 2. Change in “Most” Hunger Score From Baseline at Week 14 Experienced by Participants With BBS^{a,b}

	Treatment group		
	Setmelanotide, mean (SD) (n=5)	Placebo, mean (SD) (n=9)	Mean difference (95% CI)
Change	−2.4 (1.2)	−1.0 (1.2)	−1.4 (−2.8, 0.1) P=0.0311
Percent change	−34.8% (18.5)	−14.5% (15.8)	−20.4% (−40.7, 0) P=0.0249

BBS, Bardet-Biedl syndrome; CI, confidence interval; SD, standard deviation. ^aAged ≥12 years and without cognitive impairment. ^bWeekly average of hunger scores.

FC2.3

A Phase 2 Trial of the Melanocortin-4 Receptor Agonist Setmelanotide in Obesity Due to SRC1 Insufficiency: Body Weight, Body Mass Index Z Score, and Safety Results

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Background: Rare genetic diseases of obesity can be caused by genetic variants leading to disrupted activity of the melanocortin-4 receptor pathway (MC4R). Setmelanotide, an MC4R agonist, is being investigated in a basket study of populations with rare variants in different genes in the MC4R pathway who have early-onset, severe obesity and hyperphagia.

Methods: This ongoing, Phase 2, open-label study (NCT03013543) enrolled patients aged ≥6 years with obesity due to steroid receptor coactivator 1 (SRC1) insufficiency. Obesity was defined as body mass index (BMI) ≥30 kg/m² or BMI ≥95th percentile in those aged ≥16 years or 6–15 years, respectively. Patients received open-label setmelanotide treatment until Month 3, following dose titration. Adverse events (AEs) and mean percent change in body weight (in those ≥18 years old) or mean change in BMI Z score (in those <18 years old) were assessed at Month 3, as was the proportion of responders (defined as ≥5% weight loss in those ≥18 years old or ≥0.15 reduction in BMI Z score in those <18 years old).

Results: A total of 30 patients with SRC1 insufficiency were enrolled in the trial. At baseline, the mean patient age was 30.6 (range, 9.0–66.0) years, with 20 patients aged ≥18 years; for patients ≥18 years old, mean (standard deviation [SD]) body weight was 139.7 (25.1) kg and for patients <18 years old, BMI Z score was 3.0 (0.6); 24 patients (80.0%) were female and none were cognitively impaired. Nine patients (30.0%) experienced ≥5% weight loss (≥18 years old; n=6) or ≥0.15 reduction in BMI Z score (<18 years old; n=3) at Month 3 and were considered responders. For patients ≥18 years old, mean (SD) percent weight change was −7.9% (2.2%; n=6) for responders, −2.3% (1.9%; n=14) for nonresponders, and −3.9% (3.3%; n=20) overall. For patients <18 years old, mean (SD) change in BMI Z score was −0.48 (0.28; n=3) for responders, −0.09 (0.03; n=7) for nonresponders, and −0.21 (0.23; n=10) overall. No serious AEs occurred. Common AEs included skin hyperpigmentation (66.7%), nausea (36.7%), and injection site bruising (30.0%). One patient (3.3%) withdrew from setmelanotide because of an AE.

Conclusions: Patients with SRC1 insufficiency had severe obesity despite a relatively young age; 30% achieved a clinically meaningful response to setmelanotide in 3 months. A 12-week trial may be useful to identify setmelanotide-responsive variants in the MC4R pathway.

FC2.4

PTEN germline mutations lead to adipose tissue overgrowth mediated via FOXO1 and SREBP1

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Background and Aim: Pediatric patients with germline mutations in the tumor suppressor gene *PTEN* (PTEN hamartoma tumor syndrome, PHTS) frequently develop lipomas. PTEN antagonizes phosphoinositide 3-kinase (PI3K) signaling, which can induce adipogenesis upon activation through insulin. The PI3K downstream target AKT can deactivate FOXO1 via phosphorylation, initiating the expression of the lipogenesis activating transcription factor SREBP1. To study the underlying mechanisms of lipoma formation in patients with PHTS, we asked whether there is a link between reduced PTEN in adipose progenitor cells (APCs) and aberrant growth of adipose tissue.

Methods: We downregulated PTEN via siRNA (KD) or CRISPR (CR) in APCs and compared proliferation, in vitro differentiation and gene expression (RNA sequencing, RT-qPCR, Western blots) in control and knockdown cells. To investigate whether the effects observed in cells with PTEN downregulation could be reversed, we overexpressed constitutively active FOXO1 in PTEN CR cells.

Results: PTEN downregulation led to an increase in proliferation (1.4 ± 0.2 fold in KD, 1.5 ± 0.1 fold in CR $p < 0.05$) and differentiation (1.77 ± 0.07 fold in KD, 5.6 ± 1.9 fold in CR, $p < 0.01$) of APCs. Protein levels of the senescence associated protein p21 were reduced (0.33 ± 0.07 fold, $p < 0.001$) in PTEN KD APCs explaining the accelerated growth. RNA sequencing and qPCRs revealed a downregulation of *FOXO1* (0.75 ± 0.03 fold, $p = 0.018$) on mRNA level while inactivation through phosphorylation increased (6.6 ± 3.5 fold, $p = 0.046$). SREBP1 protein levels (1.5 ± 0.1 fold, $p = 0.047$) were higher after PTEN KD and may account for the enhanced adipogenesis. To validate this we overexpressed constitutively active FOXO1 in PTEN CR cells and observed that adipogenesis was attenuated (0.73 ± 0.07 fold, $p = 0.065$) while SREBP1 protein levels were reduced (0.49 ± 0.14 fold, $p = 0.024$).

Conclusion: We found enhanced proliferation through cell cycle activation in APCs with PTEN downregulation. Additionally, adipogenesis increased mediated through inhibition of FOXO1 signaling. These effects may account for the adipose tissue overgrowth observed in patients with *PTEN* mutations.

FC2.5

Reference values for longitudinal body composition in children aged 0-5 years, using Dual-energy X-ray (DXA) absorptiometry

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Background and Objectives: Childhood obesity is a global public health threat, with an alarming rise in incidence. Obesity at young age has short-term consequences, as well as long-term morbidity. It is, therefore, important to determine body composition longitudinal throughout infancy and childhood to prevent excess adiposity. Multiple methods are used to determine body composition in infants and young children, but none are described as suitable for longitudinal use in infancy and throughout childhood. Our research group has published sex-specific reference values for measurements with ADP and DXA with vacuum cushion to prevent movement artifacts, for infants aged 1 month – 2 years, but not yet for older ages. Our primary objective was to construct sex-specific body composition reference values for children aged 2-5 years using DXA, which could be longitudinally used in clinical practice and research.

Methods: In the Sophia Pluto cohort, longitudinal DXA-measurements were performed in 340 term-born children aged 2 – 5 years, using Lunar Prodigy with Encore software (V14.1). Using LMS-method, sex-specific reference values were created for fat mass (FM), fat mass percentage (FM%) and fat free mass (FFM). Bland-Altman analysis was used to determine if DXA measurements with vacuum cushion, performed in 0-2 year old infants in our cohort, were comparable with DXA measurements without vacuum cushion after age 2 years. A random sample of 2 year old children was measured in duplicate.

Results: Sex-specific body composition values for age 2-5 years were constructed. In boys and girls, FM and FFM increased from 2-5 years and FM% decreased. Girls had higher FM and FM% and lower FFM compared to boys.

Absolute measurements FM, FM% and FFM were different between DXA with and without vacuum cushion, with mean difference [limits-of-agreement(LOA)] of 1.86 kg [1.39;2.33], 13.75% [9.56;17.94] and -1.54kg[-1.99;-1.09], resp., there was a fixed bias, no proportional bias. At age 2 years, the SD-scores based on the existing reference values for 1 month-2 years (with cushion) and for present references for 2-5 years (without cushion) were comparable.

Conclusions: We constructed sex-specific reference values for fat mass, fat mass percentage and fat free mass measured by DXA for children aged 2-5 years. These reference values can be used longitudinally in children aged 1 month to 5 years, because the SD-scores were comparable with existing reference values for children aged 0-2 years.

FC2.6

Association between MRI Evidence of Hypothalamic Gliosis and Pubertal Development in Girls with Obesity

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Early puberty is associated with obesity in young girls and has physical, psychosocial, and reproductive implications. In adults and children, MRI evidence of cellular inflammation in the medio-basal hypothalamus (MBH gliosis) is seen in obesity, and its anatomic location overlaps with key neuronal populations controlling reproduction, fertility, and feeding. We sought to assess whether MRI evidence of MBH gliosis associates with pubertal development in girls and if that differs based on weight status.

This retrospective cohort study included a subsample of 156 female participants from the NIH Adolescent Brain Cognitive Development (ABCD) study, a longitudinal, observational study. Self-reported pubertal developmental scale (PDS) at baseline and at 1y was used to classify subjects into one of 4 groups of change in puberty:

Group Change in puberty	Puberty stages by PDS (baseline to 1y follow-up)
1	Pre to early puberty
2	Early to mid-puberty
3	Mid-puberty
4	Mid to post or late puberty

Using a validated technique, baseline T2-weighted MRI scans were analyzed for evidence of MBH gliosis based on a signal ratio comparing the T2 signal intensity of the mean bilateral MBH to the Amygdala (MBH/AMY). Putamen (PUT)/AMY and MBH/PUT were used as negative and positive control ratios, respectively. Linear mixed models were adjusted for study site and tested for the interaction between T2 signal ratios, change in puberty stages and weight group.

At baseline, mean age was 10±0.6y, and participants were well distributed across the 3 weight groups [healthy weight (HW) N=51, overweight N=52, and with obesity N=53]. Subjects with obesity had a significant interaction between T2 signal ratios and change in puberty stages ($\chi^2(6,53)=19.4$; $p=0.004$). This association was not seen among girls of HW ($p=0.37$) and overweight ($p=0.25$). Participants with obesity in the earlier stages of puberty presented greater MBH/AMY signal ratio than girls at mid and late stages of puberty (group 1 vs. group 3 and group 4 $p<0.05$). Results were confirmed with the positive control ratio and absent with PUT/AMY signal ratio.

Our data suggests that girls with obesity present greater MRI evidence of MBH gliosis at early vs. later stages of puberty. MBH gliosis may contribute to the link between childhood obesity and disturbances in initial stages of pubertal development. Due to its long-term ramifications for reproductive health, further studies

are needed to understand the neurobiological mechanisms that regulate puberty onset and progression in girls with obesity.

Growth Disorders

FC3.1

iPPSD: focus on neonatal features, preliminary data from a retrospective analysis of a large cohort of patients

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Since the first description of pseudohypoparathyroidism (PHP), a remarkable clinical variability, which translates in several PHP subtypes, was observed. In 2016 a new classification of this group of diseases have been published by the European Network on PHP and related disorders, proposing "inactivating PTH/PTHrP signaling disorder" (iPPSD) as a new term that encompasses all the clinical entities, stressing the common mechanism responsible for all diseases. iPPSDs vary in clinical presentation and disease severity, and the clinical features usually develop during mid and late childhood. There are only few reports in literature about neonatal and early infancy iPPSDs, describing patients who presented with hypocalcemic seizures in late neonatal or early infantile period. To our knowledge no others neonatal complications are described as associated to iPPSDs. The aim of this study is to describe a large cohort of iPPSDs patients, with special focus on neonatal complications. We collected data from 136 patients diagnosed with iPPSDs and in regular follow-up at the Endocrinology Unit of Ospedale Maggiore Policlinico (Milan, Italy) and at the Pediatric Endocrinology Unit of Hôpital Bicêtre (Paris, France). We have retrospectively collected data about birth and we have investigated the rate and the severity of neonatal complications occurring in each iPPSD category. We conducted univariate and multivariate analysis to assess potential predictors of neonatal complications and correlation between neonatal complications and severity of the disease. We analysed data from 83 children and 53 adults with diagnosis of iPPSDs (81 female, mean age 18 ± 11, range 0.9 - 60.7 years). At least one neonatal complication occurred in 36% of patients. iPPSD2 patients represent the majority of our cohort (55.9%) and 47% of them experienced neonatal

complications at birth, being the category more affected ($p=0.001$). Neonatal complications in iPPSDs patients correlate with the risk of developing neurocognitive impairment ($p=0.02$), constipation ($p=0.04$) and ectopic ossification ($p=0.008$) later in life. Importantly, we found no genotype/phenotype relationships in iPPSD2 patients. To now, we can conclude that iPPSDs, and especially iPPSD2, newborns need special care at birth, for the risk of developing neonatal complications. Moreover, it is worth signalling that among our total cohort of patients 79.4% developed neonatal complications or any signs of iPPSD within the first year of life. Mean age at diagnosis of our patients was 8.7 ± 7.3 (range 0.1–34) years, it becomes clear that exists a huge delay in diagnosis and maybe diagnostic criteria should be adapted for early infancy iPPSDs patients.

FC3.2

Identification of a FBN1 variant in a pedigree affected with Severe Short Stature with a Mild Form of Geleophysic Dysplasia Type 2

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Objective: To explore the genetic basis for a Chinese three-generations pedigree affected with Severe Short Stature with a mild form of Geleophysic Dysplasia Type 2 (GD2)

Methods: We collected 11 related family members from a Chinese 3-generation pedigree with severe short stature with a mild form of Geleophysic Dysplasia Type 2 GD2. Clinical data of the 11 family members was collected. With genomic DNA extracted from the peripheral blood samples of 5 of the seven patients, potential mutation was detected by targeted exome sequencing. Candidate variants were validated by Sanger sequencing and bioinformatic analysis.

Results: Seven patients showed severe and disproportionate short stature with normal birth weight and birth length. They had shown progressive postnatal growth failure with normal developmental milestones and normal cognition and no distinct facial features. The patient II1 male adult height 139 cm ($-5.52SD$) with a markedly elevated sitting height/leg length (SH/LL) $1.438(+4.3SD)$. He once experienced balloon dilatation due to pulmonary stenosis. A skeletal survey was normal. Targeted exome sequencing and Sanger sequencing revealed a missense c.5099A>G (P.Tyr1700Cys) variant in the exon 42 of FBN1 gene in 5 of the seven patients, which was reported in patients with Acromicric Dysplasia (AD). Bioinformatics analysis suggested that the variant can cause amino acid replacement and affect the structure and function of fibrillin-1.

Conclusion: A missense variant of the FBN1 gene was identified, which probably underlies the autosomal dominant severe and disproportionate short stature with a mild form of Geleophysic Dysplasia Type 2 (GD2) in this pedigree.

FC3.3

Genetic characterization of a cohort of children with short stature

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Background: Short stature is defined as a height more than two standard deviations below the mean for age and sex. Pathologic causes of short stature include growth hormone deficiency, hypothyroidism, celiac disease, inflammatory bowel disease or other chronic diseases, hormonal abnormalities, and genetic disorders, such as Turner syndrome. Moreover, among other variants of short stature, scholarship also described familial short stature, constitutional delay of growth and puberty, and idiopathic short stature (ISS). ISS comprises a wide range of conditions associated with short stature that elude the conventional diagnostic work-up and are often caused by still largely unknown genetic variants. In the last decade, the improvement of diagnostic techniques has led to the discovery of causal mutations in the genes involved in the function of the growth hormone/insulin-like growth factor-I axis as well as in growth plate physiology. However, many cases of ISS remain idiopathic.

Aim: focusing on genetic investigations, our study aims to better understand the etiology of short stature in a cohort of children initially identified as affected by ISS.

Patients and Methods: 120 children with ISS aged between 3 and 18 years were enrolled. All children were submitted to auxological, hormonal and imaging investigations, aimed to exclude the most frequent causes of hyposomia. Successively, genetic screening was performed with the help of the Next Generation Sequencing (NGS) panel. All the coding regions and exon-intron boundaries of 105 genes were included in the panel. To clarify the pathogenicity of these mutations, their clinical data were reviewed and analyzed.

Results: Pathogenic variants were found in 26 patients (21.7%) of our cohort. In 10 children, a syndromic condition was diagnosed. Moreover, in 91 children we found 253 variants of uncertain clinical significance that in some cases might be responsible for their clinical phenotype.

Conclusion: The NGS panel resulted effective for the rapid screening of genetic etiologies associated with short stature and allowed a definitive diagnosis in 21.7% of cases previously identified as ISS. Genetic diagnosis for short stature is important for affected individuals and their families since it may modify the management of their clinical condition and their treatment decisions.

FC3.4

Prospective genetic analysis by a targeted gene panel of a cohort of patients classified as idiopathic short stature (ISS)

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Introduction: The majority of children with short stature are classified as ISS by the absence of findings that could elucidate the cause of their growth impairment. Several monogenic defects have already been identified in children with ISS, but the candidate gene approach is not feasible when there are no specific findings to guide a specific genetic test.

Objective: To evaluate the diagnostic yield of a targeted gene panel in children with ISS.

Methods: We prospectively analyzed 44 children with ISS. We included healthy children with adequate birth weight, height SDS < -2, normal development, and without positive results in clinical, laboratory and radiological evaluation. They were submitted to multigene sequencing analysis containing 90 genes related to growth disorders. We analyzed small variants and copy number variations (CNVs) by standard bioinformatics procedure. Rare variants with potential to be pathogenic were segregated into the family and classified according to the ACMG/AMP criteria.

Results: Forty-four children (24 boys) at the age of 7.2 ± 3.0 y were evaluated. They have a height SDS of -2.4 ± 0.6 ; BMI SDS of -0.3 ± 1.0 and SH/H SDS of 0.6 ± 1.2 . Mild body disproportion was observed in 20.5% (SH:H SDS: 2.3 ± 0.5). Twenty patients (45.5%) had familial short stature. In total, 9 heterozygous pathogenic/likely pathogenic (P/LP) variants were identified in 9 patients. Among them, 5 variants are located in genes related to growth plate: IHH (n=2), ACAN (n=1), FGFR3 (n=1), COL2A1 (n=1), 1 variant is in one gene associated with the GH-IGF1 axis: GHSR (n=1) and 3 variants are in genes related to the RASopathies: CBL (n=1), NF1 (n=1) and PTPN11 (n=1). Additionally, we identified 4 heterozygous pathogenic CNVs: 3 deletions in SHOX and 1 complex rearrangement in ACAN. Most of these P/LP variants were inherited from a short parent (n= 6) whereas 3 were de novo. Six further variants were classified as uncertain significance and are still under investigation. It is noteworthy that 5 patients have more than one genetic variant that could contribute to the patient short stature.

Conclusion: We were able to identify a genetic cause of ISS in 9/44 patients (20.5%). This diagnostic yield is remarkable in a group of children whose the regular evaluation was unable to determine the cause of growth impairment. The multigene sequencing analysis approach to ISS is useful to determine the cause of short stature with an additional perspective of guiding treatment and clinical follow-up.

FC3.5

Clinical profiles and genetic spectra of 814 Chinese children with short stature

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Context: Data and studies based on exome sequencing for the genetic evaluation of short stature are limited, and more large-scale studies are warranted. Some factors increase the likelihood of a monogenic cause of short stature, including severe short stature (<-3 standard deviation scores) and small for gestational age (SGA) without catch-up growth. However, whether these factors can serve as predictors of molecular diagnosis remains unknown.

Objectives: We aimed to define the diagnostic efficiency of associated risk factors and their exome sequences for screening.

Design, Settings, and Patients: We defined and applied factors that increased the likelihood of monogenic causes of short stature in diagnostic genetic tests based on next-generation sequencing (NGS) in 814 patients with short stature and at least one other factor.

Results: The overall diagnostic yield was 44.72%, and 34.64% and 8.85% of the patients harbored pathogenic (P)/likely pathogenic (LP) variants in genes or P/LP copy number variations (CNVs). We found P/LP variants among 114 genes, and RASopathies comprised the most important etiology. The diagnostic yield of NGS for short stature combined with intellectual disability or developmental delay was 70.71%, and 70.97% when patients had facial dysmorphisms. CNVs should be considered for screening SGA with intellectual disability or developmental delay.

Conclusions: NGS combined with risk factor screening significantly improved the diagnostic yield for short stature. Our findings provide novel insights into the current understanding of the etiology of short stature in patients with different phenotypes and indicate the importance of NGS.

FC3.6

Growth patterns in children with Mucopolysaccharidosis type I-Hurler after haematopoietic stem cell transplantation: comparison with untreated patients

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Background: Mucopolysaccharidosis I Hurler (MPS-IH is an inborn error of metabolism arising from the defective activity of alpha-L-iduronidase, an enzyme involved in the degradation of glycosaminoglycans (GAGs). As a result, the pathological lysosomal storage of GAGs in several tissues leads to multi-systemic complications, such as hepatosplenomegaly, progressive central nervous system deterioration, skeletal dysplasia and faltering growth, commonly resulting in overt short stature.

Though hematopoietic stem cell transplantation (HSCT) represents the standard-of-care for MPS-IH patients < 2 years, its impact on growth has been historically regarded as unsatisfactory. Nevertheless, the growth patterns recorded in transplanted patients have always been compared to those of healthy children.

Aims: We aimed at verifying the impact of HSCT on MPS-IH long term growth achievements by comparing the patterns of transplanted children with those of not transplanted ones.

Materials and Methods: Fifteen transplanted patients (4 males, 26.7%) aged 15.6 ± 5.4 years at the time of data collection and diagnosed with MPS-IH at a mean age of 11.4 ± 4.3 months (range: 4.9 – 18.1) were included in the study population. All these patients had been reviewed from a clinical and auxological perspective 3- to 6-monthly after transplantation for the first 5 years and annually thereafter.

The auxological data of all the patients were assessed longitudinally and compared both to the WHO growth centiles for healthy children and to the curves for not transplanted MPS-IH children published in 2020. We retrospectively processed the auxological data measured 6 months before HSCT (t_6), at the time of HSCT (t_0) and subsequently 12-monthly for the first 5 years after transplantation (t_{12} , t_{24} , t_{36} , t_{48} , t_{60}), at the age of 9 years (t_{9yrs}) and at final height.

Results: Despite a progressive decrease after HSCT with reference to the WHO growth charts, median height SDS showed a progressive and statistically significant increase when comparing the stature recorded at each timepoint with the curves of not transplanted MPS-IH (from -0.39 SDS at t_0 to +1.35 SDS 5 years after HSCT, $p < 0.001$). Median height SDS was statistically higher than t_0 from t_{24} onwards, with statistical significance progressively increasing in time. Upon t_{9yrs} , height SDS was +3.67, statistically higher than t_0 $p < 0.0001$.

Conclusions: Though not efficient enough to restore a normal growth pattern in MPS-IH patients, we hereby demonstrate that HSCT positively affects growth and provides transplanted patients with a remarkable height gain compared to untreated gender- and age- matched individuals.

Diabetes

FC4.1

Role of physical activity and sedentary behavior on early markers of cardiovascular disease in Canadian adolescents with and without type 1 diabetes: the CARDEA study

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Background: Type 1 diabetes (T1D) is a risk factor for cardiovascular disease (CVD) and alterations may manifest as early as in adolescence. Increased physical activity and reduced sedentary behavior reduce the risk of CVD development in general adult populations, but knowledge is limited on their associations with early markers of CVD risk in pediatric T1D.

Objective: Estimate associations of physical activity and sedentary behavior with early markers of CVD in adolescents and test whether associations differ based on T1D status.

Methods: Cross-sectional study of 100 adolescents (14-18 yrs) with T1D recruited at the Sainte-Justine Hospital Diabetes Clinic (Montréal, Canada) and 97 age- and sex-matched controls. Arterial stiffness was measured by pulse-wave velocity (PWV). Endothelial function was assessed with a brachial flow-mediated dilation test and quantified with post-release velocity time integral (VTI) and acceleration. Cardiac magnetic resonance assessed ejection fraction, left ventricular mass indexed by height (LVMH), papillary mass and wall thickness. Moderate-to-vigorous physical activity (MVPA) and sedentary time were estimated with seven-day accelerometry. Recreational screen time and ethnicity were assessed by questionnaire. Weight and height were measured to compute body mass index z-scores (zBMI). Distinct multivariable linear regression models were estimated for each CVD marker, adjusting for

T1D status, age, sex, ethnicity, zBMI, and screen time (MVPA models) or MVPA (sedentary and screen time models), and additionally systolic blood pressure z-score and heart rate in models including endothelial function and cardiac magnetic resonance markers. Interaction terms for exposures of interest and T1D status were tested.

Results: Adolescents with T1D had a lower LVMH than controls (previously reported), and higher PWV. Each 10 minutes/day increment in MVPA was associated with a higher LVMH (beta [95% CI]: 0.88 g/m [0.04; 1.72]) in all participants, with no difference across groups. The association between sedentary time and wall thickness differed depending on T1D status. Each supplemental hour/day of sedentary time among adolescents with T1D was associated with a 0.10 mm greater wall thickness, while in controls, sedentary time was associated with a 0.12 mm reduction in wall thickness (p interaction < 0.05). No other associations were noted in multivariable models.

Conclusion: Associations between sedentary behaviors and early markers of CVD differ between adolescents with T1D and healthy controls, sedentary time being possibly more deleterious in this vulnerable population. MVPA could potentially mitigate early CVD risk in adolescents.

FC4.2

A Randomised Controlled Cross-Over Trial of the Hybrid Closed-Loop Insulin Delivery System Diabeloop vs. Sensor-Augmented Pump Therapy in Children Aged 6-12 Years

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Introduction: HbA1C goals are rarely achieved in children with Type 1 diabetes (T1D) except at the cost of increased hypoglycaemia episodes. The Diabeloop Hybrid Closed-Loop system improves time in range and glycemic control in adults. However, the efficacy and safety of the system had not yet been evaluated in children.

Our objective was to evaluate the safety and efficiency of the Diabeloop hybrid closed-loop system in prepubescent children (DBL4K).

Materials and Methods: We performed an open-label, multi-centre, randomised, controlled, two-session crossover study in patients aged 6-12 years with T1D, HbA1C <9%, and insulin pump treatment. Patients were randomised to the closed-loop ((Kaleido pump + Dexcom G6 = CL) device or sensor-augmented pump (open loop = OL) therapy. The CL and OL were worn for 4 days in hospital, followed by 6 weeks at home. Questionnaires on satisfaction, quality of life, and acceptance were completed independently by the children and parents.

Results: Twenty-one patients (mean age: 8.3+/- 1.6 years; 10 boys) were included between March and December 2019. The percentage of time spent in hypoglycemia (< 3.85 mmol/L) was significantly lower in the CL group during the 72 hours in hospital (2.04% in CL vs 7.06% in OL, p <0.001) and the 6 weeks at home (2.62% in CL vs 5.24% in OL, p <0.0001). The percentage of time spent in range (4-10 mmol/L) was identical in both groups during the 72-hour phase in hospital (68.73% in CL vs 70.53% in OL, p =0.539) and then significantly higher in the CL group during the 6 weeks at home (66.19% in CL vs 58.68% in OL, p <0.001). No events of ketoacidosis or severe hypoglycemia were recorded. Acceptance of and adherence to the CL device were good, and most patients and parents wanted to continue using this device.

Conclusions: The DBL4K Closed-Loop System is suitable for prepubescent children. It decreases hypoglycaemic episodes and provides good metabolic control in pre-pubescent children with type 1 diabetes, under real-life conditions. It also decreases the burden of diabetes management. It could allow for better long-term glucose control in children with diabetes.

FC4.3

Aldosterone and pro-atrial natriuretic peptide kinetics in response to rehydration in children with diabetic ketoacidosis

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Background: Diabetic ketoacidosis (DKA), a frequent complication of type 1 diabetes (T1D), is characterized by hyperosmolar hypovolemia. The response of water-regulating hormones to DKA treatment in children is not well known. While arginine vasopressin (AVP) is thought to respond to changes in osmolality, aldosterone and atrial natriuretic peptide (ANP) are expected to respond

to volume changes (dehydration and overhydration, respectively). The objective of this analysis was to describe the change of aldosterone and pro-ANP during rehydration therapy in children with DKA.

Methods: An observational multi-centre study was conducted in 2015-2019, including paediatric T1D patients treated for DKA according to ISPAD guidelines. Aldosterone and pro-ANP concentrations were measured at 0-4-8-12-24-72h after start of hydration therapy. Data were log-transformed to calculate the mean (95%CI) and coefficient of variation [CV] for each time point. Assumed dehydration and correction was calculated based on protocol fluid infusion rates, weight and DKA severity [mild (pH<7.2-7.3): 5%, moderate (pH 7.1-7.2): 6%, severe (pH<7.1): 8.5%]. A semi-mechanistic modelling approach was further applied to describe aldosterone kinetics as a function of a volume-dependent secretion rate (non-linear mixed effects regression).

Results: 95 pro-ANP and 92 aldosterone samples were obtained from 20 (male: 14) children (median age: 12 years [IQR: 9.8-14]) with mild (n=1), moderate (n=9) or severe (n=10) DKA. Pro-ANP levels were normal and did not change significantly during the study. Mean aldosterone concentration at start of rehydration was increased (4672 pmol/L, 95%CI: 2561-8524, CV: 106%), remained elevated up to 8h (5135 pmol/L, 95%CI: 3595-7335, CV: 94%) and reached 748 pmol/L (95%CI: 514-1088, CV: 67%) at 72h. Mean time to correction of dehydration was calculated to 14.1h (mild), 16.5h (moderate) and 22.7h (severe DKA). Under the assumption of fast aldosterone degradation (expected turnover half-life <1h), semi-mechanistic modelling showed a delayed aldosterone response to rehydration (turn-over half-life in the order of 10-20h).

Conclusion: Stable pro-ANP levels suggest that the treatment protocol did not result in volume overload. While copeptin levels described previously declined immediately after start of treatment, the decrease in aldosterone levels was delayed. Compared to reported paediatric reference intervals, aldosterone levels were still elevated at 72h, whilst dehydration had already been restored. One possible explanation for this delayed adaptation of aldosterone levels could be chronic upregulation of aldosterone synthase (CYP11B2) expression caused by prolonged exposure to angiotensin II and potassium in response to longstanding polyuria during DKA development.

FC4.4

Effect of newer CFTR modulator therapy on glycaemic control in adolescents with CFRD

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Background: Cystic fibrosis related diabetes (CFRD) affects 40-50% of adults with Cystic Fibrosis (CF) and significantly decreases pulmonary function and affects life expectancy. Previous data highlighted that CFRD may be preventable or curable with the use of CFTR modulators, namely Ivacaftor. Kaftrio (Ivacaftor,

tezacaftor and elxacaftor) has recently been licensed for use in CF. To our knowledge, its effect on glucose regulation in children and young people (CYP) with CFRD has not been described.

Objective: To describe the effect of Kaftrio on blood glucose control in CYP with CFRD who have previously been treated with insulin.

Methods: 7 patients (M:F = 1:6) with at least one $\Delta F508$ gene and one other licensed gene change were commenced on Kaftrio. A Freestyle Libre glucose monitoring system (Libre) was inserted three to five days prior to the initiation of the drug and monitoring was continued for the first 10 days after Kaftrio and then at regular intervals. Insulin dose was reduced prior to commencement of the drug or stopped if the dose was small. Regular blood glucose monitoring via finger prick and libre scanning, along with clinical symptoms were used to determine ongoing insulin requirement.

Results: 5/7 (71%) patients no longer require insulin, 1/7 (14.2%) required significantly less insulin, 1/7 (14.2%) showed increasing insulin requirements (as detailed in table below).

Table 1. Demographics of population

Parameter	Mean $\pm$ SD
Age at diagnosis of CFRD (years)	11.5 $\pm$ 1.9
Age when Kaftrio commenced (years)	14.0 $\pm$ 1.1
Length of time on Kaftrio (months)	7.0 $\pm$ 2.7

Table 2. Insulin requirements before and after Kaftrio therapy

Patient	Dose of insulin prior to commencing Kaftrio (units/day)	Dose of insulin post Kaftrio (units/day) (at a variable duration of 5-13 months)
1	6	0
2	8	0
3	25	1
4	2	0
5	10	0
6	28 units Tresiba + ICR* 1:12 + ISF** 1:4	30 units Tresiba + ICR* 1:15 + ISF** 1:4
7	4	0

*ICR = insulin to carbohydrate ratio **ISF = insulin sensitivity factor

Discussion: The data from our study suggest that Kaftrio leads to significant improvement in blood glucose control in CYP with CFRD which is sustained over five to thirteen months. Further data on long term effect needs to be assessed. Insulin doses should be reduced and CYP should be monitored closely when commencing treatment with Kaftrio.

FC4.5

Molecular Genetic Diagnosis and Research of Candidate Genes by Targeted Next Generation Sequence Analysis and Whole Exome Sequencing Method in Monogenic Diabetes: MODY-TURK Project

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Introduction: MODY; is a rare type of diabetes that occurs clinically and genetically due to a single heterogeneous gene defect. To date, 14 different genes have been identified. In order to develop a holistic genetic diagnosis approach to monogenic DM, it is aimed to investigate molecular genetic diagnosis and responsible candidate genes with targeted new generation sequence analysis and whole exome sequencing (WES) method.

Method: With the prediagnosis of MODY, 100 subjects between 0-25 years of age, were included in the study. In the first step, a targeted new generation sequence analysis panel including ABCC8, GCK, HNF1A, HNF4A, INS, KCNJ11, PDX1, PAX4, TCF2 / HNF1B, NEUROD1, KLF11, CEL, BLK and APPL1 genes analysis was done. Whole exome sequencing was planned in cases where no variant was detected in these genes. Pathogenicity of the detected variants was determined according to the criteria of "American College of Medical Genetics and Genomics" (ACMG).

Results: Thirty-three different variants in 8 different genes were detected in thirty-nine (39%) cases with the NGS. Most common pathogen variant was found in GCK gene in 25 (25%) cases. Six different variants were detected in 6 (6%) patients in ABCC8 gene, but 4 (4%) cases were associated with the disease and these cases were diagnosed as ABCC8 MODY. In one (1%) case, c.584G>T variant was detected in KCNJ11 gene. In two (2%) cases, 2 different variants were detected in HNF1A gene. In one (1%) case, heterozygous variants were detected in BLK, PDX1, PAX4 genes. One (1%) case was homozygous in the KLF11 gene and one (1%) case was heterozygous, homozygous variant was classified as "benign", heterozygous variant was not associated with the disease in segregation analysis.

In 45 of 65 cases; WES was done. Ten different variants were detected in eight different susceptibility genes in eight (8%) cases. Nine of the variants were not related with MODY phenotype as they did not show a distribution compatible with the pedigree with segregation analysis. Heterozygous c.2635C>T (p.Gln879Ter) variant was detected in IFIH1 gene in a patient with incidental hyperglycemia. Mother carried the same variant heterozygously shown with segregation.

Conclusion: Genetic etiology was determined in 35 (35%) of the 100 cases with the NGS panel. 17 new variants in MODY genes have been identified. A candidate gene determined by WES analysis in a case that could not be diagnosed with NGS in the MODY-TURK project.

FC4.6

Clinical and genetic heterogeneity of HNF4A/HNF1A mutations in a multicentre paediatric cohort

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Objective: The complex clinical phenotypes arising from HNF4A and HNF1A mutations are similar and include diazoxide-responsive CHI from infancy and maturity-onset diabetes of the young (MODY) from adolescence. We aimed to characterise the clinical and genetic aspects of a cohort of paediatric patients with HNF4A or HNF1A mutations.

Methods: Patients from five international centres over a 25-year period (1995-2020) with confirmed HNF4A/HNF1A mutations were included. Clinical and molecular genetic analysis data were obtained following case note review. Diazoxide responsiveness was defined as the ability to maintain normoglycaemia without intravenous glucose. Macrosomia was defined as a birth weight $\geq 90^{\text{th}}$ centile (≥ 1.3 SDS). Data are presented as median (interquartile range (IQR)) or mean (standard deviation (SD)).

Results: A total of 30 patients (70.0% female, n=21) with a mean age of 8.0 years (SD 6.2) were included. Most developed hypoglycaemia within the first two days of life (median age 1 day, IQR 1-1.25). The mean birth weight was 3.8kg (SD 0.8), with most infants macrosomic (n=19, 63.3%). Babies were born preterm (<37 weeks gestation) in 33.3% (n=10) of cases. The mean glucose requirement at diagnosis was 13.1mg/kg/min (SD 4.7). Diazoxide was commenced in 25 patients (83.3%) at a median of 10.0 days of life (IQR 2.0-15.8) of which all responded. CHI resolved in nineteen patients (63.4%) following a median of 3.7 years (IQR 0.2-6.9). Nine (n=9, 30%) had developmental delay. Two children were diagnosed with Fanconi syndrome (p.Arg63Trp, HNF4A). Four patients had hepatic or renal findings: deranged liver function tests (p.Gly292fs, HNF1A); hepatic enlargement (p.Arg311Cys, HNF4A); renal hypoplasia (p.Arg159Gln, HNF1A); liver cysts (p.Arg63Trp, HNF4A). Five patients (16.6%) developed MODY at a median of 11.0 years (IQR 9.0-13.9). A positive family history of diabetes mellitus was present in 22 (73.3%). Five parents were diagnosed with HNF4A/HNF1A MODY after their child's diagnosis. De novo mutations in HNF4A were found in six unrelated

patients; the remainder of mutations were inherited. Three different previously reported heterozygous *HNF1A* mutations were identified in four patients. Eighteen different heterozygous *HNF4A* mutations were identified in twenty six patients, including five novel mutations in seven patients (p.Val147fs; p.Met103Ile; p.Tyr300*; p.Gln349*; p.Gly60Val).

Conclusions: We expand on the natural history and the pancreatic and extra-pancreatic phenotypes of *HNF4A/HNF1A* mutations and illustrate the clinical and genetic heterogeneity of this condition.

Sex Development and Gender Incongruence

FC5.1

Growth and growth reduction in transgirls

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Introduction: Little is known about the effects of puberty suppression (PS) and hormone therapy (HT) on growth and adult height in transgender adolescents. These are topics of interest since height differs between sexes and some transgirls wish to limit their growth. In this longitudinal cohort study, we investigated the influence of PS and HT on growth and the efficacy of growth reduction therapy in transgender girls.

Methods: 88 transgirls who were treated with gonadotropin-releasing hormone agonists (GnRHa) and estradiol, with a bone age ≤ 16 at start PS and who had reached adult height were included. Adult height was compared to predicted adult height (PAH, using bone age according to B&P) at start PS, and to target height. Outcomes were compared between transgirls treated with a regular estradiol dose (regular increase up to adult dose of 2 mg) and high dose estradiol to reduce growth (fast increase up to 6 mg).

Results: Transgirls treated with a regular estradiol dose ($n=47$) had a mean ($\pm$ SD) age of 13.8 ± 1.0 years at start PS and 16.2 ± 0.5 years at start HT. They reached an adult height of 180.8 ± 5.4 cm (male height SDS -0.51 ± 0.77 ; female SDS $+1.51 \pm 0.88$). Adult height was 0.5 ± 4.1 cm above target height and 3.3 ± 4.7 cm below PAH at start PS. Transgirls treated with high dose estradiol ($n=20$) were 13.0 ± 1.0 years at start PS and 15.3 ± 0.8 years at start HT. Their adult height was 184.9 ± 5.7 cm (male height SDS $+0.20 \pm 0.81$; female SDS $+2.30 \pm 0.91$). Adult height was 0.2 ± 6.9 cm below target height and 4.5 ± 5.5 cm below PAH. The distance between target height and adult height or between PAH and adult height was not significantly different between adolescents treated with regular versus high dose estradiol, respectively 0.8 cm (95% CI -2.4 to 4.0) and 1.2 cm (95% CI -1.7 to 4.1).

Conclusion: In both treatment groups, mean adult height was close to target height but lower than PAH. This indicates that

treatment with GnRHa and estradiol might have an impact on adult height. Alternatively, prediction formulas might overestimate adult height in transgirls. Remarkably, treatment with high dose estradiol did not result in a significant growth reduction compared to the regular dose. The effect of timing and duration of PS and estradiol treatment on growth deserves further study.

FC5.2

Unexpected impact of sex hormones on B-cells in trans- and cis-gendered healthy young people

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Background: Cis-gender females are known to mount stronger immune responses to invading pathogens or vaccines than cis-gender males. However, this is also associated with increased risk of autoimmunity. Little is known about the immunophenotypes of transgender individuals on gender-affirming hormonal treatment, despite growing evidence that hormones influence the immune system.

Via the process of class-switch recombination (CSR), B-cell immunoglobulin isotype 'switches' from early IgM/IgD classes to IgG/IgA/IgE. Whilst important in infection or vaccine responses; switched isotypes play a significant role in autoimmunity pathogenesis. T-follicular helper cells (Tfh) provide vital assistance to B-cells in CSR.

This study sought to investigate the impact of a person's chromosomal complement and hormonal milieu on B-cell CSR. In testing samples from healthy cis- and trans-gendered individuals, an *in vivo*, age-adjusted model of these effects was created.

Methods: Peripheral blood samples were collected with informed consent from cis-gender male ($n=35$) and female ($n=53$) post-pubertal volunteers (14-28 years), and trans-gender male (on testosterone and/or GnRH-analogue; $n=25$) and female (on oestradiol and/or GnRHa; $n=19$) volunteers (16-19 years). In-depth phenotyping of peripheral blood mononuclear cells was performed using multiparameter flow cytometry. GraphPad Prism was used for statistical testing appropriate to the data distribution and number of groups (unpaired t-test/Mann-Whitney U, one-way ANOVA/ Kruskal-Wallis).

Results: Cis-females had greater percentages of class-switched B-cells than cis-males. In trans-males, just treatment with GnRHa was sufficient to also significantly decrease the levels of class-switched B-cells, and the addition of testosterone treatment saw no further decrease.

Treatment with GnRHa with or without oestradiol in trans-females, however, was not associated with the increase seen in

cis-females. Indeed, trans-females had the lowest percentage of class-switched B-cells of all groups.

These patterns were replicated when B-cells were stained specifically for IgG/A/M/D.

Cis-females and -males had similar levels of Tfh cells. Both trans-females and trans-males however, trended toward lower levels of Tfh cells, with little distinction between those on GnRHα versus gender-affirming-hormones.

Conclusions: Sex hormones may differentially affect the humoral immune responses of those assigned female at birth versus those assigned male. Whilst trans-males followed the same decreased class-switching pattern as cis-males, a surprising and significant decrease was seen in trans-females, that did not mirror the immune phenotype of cis-females. These data support the need for further research into the interactions between hormones and chromosomal sex, as immunological outcomes in trans-gender people may differ from those in cis-gendered individuals.

FC5.3

Fetal Anogenital Distance (AGD) by Ultrasonography: a Marker of Early Androgen Exposure *in utero*?

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Background: The anogenital distance (AGD) is defined as the distance from the anus to genital tubercle. AGD is an established method for sex determination of pups in rodents, and in animal studies, AGD is strongly affected by androgen exposure during fetal life. In accordance, human studies have reported reduced postnatal AGD following prenatal exposure to anti-androgenic agents, suggesting AGD to be a sensitive postnatal read out of *in utero* exposure to androgens. Little is known on AGD in humans during fetal life.

Aim: The aim of this sub-study is to evaluate fetal AGD in healthy males and females.

Methods: The Copenhagen Analgesic Study (COPANA) (ClinicalTrials.gov NCT04369222) is an ongoing prospective cohort study, designed to evaluate prenatal exposure of mild analgesics on reproductive function in offspring (currently ongoing inclusion aim 600 families). Fetal AGD was measured by transabdominal ultrasound at gestational week (GW) 29-34 in healthy, singleton fetuses who are subsequently born AGA. Measurements were performed in the axial plane from the center of the anus to the posterior converge of the fourchette (females), and to the posterior base of the scrotum (males). All scans were performed by a

single sonographer with a minimum of three repeated measurements. The reproducibility of the AGD measurements were assessed by Intraclass Correlation Coefficients (ICCs).

Results: Fetal AGD measurements were available for this sub-analysis in 183 fetuses (98 males), with no difference in GW or estimated fetal weight (EFW) between males and females (median 31.2 GW vs. 31.1 GW, $p=0.683$ and 1809g vs. 1680g, $p=0.134$). Male AGD; median (IQR) 21.9 mm (19.1-23.9) was significantly longer than female AGD; 13.6 mm (12.2-14.7), $p=0.001$ (Mann Whitney U (MWU)). AGD showed near complete separation of AGD between sexes. Male and female AGD levels were moderately correlated with GW (Spearman $r^2=0.39$ and $r^2=0.41$ (both $p=0.001$), respectively. Adjusting AGD for weight (AGD/EFW) did not alter the above findings concerning sex-specific AGD levels ($p=0.001$ MWU). AGD measurements were strongly reproducible; ICC 0.95 and 0.81 for males and females, respectively.

Conclusions: Fetal AGD determination by ultrasonography is sexually dimorphic as early as GW 29. Thus, fetal AGD candidates as a key endpoint in clinical research evaluating compounds affecting androgen exposure during early fetal life.

FC5.4

Reproductive hormone levels in Minipuberty as a predictor of Testicular Endocrine Function and Penile Length in Healthy Young Men: An 18-year longitudinal Cohort Study

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Background: Minipuberty denotes a period 1–6 months postnatally in boys during which a transient activation of the hypothalamic-pituitary-gonadal axis is observed. This early hormone activation can be used diagnostically in patients suspected of pituitary deficiency and differences in sex development. However, its significance for prediction of reproductive function in healthy young men is unknown.

Objective: To evaluate minipuberty as a potential ‘window of opportunity’ that allows prediction of future reproductive health in men.

Methods: In a population-based birth cohort, sons were examined 3 months postnatally and again around 19 years. Reproductive measures included reproductive hormones, penile length and testicular volume assessed by ultrasonography. For each outcome, participants were categorised in tertiles based on their

minipuberty measurement, and median adult values were compared between tertiles using Mann-Whitney U test.

Results: Boys in the lower FSH tertile in minipuberty had lower FSH levels in adulthood compared to the middle ($P<.01$) and upper tertiles ($P<.001$). For inhibin B and testicular volumes, boys in the upper tertiles in minipuberty had higher inhibin B levels and larger testicular volumes, respectively, in adulthood than those in the lower tertile ($P<.05$). For testosterone and SHBG, boys in the upper tertiles in minipuberty had higher testosterone and SHBG, respectively, in adulthood than those in the other tertiles ($P<.05$). Differences in LH were non-significant. Finally, boys in the upper tertile for penile length in minipuberty had longer penile length in adulthood than those in the lower tertile ($P<.05$).

Table 1.

Reproductive parameters		Adult outcome in relation to minipuberty tertiles		
		Lower	Middle	Upper
	<i>n</i>	Median (25–75 percentiles)		
FSH (U/L)	149	2.31 (1.78–3.04)	2.92 (2.35–4.79)	3.61 (2.48–4.91)
Inhibin B (pg/mL)	146	162 (132–217)	167 (141–211)	216 (158–249)
Left testicular volume (mL)	238	12.9 (11.0–15.1)	13.7 (10.9–15.7)	14.2 (12.3–16.5)
Right testicular volume (mL)	236	13.4 (11.7–15.1)	14.0 (11.6–16.8)	14.7 (12.6–17.0)
LH (U/L)	149	4.01 (3.24–4.93)	4.17 (2.97–5.31)	4.23 (3.04–5.70)
Testosterone (nmol/L)	150	19.8 (18.0–22.3)	19.5 (16.7–23.4)	21.9 (18.4–26.0)
SHBG (nmol/L)	149	31.9 (22.2–39.0)	28.1 (23.0–35.1)	34.3 (29.0–44.2)
Penile length (cm)	231	9.0 (8.0–9.6)	9.0 (8.2–9.5)	9.2 (8.5–10.1)

Conclusion: Reproductive hormones, penile length and testicular volume during minipuberty were predictive of adult outcomes. This indicates that minipuberty can be used as a ‘window of opportunity’ and a forerunner of adult reproductive health.

FC5.5

Individuals with *NR5A1* (*SF1*) mutations and atypical sex development and their asymptomatic family member carriers are at high risk of hyposplenism

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Background: Hetero- and homozygous mutations in *Steroidogenic Factor1* (*SF1*, *NR5A1*) cause 46,XY and 46,XX disorders of sex development (DSD), azoospermia, and primary ovarian insufficiency. *NR5A1* is also involved in embryonic spleen development, by transactivation of *T-cell Leukemia Homeobox 1* (*TLX1*). Hypo- or asplenia have occasionally been observed in DSD patients with *NR5A1* mutations.

Aims: We aimed to determine the prevalence and functional consequences of splenic defects associated with *NR5A1* mutations. We assessed spleen anatomy and function in 22 DSD patients (5 homozygous; karyotypes: 46,XY in 17; 46,XX in 5) and 5 asymptomatic carriers from 18 families, harboring 14 different *NR5A1* mutations, all classified as (likely) pathogenic. Spleen function was investigated by total blood and thrombocyte counts, % pitted red blood cells (PRBC), Howell-Jolly Bodies (HJB) and relative counts of spleen-dependent non-switched memory B cells. Spleen

anatomy was studied by ultrasound, the functional impact of 7/14 *NR5A1* variants on *TLX1* transactivation capacity was assessed by luciferase assays.

Results: One 46,XY girl homozygous for a *NR5A1* mutation, experienced a pneumococcal sepsis at 9 months. Fifty-nine percent of patients and 40% of carriers had thrombocytosis. Increased % PRBC was not observed; HJB were present in 5/19 (26%) tested patients and 0/5 carriers. Non-switched memory B cells were significantly lower in heterozygous patients and family member carriers as a group in comparison with age-matched controls ($p < 0.05$), but significantly higher than in patients with non-*NR5A1* related asplenism ($p = 0.003$), with no differences between heterozygous patients and carriers (ns). Anatomical spleen defects, mostly hypoplasia, were observed in 14/22 (63%) patients and 2/5 (40%) carriers. Asplenism was diagnosed in 4/5 individuals with homozygous mutations. *In vitro* transactivation of *TLX1* by *NR5A1* mutants relative to WT was significantly decreased for 4/7 tested variants, increased for 1 and did not significantly differ from WT for 2 variants.

Conclusions: Anatomical and/or functional hypo- or asplenism is suggested by at least one test in 77% of patients and 60% of family member carriers with *NR5A1* mutations. Any single test is not sufficiently sensitive or specific to indicate functional hyposplenism, and clinically applying a combination of techniques is complex and expensive. Given our findings, extensive assessment of splenic anatomy and function and consequent management of hypo- or asplenism is crucial in both patients with homozygous and heterozygous *NR5A1* mutations as well as their asymptomatic family member carriers. This includes low-threshold use of antibiotics and preventive vaccination against encapsulated bacteria.

FC5.6

Investigation of The Molecular Genetic Causes Of Non-Syndromic Premature Ovarian Failure By Next Generation Sequence Analysis

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Introduction: Premature ovarian failure (POF) is defined as ovarian failure developing before the age of 40. The etiology of genetic POF is quite heterogeneous and can be due to genetic, autoimmune, environmental, viral infections or iatrogenic causes.

Objective: The aim of this study is to investigate the molecular genetic causes of non-syndromic POF cases with the gene panel based on next generation sequence analysis and to establish the relationship between genotype and phenotype.

Methods: 23 cases aged 14-40 years followed up with POF were included. Patients with a karyotype of 46, XX, primary or secondary amenorrhea before the age of 40, with elevated FSH (> 40 IU / mL) and low anti-Müllerian hormone levels (< 0.03 ng / mL) were

included in the study. Those with anti-cancer therapy, pelvic surgery, ovarian infection and/or autoimmune disease history were excluded. Molecular genetic analyzes were performed with Illumina Nextseq550 platform with the next generation sequence analysis method targeted with the Trusight One kit. The variants in the genes that may be related to the POF included in the panel were analyzed by filtering method. Pathogenicity of the detected variants was determined according to the criteria of "American College of Medical Genetics and Genomics" (ACMG).

Results: Median age of the cases was 17.8 (14.0-24.3) years, and 12 (52%) cases admitted before the age of 18. Fifteen (65%) of the cases had consanguineous parents. Mean weight, height and BMI SDS were -0.5 ± 1.3 SD, -0.3 ± 1.7 SD, -0.0 ± 1.4 SD respectively. 4 of the cases had short stature and 3 of these patients received growth hormone treatment. Mean FSH level of the cases was 82.73 ± 35.21 IU/mL. In 2 (8.6%) patients, mutations detected were in genes that have been previously proven to cause POF. One was homozygous c.339T> G (p.Tyr113Ter) in *FIGLA* gene and the other was homozygous c.215T> C (p.Phe72Ser) variants in *PSMC3IP* gene. In addition, in one (4.3%) case, heterozygous c.5420A> G (p.Asn1807Ser) variant was detected in the *CHD7* gene, which was previously identified as a possible gene responsible for oligogenic inheritance in POF molecular etiology. In cases without mutation, all exome/genome sequence analysis, comparative genomic hybridization and advanced genetic analysis are ongoing.

Conclusion: Genetic panels based on next generation sequence analysis technologies can be used to determine the molecular genetic diagnosis of POF, which has a highly heterogeneous genetic basis.

Bone and Mineral Metabolism

FC6.1

Evaluation of the potential benefits of biposphonate treatment on symptomatic vertebral fractures in children treated for acute lymphoblastic leukemia

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Background and Aim: Vertebral fractures (VF) in children with acute lymphoblastic leukemia (ALL) are often symptomatic and impairing life quality. Prevalence of children with VF at ALL diagnosis has been reported as 16% with peak incidence occurring

during the first year after diagnosis and a 6-year cumulative incidence of 32.5%. Moreover, only 15.8% of these patients will have vertebral reshaping 24 months after ALL diagnosis. Additionally, 23% of ALL survivors will sustain vertebral deformities 15 years after diagnosis from whom 34% will report back pain in adulthood. Intravenous bisphosphonates (BP) can increase bone density and decrease bone pain. Our aim was to describe the bone health trajectory of a cohort of children with symptomatic VF treated with BP during their ALL treatment.

Methods: This retrospective cohort study included children treated with DFCI11-001 and DFCI16-001 protocols. As per institutional protocol, lateral spine X-rays and dual-energy X-absorptiometry scans were obtained within the first month of diagnosis, annually, and if new back pain occurred during the treatment period. Patients with symptomatic VF after induction treatment were treated with IV BP. VF were graded according to the Genant classification.

Results: 139 children (52% male) with a median age of 5.2 years (IQR 3.3-10.5 years) at diagnosis were included. Prevalence of patients with VF at ALL diagnosis was 10%. Sixteen patients with symptomatic VF after induction (total of 24 VF) were treated with BP for a median duration of 18 months (IQR 13.8-21). Among BP-treated patients, six (37.5%) presented VF at diagnosis while the remaining ten experienced their first VF within the 2nd to 12th month period after diagnosis. After BP initiation, patient-reported pain subsided in all children. One patient had an incident VF 6 months after BP initiation. One patient experienced a febrile acute phase reaction. At the end of ALL treatment, 46.7% of BP-treated patients had completely reshaped VF. Among those with persistent VF at 24 months of diagnosis (53.3%), 50% had improved Genant grading. Moreover, among BP-treated patients, children with fully reshaped VF had higher BMD Z-scores at the end of ALL treatment compared to patients with persistent VF (mean BMD Z-scores increase: 0.85 vs 0.73).

Conclusion: We report preliminary results from the first pilot study exploring VF trajectory in children with ALL treated with BP for symptomatic VF. Prospective trials are needed to confirm if BP influence VF reshaping in this population.

FC6.2

Long-term effectiveness of PTH(1-34) infusion therapy for autosomal dominant hypocalcaemia type 1

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Background: Patients with autosomal dominant hypocalcemia type 1 (ADH1), due to germline gain-of-function calcium-sensing receptor (CASR) mutations, have hypocalcemia and seizures, hyperphosphatemia, hypercalciuria and inappropriately low parathyroid hormone (PTH) concentrations. Treatment for ADH1 comprises calcium and vitamin D analogs, however, their use predisposes to nephrocalcinosis and renal impairment. In contrast, recombinant human PTH(1-34) may increase serum calcium, without causing hypercalciuric renal disease, in ADH1 patients. We evaluated the effectiveness of continuous subcutaneous PTH(1-34) infusion (CSPI) in a retrospective cohort of six patients with severe forms ADH1 characterised by recurrent seizures in childhood.

Methods: Retrospective observational study of six ADH1 patients (age 5 weeks–22 years) treated with CSPI (mean duration = 3.2 ± 0.6 years). All patients had recurrent hypocalcemic seizures requiring hospital admission and/or prolonged hospitalization despite treatment with calcium and vitamin D and/or bolus PTH injections. Effects on serum and urinary mineral concentrations, seizure frequency, and hospital admissions were assessed. CASR sequence analysis was undertaken, and the signalling responses of ADH1 mutants were assessed in HEK293 cells.

Results: All patients had germline heterozygous CaSR gain-of-function mutations, with three being constitutively active mutations that had arisen de novo and showed diminished signaling responses to the calcilytic, NPS-2143.

CSPI treatment over a period of 0.8–5.5 years, significantly increased serum adjusted-calcium concentrations from 1.79 ± 0.06 to 2.10 ± 0.04 mmol/L ($p < 0.01$), and reduced serum phosphate concentrations from 3.06 ± 0.24 to 2.15 ± 0.20 mmol/L ($p < 0.001$) without causing hypercalciuria in all the six studied patients. CSPI was also associated with decreased mean calcium-phosphate product from 5.45 ± 0.33 mmol²/L² to 4.46 ± 0.39 mmol²/L² ($p < 0.01$) in 5 patients, and increased mean serum magnesium by 0.09 mmol/L (95%CI, 0.03 to 0.14) in 4 patients.

CSPI dramatically decreased frequency of hypocalcemic seizures per month from 2.0 ± 1.4 to 0.01 ± 0.005 ($p < 0.05$), that led to fewer hospital admissions per month from 9.9 ± 4.7 to 0.8 ± 0.4 in 5 patients.

Serious adverse effects were not observed during the treatment with CSPI. Bone mineral apparent density was measured in three of the patients, and remained normal. One patient who was suspected to develop tachyphylaxis to PTH(1–34), sustained a unilateral slipped upper femoral epiphysis. CSPI did not worsen nephrocalcinosis or increase calcium excretion, which was reduced in three patients.

Conclusion: CSPI is well tolerated and represents a long-term therapy for children and young adults with ADH1, increasing serum calcium, ameliorating seizures and reducing hospital admissions. A prospective study is required to confirm these findings.

FC6.3

Off-label use of cinacalcet in pediatric primary hyperparathyroidism: a French multi-centre experience

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Background: For adult patients who do not meet indications to surgery, the calcimimetic cinacalcet is approved for primary hyperparathyroidism (HPT), decreasing calcium and parathyroid hormone (PTH) levels. This drug is largely used in adults, but may

be a challenge in daily practice in children, because of the risk of hypocalcemia, increased QT interval and drug interactions. A few pediatric cases have highlighted its potential interest in children with HPT; the aim here is to report the French pediatric experience in this setting.

Methods: We retrospectively analyzed data from 19 pediatric patients from 7 tertiary French centres who received cinacalcet for HPT. The results are presented as median (interquartile range).

Results: At a median age of 12.2(2.5–14.8) years, 19 patients received Cinacalcet for primary HPT (12 patients with inactive *CaSR* mutation, 1 patient with *CD73* mutation, 1 patient with *PHEX* mutation, 1 patient with multiple endocrine neoplasia and 4 patients with primary HPT of unknown etiology). Cinacalcet was introduced at an estimated glomerular filtration rate (eGFR) of 123(120–131) mL/min/1.73 m², plasma calcium of 2.98 (2.87–3.10) mmol/L, age-standardized (z score) phosphate of -2.7(-3.2; -1.9), total ALP of 214(111–225)UI/L, 25-D of 42(22–46) nmol/L, and PTH of 59(42–80) ng/L. The starting daily dose of cinacalcet was 0.7(0.6–0.9) mg/kg, with a maximum dose of 1.0(0.9–1.3) mg/kg per day. With a follow-up of 2.3(1.3–4.3) years on cinacalcet therapy, PTH remained stable at 44(35–59) ng/L (p=NS), as did eGFR, 25-D, ALP and phosphate and urinary calcium levels. In contrast, plasma calcium levels significantly decreased to 2.73(2.58–2.90) mmol/L (p=0.03). Nephrocalcinosis was not reported but one patient displayed nephrolithiasis. Cinacalcet was withdrawn in one patient (no side effect was reported).

Conclusions: These results suggest that off-label cinacalcet in pediatric HPT controls hypercalcemia without significant side effects.

FC6.4

Use of Aids, Assistive Devices and Adaptations (AADAs) by Individuals Aged <25 Years with Fibrodysplasia Ossificans Progressiva (FOP): 36-Month Results from a Global Natural History Study (NHS)

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Background: Individuals with the ultra-rare genetic disorder FOP experience progressive heterotopic ossification. Median age at diagnosis is 5 years; patients are supported by multiple specialties. Most patients become immobilised by the third decade of life, requiring lifelong assistance. We characterise AADA use as an indicator of disease severity in younger individuals with FOP enrolled in a 36-month, prospective, global NHS (NCT02322255).

Methods: Individuals with FOP aged ≤65 years with documented *ACVRI*^{R206H} mutation participated for up to 36 months. Use of and new-onset AADAs are reported for up to 36 months for participants aged <25 years, indicated via a list grouped into 12 categories. Data were analysed using descriptive statistics.

Results: 87 participants aged <25 years at Baseline were included in the Full Analysis Set. The most used AADA categories at Baseline and Month 36 are reported (Table). At Month 36, utilisation of the most common AADA categories was greater in participants aged 8-<25 years at Baseline versus those aged <8 years (Table).

At Month 36, 27 participants reported ≥1 new-onset AADA versus Baseline. The most common new-onset categories were bedroom aids and devices, school and medical therapies for daily living for participants aged <8 at Baseline (71.4% each [5/7 participants]), medical therapies for daily living for participants aged 8-<15 (50.0% [5/10]) and personal care tools/aids and care attendants for participants aged 15-<25 (60.0% each [6/10]).

Conclusions: High proportions of younger participants used AADAs at Baseline and Month 36. New-onset AADA use was increased at Month 36 versus Baseline, suggesting disease progression and increased functional impairment over time.

Table. Most common AADA categories at Baseline and Month 36 by age at Baseline

Category (%)	<8 years				8-<15 years				15-<25 years			
	BL (n ^a =16)	M12 (n ^a =17)	M24 (n ^a =13)	M36 (n ^a =9)	BL (n ^a =34)	M12 (n ^a =30)	M24 (n ^a =24)	M36 (n ^a =11)	BL (n ^a =34)	M12 (n ^a =28)	M24 (n ^a =17)	M36 (n ^a =11)
School	81.3	70.6	92.3	88.9	79.4	80.0	79.2	81.8	52.9	39.3	47.1	45.5
Personal care tools/aid	68.8	58.8	69.2	55.6	82.4	86.7	87.5	90.9	79.4	85.7	82.4	72.7
Bedroom aids/devices	62.5	64.7	76.9	77.8	79.4	70.0	79.2	100.0	73.5	75.0	76.5	90.9
Bathroom aids/devices	50.0	41.2	69.2	55.6	64.7	66.7	79.2	81.8	61.8	60.7	76.5	90.9
Care attendants	68.8	64.7	69.2	55.6	79.4	66.7	91.7	90.9	70.6	75.0	82.4	90.9

^aParticipants reporting AADA use at BL/M12/M24/M36. Includes categories with highest utilisation at BL/M36 by any age group. Darker shading indicates higher utilisation. BL: Baseline; M12/24/36: Month 12/24/36.

FC6.5

What is the natural history of cervicomedullary compression without signal change in infants with achondroplasia? Investigating foramen magnum stenosis evolution

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Background: Foramen magnum stenosis (FMS) is a common, serious complication of achondroplasia in infancy. The Achondroplasia Foramen Magnum Score (AFMS; 1-4) was developed to facilitate early detection of stenosis and inform appropriate neurosurgical management. All infants have a baseline screening MRI, of which approximately half of cases demonstrate AFMS3 (craniovertebral junction (CVJ) narrowing with flattening of the cervical cord) or AFMS4 (CVJ narrowing and cervical cord signal change). Children with AFMS4 are referred for neurosurgery; however, the natural history of children with AFMS3 is currently unclear so repeat MRI is performed after 12 months.

Aim: The aim of this study was to review follow-up clinical and MRI assessments of infants initially classified with AFMS3 to

define more clearly the natural history of this degree of stenosis. This knowledge would aid informing parents and refine our screening approach.

Study Design: This single institution retrospective cohort study identified all infants with a confirmed diagnosis of achondroplasia and AFMS3 on initial MRI who had subsequently undergone repeat MRI between February 2016 and March 2021.

All MRI images were evaluated by a paediatric neuroradiologist and a specialist achondroplasia paediatrician to identify and grade CVJ changes using the AFMS as an objective assessment of FMS. Neurological examination was assessed at time of initial MRI and at follow-up.

Results: 12 cases of AFMS3 satisfied the inclusion criteria. Median age at first scan was 6.5 months (IQR=4.5-10.3) and at second scan was 18.5 months (IQR=14.8-23.5). Follow-up MRI showed improvement in four cases to AFMS1 (CVJ narrowing with preservation of the cerebrospinal fluid (CSF) space around the cord, n=3) or AFMS2 (CVJ narrowing with loss of the CSF space, n=1). There was no change in four cases (AFMS3) and progression in four cases to AFMS4. Neurological examination of these children was normal at baseline and follow-up.

Conclusion: These results support the argument for MRI screening of infants with achondroplasia. Furthermore, the results suggest that all infants with AFMS3 should have a follow-up MRI scan as approximately one third progress to AFMS4 after one year, prompting neurosurgical referral.

There is no consensus currently on frequency of screening for FMS; however, we suggest that guidance for follow-up scanning is modified to six months to detect progression earlier in this at-risk cohort.

FC6.6

Use of lateral DEXA scanning for identifying and monitoring vertebral fractures in patients affected by Duchenne Muscular Dystrophy

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Introduction: International guidelines for management of Duchenne Muscular Dystrophy (DMD) advise active screening for vertebral fractures (VF), complications of which include pain, scoliosis and impact on ambulation.

Vertebral fracture assessment (VFA) is a technique of visualising thoracic and lumbar vertebrae with a lateral view on dual energy X-ray absorptiometry (DEXA) to identify VF. This is at reduced cost and radiation exposure when compared to spinal X-ray and is more convenient for the non-ambulant.

Previous studies have shown VFA to be a useful tool in actively screening for VF in DMD. Our aims were to assess whether similar outcomes would be seen in our department when introducing routine VFA screening.

Method: We undertook an audit on bone health specifically looking at VF and vitamin D status in boys with DMD exposed to corticosteroids, who were seen in outpatient clinic at a large paediatric neuromuscular centre after routine VFA screening was introduced.

Results: 37 patients were included for analysis. Median age was 10.2yrs (4.5-17.8yrs). Median steroid duration was 4.6yrs (0.99-12.6yrs). 62.2% (n=23) were taking deflazacort, 32.4% (n=12) taking prednisolone and in 5.4% (n=2) steroids had been discontinued.

48.6% (n=18) of VFA scans showed signs of VF. Of these, 72.2% (n=13) showed newly identified fractures, 16.7% (n=3) showed stable old fractures and 11.1% (n=2) were old fractures that had progressed. Five boys had fractures that were reported as "possible" due to difficulties visualising the vertebrae. One boy with inadequate imaging on VFA underwent subsequent spinal x-ray highlighting multi-level fracture. Of the 19 with VF, 42.1% (n=8) were single level and 57.9% (n= 11) were multi-level.

Median lumbar spine BMD z scores of those with and without VF was -1.65 (-3.1 - -0.2) and -1.05 (-2.9 - +1.1) respectively. Median vitamin D of boys with VF was 57.5nmol/L (38-93) and 44.5nmol/L (19-81) in those without VF. 84.2% (n=16) of all boys with VF were asymptomatic.

Of all 37 who underwent VFA, 35.1% (n=13) had a change in management following the image findings; five started zoledronic acid, three recommenced zoledronic acid and five were referred for testosterone initiation.

Conclusion: Our findings parallel that of prior studies and support the use of VFA as a screening tool for identifying VF in boys affected by DMD. This adds weight to the current evidence base that forms the recommendations for routine spinal imaging in DMD and promotes proactive bone health surveillance.

Fetal Endocrinology and Multisystem Disorders

FC7.1

The Use Of e-REC For Capturing The Occurrence Of COVID-19 Infections In People With Rare Endocrine Conditions

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Introduction: Following the onset of the COVID-19 pandemic in early spring 2020, there was a need to identify the burden of this infection on people with rare endocrine conditions. The European Registries For Rare Endocrine Conditions (EuRECa) was launched in 2018 in collaboration with Endo-ERN, ESPE and ESE to support the needs of the wider endocrine community. The project consists of an e-reporting (e-REC) platform that allows monthly reporting of new clinical encounters.

Methods: The ESE's Rare Disease Committee, formed in April 2020, created a COVID-19 taskforce which disseminated the use of e-REC through broad condition-specific study groups. The e-REC platform does not collect personally identifiable information and does not require individual patient consent. The platform was made available to all centres to report new encounters of confirmed or suspected cases of COVID-19 in patients with an existing rare endocrine or metabolic bone condition.

Results: Since launching the e-REC platform for notification of COVID-19 infections in March 2020, a total of 24 centres from 12 countries are participating. Of these 24 centres, 10 were reporting patients <18yrs (ie children) and 17 were reporting those >18yrs old (adults). Of the 24 centres, 20 (83%) centres from 12 (100%) countries have used e-REC to notify 194 cases of which 140 were

confirmed COVID-19 infections and the remainder were suspected. The median number of cases reported per centre was 4.5 (range 1, 46) and the median number of cases reported per month was 11 (0, 36). Of the 194 cases, 164 were in adults. This total 194 cases can be further categorized as broad thematic categories of pituitary disorders (n, 72), adrenal disorders (n, 54), genetic (neuro)endocrine tumours (n, 24), growth and genetic obesity disorders (n, 13), calcium/phosphate disorders (n, 10), thyroid disorders (n, 8), bone dysplasia (n, 6), disorders of sex development and maturation (n, 5) and glucose and insulin disorders (n, 2).

Conclusion: The use of the e-REC platform for identifying COVID-19 infection in people with rare endocrine conditions has been accepted in several centres and the platform is open for new centres. The majority of cases that have been reported are in adults and a high percentage are confirmed cases. Preliminary data suggest that COVID-19 infections are being reported more often in some endocrine conditions and there is a need to understand the reason for these differences and the impact of the infection on these patients.

FC7.2

Maternal, rather than fetal, genetic variation in vitamin D metabolism is associated with umbilical cord blood 25-hydroxyvitamin D in pregnancies supplemented with cholecalciferol: findings from the MAVIDOS randomized controlled trial

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Background: Neonatal vitamin D deficiency (VDD) can result in symptomatic hypocalcemia, seizures and cardiomyopathy and has been associated with reduced bone mineralization in childhood, but is potentially preventable with antenatal cholecalciferol supplementation. Single nucleotide polymorphisms (SNP) in the vitamin D metabolism pathway are associated with serum 25-hydroxyvitamin D [25(OH)D] in adulthood. We assessed whether maternal and/or offspring SNPs in *DHCR7* (7-dehydrocholesterol reductase), *CYP2R1* (25-hydroxylase), *CYP24A1* (24-hydroxylase), and *GC* (vitamin D binding protein [DBP]) are associated with umbilical cord blood (UCB) 25(OH)D, and if antenatal vitamin D supplementation modifies the relationships.

Methods: MAVIDOS is a randomized placebo-controlled trial of 1000 IU/day cholecalciferol from 14 weeks gestation until delivery. UCB 25(OH)D was measured by tandem mass spectrometry. Maternal and offspring SNPs at rs12785878 (*DHCR7*), rs10741657 (*CYP2R1*), rs6013897 (*CYP24A1*), and rs2282679 (*GC*) were genotyped. Associations between de-seasonalized UCB 25(OH)D (generated by Fourier analysis) and the SNPs were assessed by linear regression for each treatment group using an additive model. β is the change in 25(OH)D per additional common allele. Models were adjusted for maternal age, triceps skinfold thickness and smoking in late pregnancy to increase precision as these were identified as associated with UCB 25(OH)D.

Results: 329 mother-offspring pairs were included (185 placebo; 165 cholecalciferol). UCB 25(OH)D was higher in the intervention group (mean 42.3 nmol/l; SD 13.1) than the placebo group (mean 28.6 nmol/l; SD 12.1), $p < 0.001$.

In the cholecalciferol group, the maternal SNP at rs2282679 (*GC*) was associated with UCB 25(OH)D ($\beta = 4.2$ nmol/L per allele; 95%CI 1.0, 7.3). The effect size of this SNP in the placebo group was smaller ($\beta = 1.9$ nmol/L per allele; 95%CI -0.6, 4.4). The other maternal SNPs and offspring SNPs were not associated with UCB 25(OH)D in either group.

Conclusion: Maternal, rather than offspring, genetic variation in *GC*, encoding DBP, is associated with fetal 25(OH)D. The effect was larger in pregnancies supplemented with cholecalciferol, suggesting the SNP modifies vitamin D status when 25(OH)D is more readily available. This could be due to an effect of the SNP on DBP concentration or binding affinity. Future work needs to establish the effect variation at rs2282679 on DBP levels in pregnancy and the role of maternal DBP in the transport of 25(OH)D to and across the placenta.

FC7.3

European Training Requirements for Competency in Paediatric Endocrinology and Diabetes 2021

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Background: A Europe-wide training program in Paediatric Endocrinology and Diabetes (PED) was initiated by Professor Leo Van den Brande in 1976. PED was recognised as a subspecialty in 1996 by the European Board of Paediatrics (EBP), which is a

section of the Union of European Medical Specialists (UEMS). UEMS aims to ensure high standards for training across Europe and the minimum requirements are set out in the European Training Requirements (ETR).

The first PED training syllabus (that explicitly describes the content to be learnt in a subject) was submitted to UEMS for approval in 1996. Regular updates that reflect scientific and medical progress are recommended at approximately 5-yearly intervals, and were undertaken in 1997, 1998, 2005 and 2013. Thus our aim in 2019 was to update the PED ETR.

Methods: A Syllabus Taskforce, comprising a lead and four members, was established in 2019. All were consultants in PED, interested in education and from different countries. During 2020, they reviewed the 2013 ETR along with advances in PED, and prepared a revised ETR. Contributions and critique were sought from trainees, consultants, ETC members, and members of ESPE Council. Thereafter the PED ETR was submitted to the European Academy of Paediatrics (EAP), EBP and UEMS.

Results: Members of the EAP, EBP and UEMS provided constructive comments. These informed amendments to the PED ETR. Major changes were made to the section on 'Cross cutting and non-technical skills' and 'Levels of competence for clinical knowledge, skills and reasoning' adapted from those defined by UEMS.

The finalised PED ETR was approved by UEMS on 24 April 2021. It specifies the requirements for training institutions, trainers and trainees. It also provides the detailed syllabus/core content that trainees are expected to achieve in order to become competent independent clinicians in PED. References to consensus guidelines and statements produced and/or endorsed by ESPE, and seminal papers relevant for practicing clinicians are included.

Discussion and Conclusions: The process to develop and approve this 2021 ETR has been rigorous. The latter strengthens the validity of the recommendations. Implementing these will complement professional regulatory requirements for postgraduate training in PED in different countries and allow harmonising standards across Europe.

References

<https://www.eurospe.org/education/education-training-syllabus/>
<https://www.uems.eu/areas-of-expertise/postgraduate-training/european-standards-in-medical-training>

FC7.4

Endocrine sequelae in 157 paediatric survivors of haematopoietic stem cell transplantation

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Introduction: As successful rates of haematopoietic stem cell transplantation (HSCT) are on the rise, late endocrine and metabolic effects of these survivors have become more prevalent.

Aims: We aimed to characterise the endocrine abnormalities observed following HSCT.

Subjects and Methods: A retrospective descriptive study in paediatric post-HSCT patients (< 18 years-old) followed at an endocrine department between the years 2009 and 2019 was performed, with 157 individuals (62 females and 95 males) being identified. The reasons for HSCT were: **haematopoietic pathology** (42 cases of lymphoblastic leukaemia, 34 myeloblastic leukaemia, 5 lymphomas, 13 congenital anaemias and 12 cytopaenias), **solid tumours** (40 cases, with the most prevalent conditions being: 12 Ewing sarcomas, 9 neuroblastomas and 5 medulloblastomas) and 11 **rare entities**. Endocrinopathies were assessed according to the underlying diagnosis and treatment received (chemo +/- radiotherapy, surgery, type of HSCT) and regression analysis was used to ascertain association.

Results: Of all patients 58.7% presented at least one endocrine abnormality during follow-up; 15.4% of whom manifested it prior to HSCT (mainly: 5.4% short stature, 2.0% hypogonadism, 1.3% cortisol deficiency). Post HSCT patients developed primary hypogonadism ($p<0.001$), had higher body mass index ($p<0.01$) and iatrogenic Cushing features ($p<0.05$).

Endocrinopathies were most frequently developed in anaemias (82% of them) and rare entities (72% of them) and were 15% more common in females than males. A later age at HSCT [median (25th-75th quartiles): 9.78 years (6.25-12.25) versus 6.78 years (4.06-9.75)] was associated with endocrinopathy ($p<0.005$), so that 75% of individuals transplanted ≥ 10 years of age developed endocrinopathies as opposed to 48.4% of those <10 years-old ($p<0.001$). Similarly, pubertal Tanner stage V was associated with development of endocrinopathy ($p<0.001$). Direct gonadal therapy was associated with endocrinopathies ($p=0.026$) and patients who had received radiotherapy had 18% higher frequency of endocrinopathies, akin to those previously on steroids (17.4% increase). Allogenic HSCT recipients had a 7% higher rate of endocrinopathy. Although recipients of thymoglobulin or cyclophosphamide had higher incidence of endocrinopathies, there was no statistical

association between conditioning agents, or their combination, and endocrinopathies. Chronic graft versus host disease was associated with endocrinopathy ($p=0.022$). No significance was identified between endocrine abnormalities and follow-up duration.

Conclusions:

1. Over half of children surviving a HSCT will develop endocrine abnormalities.
2. Ascribing causality to the underlying pathology and to former therapies is challenging.
3. Following established pre- and post-HSCT protocols will enable a prompt diagnosis and treatment.

FC7.5

Rituximab therapy in Rapid-Onset Obesity, Hypothalamic Dysfunction, Hypoventilation, and Autonomic Dysregulation (ROHHAD) Syndrome

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Introduction: Rapid-onset obesity with hypoventilation, hypothalamic dysfunction and autonomic dysregulation (ROHHAD) is a rare syndrome that presents during early childhood and is associated with high morbidity and mortality. 40-50% of patients have neural crest tumours, most commonly ganglioneuromas or ganglio-neuroblastomas denoted by the suffix ROHHAD(NET) in a subset of patients. Currently, there is no specific diagnostic biomarker available and diagnosis is based on the clinical constellation of signs and symptoms. With no curative treatment for ROHHAD, management is largely supportive. The exact aetiology remains unclear but an autoimmune origin has been postulated and various immunosuppressive agents have been used with variable benefit.

Case: The patient presented in cardio-respiratory arrest at 4 years of age following a 6-month period of rapid weight gain. She weighed 27kg (>99.6th centile for weight) and was on the 9th centile for height (BMI 26.4kg/m²; SDS +3.1). Despite parental attempts at restricting calories and regular physical activity weight reduction had been unsuccessful. A cardio-pulmonary sleep study showed central hypoventilation and she was commenced on nocturnal bi-level non-invasive ventilation (BiPAP). She was diagnosed with central diabetes insipidus, hyperprolactinaemia (1700 mIU/L, NR <699) and subsequently growth hormone deficiency on glucagon stimulation testing (growth hormone peak 4.4 ug/L, NR >6.7 ug/L) therefore she will soon commence growth hormone therapy. MRI pituitary, abdomen and pelvis were normal except for generalised adiposity.

Cytokine serology, taken when she was otherwise well, demonstrated elevated levels of interleukin-6 (25pg/ml, NR 0-2). The patient received two courses of rituximab (750g/m²) four weeks

apart in an attempt to suppress any underlying immune dysregulation. Dietary intake was restricted to 60% recommended daily allowance. Following these interventions, weight reduced from well above the 99.6th to the 50th centile in nine months (BMI 17.8 kg/m²; SDS +1.35; SDS reduction -1.75). Repeat plasma cytokine profiling six-months after rituximab therapy showed that the IL-6 level had normalised (<1.44 pg/ml, NR 0-2).

Discussion: This case demonstrates a patient with obesity and hypoventilation due to ROHHAD presenting with respiratory arrest, who had normalisation of interleukin-6 levels and successful weight reduction following treatment with rituximab and ongoing calorie restriction. This clinical response possibly reflects an underlying, immune-inflammatory pathology driving excess adiposity in this condition. Potentially, other aspects of the syndrome may also be mediated through immune dysregulation in which case rituximab may provide benefits for prognosis and survival.

FC7.6

Reassessment of 18F-DOPA PET cut-offs in congenital hyperinsulinism

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Introduction: Congenital hyperinsulinism (CHI) is a rare but severe condition causing persistent hypoglycaemia. Approximately 30-40% of patients require surgical treatment. Extent of surgery depends on the histological form of the disease: subtotal pancreatectomy is done in diffuse CHI, whereas pancreatic resection is recommended in focal CHI.

¹⁸F-DOPA PET scan is a gold-standard imaging technique that helps in differential diagnosis of diffuse and focal forms with the use of special calculated parameter – pancreatic index (PI). Despite its advantages, the test has its obstacles and may result in misdiagnosis.

Other new imaging techniques are unavailable in the majority of countries and require further investigation. Thus, the objective of our study is to improve diagnostic accuracy of the ¹⁸F-DOPA PET.

Materials and Methods: We analyzed ¹⁸F-DOPA PET data in consecutive CHI patients with confirmed histological forms over a 4-year period. All but one children carry pathogenic variants in *ABCC8/KCNJ11* genes. Dynamic ¹⁸F-DOPA PET scans were done on “Discovery 710” scanner (General Electric). PI was calculated in pancreatic head, body, and tail 10-20, 30-40, 40-50, and 50-60 minutes after ¹⁸F-DOPA injection. We plotted a ROC curve for pancreatic indexes to obtain optimal cut-off for differential diagnosis.

Results: The study included 19 patients with diffuse CHI and 14 patients with focal CHI. We discovered that commonly accepted PI cut-off of 1.5 for focal CHI lacks diagnostic accuracy (85%, CI: 67-94%) and has broad confidence interval for specificity (100%, CI: 66-100%). Our findings suggest that more accurate cut-off for

focal form is 1.31 registered 30-40 minutes after ¹⁸F-DOPA injection: diagnostic accuracy 91% (CI: 74-98%) and specificity 100% (CI: 81-100%). Further research revealed the highest accuracy can be achieved by a combination of the latter cut-off and visual evaluation performed by experienced radiologist: diagnostic accuracy 97% (CI: 82-100%) and specificity 95% (CI: 74-100%).

For example, ¹⁸F-DOPA PET scan in one of the patients with diffuse CHI showed PI of 1.47 that generally implies focal CHI. This situation could have resulted in unsuccessful pancreatic resection. However, based on our findings PI calculated 30-40 minutes after the injection was 1.11 that indicated diffuse form of the disease (as it is lower than proposed cut-off 1.31). Eventually, the patient underwent successful subtotal pancreatectomy.

Conclusion: ¹⁸F-DOPA PET plays a crucial role in the diagnosis of the histological form of CHI. Reassessment of ¹⁸F-DOPA PET cut-offs may preclude misdiagnosis and tailor surgical treatment.

Neuroendocrinology

FC8.1

Combined omic analysis revealed autism-linked *NLGN3* as new candidate gene associated to GnRH neuron development and disease

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During development, gonadotropin releasing hormone (GnRH) neurons are born in the nasal placode and migrate to the hypothalamus, where they position to regulate sexual reproduction by pulsatile release of GnRH. Defective GnRH neuron development or action may lead to GnRH deficiency (GD) which is characterized by absent or delayed puberty. Several GD causative genes have been identified so far, but half of the cases are still idiopathic. The employment of complementary research approaches may be useful to identify additional genes implicated in GD pathogenesis. Here, we combined the transcriptomic analysis of primary and immortalized GnRH neurons with whole exome sequencing data from GD patients to identify novel candidate genes. As a proof-of-principle, we identified pathogenic variants in the autism-linked *Neurexin 3 (NLGN3)* gene in patients with severe delayed puberty and autistic traits. We demonstrated that *NLGN3* is enriched in GnRH neurons at late developmental stages and its overexpression in a model of immortalized GnRH neurons promoted neurite extension. Complementary to this finding, identified *NLGN3* mutations resulted in prematurely truncated proteins which are retained in the endoplasmic reticulum preventing

formation of cell protrusions. Overall, our results highlighted how the combination of gene expression and exome sequencing data is a reliable approach to identify novel candidate gene for GD such as NLGN3, an autism-linked gene that we found for the first time associated with GD. These data may also suggest the existence of biological or clinical links between reproductive defects and neurodevelopmental disorders.

FC8.2

Recessive *PRDM13* mutations result in hypogonadotropic hypogonadism and cerebellar hypoplasia

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Three patients from two unrelated families in Malta; one consanguineous (siblings: Patient 1, male and Patient 2, female) and one non-consanguineous (Patient 3, male), manifested hypogonadotropic hypogonadism with delayed puberty, intellectual disability, scoliosis, and ataxia with cerebellar hypoplasia on MRI.

GnRH tests revealed low peak LH and FSH concentrations in the patients: Patient 1; LH 2.3 IU/L, FSH 4.4 IU/L (14.3y), Patient 2; LH 3.6 IU/L, FSH 6.4 IU/L (12.5y), Patient 3; LH 0.9 IU/L, FSH of 3.1 IU/L (13y). 3 day hCG tests revealed a peak testosterone of 2.2 nmol/L in Patient 1, and a sub-optimal peak testosterone of 2.3 nmol/L in Patient 3, with the latter having an excellent peak of 30.7 nmol/L after 3 weeks of hCG. Patients were treated with testosterone or oestradiol respectively. Bilateral orchidopexies were performed in both males, and all patients required corrective surgery for scoliosis. They presented with either generalised hypotonia with hyporeflexia (Patients 1 and 2) or hypertonia with hyperreflexia (Patient 3).

Whole exome sequencing revealed a novel homozygous 13bp deletion (c.398-3_407delCAGGGGAGGAGCG) in *PRDM13* in the three patients, inherited from their heterozygous parents. *PRDM13* (PR Domain containing 13) is a putative chromatin modifier and transcriptional regulator that functions downstream of the transcription factor PTF1A. Human and mouse expression studies revealed *Prdm13/PRDM13* transcripts in the developing hypothalamus and cerebellum. Mice homozygous for a *Prdm13* mutant allele manifested with cerebellar hypoplasia, however male gonadal development appeared unaffected in these mutants. As PTF1A has been linked to early GABAergic neuronal cell fate regulation in the spinal cord, we examined GABAergic neuron progenitor development in the hypothalamus and cerebellum. Results showed a significant reduction in Kisspeptin neurons in the hypothalamus and PAX2+ progenitors emerging from the cerebellar ventricular zone. The latter was accompanied by ectopic expression of the glutamatergic lineage marker TLX3. Microarray analysis of the patients and an unrelated heterozygous Maltese carrier of the 13bp deletion, shared an identical 0.2Mb region of homozygosity encompassing *PRDM13*, suggesting a common haplotype within the Maltese population.

Our studies identify *Prdm13/PRDM13* as a critical regulator of GABAergic cell fate during neurodevelopment, providing a mechanistic explanation for the co-occurrence of hypogonadotropic hypogonadism and cerebellar hypoplasia in this recessive syndrome. Therefore, patients with a combination of these phenotypes should be screened for *PRDM13* mutations. To our knowledge, this is the first evidence linking disrupted regulation of Kiss1 neurons to congenital hypogonadotropic hypogonadism in humans.

A novel clinical risk score that can accurately predict recurrence of craniopharyngioma - a multicentre cohort study

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Background: Recurrence of craniopharyngiomas influences mortality. Apart from the extent of surgical resection, few clinical parameters have been consistently shown to be associated with

recurrence. Radical resection is difficult due to infiltration of surrounding tissue and unacceptable morbidity. Predictors of recurrence are therefore needed.

Aim: To establish a multinational cohort of patients with craniopharyngioma and employ their clinical parameters to design a clinical tool that can predict the risk of recurrence.

Methods: 225 patients from 15 centres (8 countries) participated in our prospective and retrospective observational cohort study. Tumour subtyping was performed by three histopathologists. Detailed clinical and neuroimaging data was collected. Statistical analyses were performed using R software; the primary end-point for prediction was 'time-to-first-recurrence'.

Results: 47% were <18 years; 89% were adamantinomatous. Median age in children was 10.4 (IQR 6.3-13.2) and adults 46.1 (IQR 31.7-58.5). 56% had a recurrence with median 'time-to-first-recurrence' of 23 months (IQR 9-44). A multivariate ridge Cox proportional hazards regression model was performed using age, gender and clinical parameters as risk predictors of time-to-first-recurrence (diagnosis decade; symptom duration; tumour subtype, size, consistency, location; hypothalamic invasion; endocrinopathies; transsphenoidal/craniotomy; complete/incomplete resection; radiotherapy). A risk-score was computed as the linear predictor of the fitted multivariate Cox model. For each year post-treatment and for up to 10 years, a risk score cut-off value with a sensitivity nearest to 90% was selected, which had an accompanying specificity. At 5-year follow-up, a cut-off value of 0.463 for the score gives a sensitivity of 89.9% (95% CI: 84-95%) and a specificity of 50.4% (95% CI: 39-64%). The corresponding area under the curve (AUC) at 5-year follow-up is 0.776 (95% CI: 0.701-0.867). The AUC is maintained above 80% for up to 10-year follow-up indicating a good prognostic ability of the score. A univariate Cox regression model showed that for every increase in the risk score by 1 unit, the IQR Hazard Ratio is 2.052 (95% CI: 1.663-2.532, LR χ^2 49.742; $p=1.8e-12$) with a Harrell's C-index of 0.659 (95%CI: 0.605-0.712) further indicating good predictive performance. Kaplan-Meier curves showed that radiotherapy resulted in significantly longer recurrence-free-survival ($p=0.00046$).

Conclusion: This study is the first to use a large comprehensive clinical dataset that combines several clinical features to design a model that predicts the risk of craniopharyngioma recurrence. This model facilitates the identification of risk factors and following external validation, could be used in clinical practice to aid more individualised management.

FC8.4

Cerebral infarction in childhood-onset craniopharyngioma patients: results of KRANIOPHARYNGEOM 2007

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Background: Cerebral infarction (CI) is a known vascular complication following treatment of suprasellar tumors. Risk factors for CI, incidence rate, and long-term prognosis are unknown for patients with childhood-onset craniopharyngioma (CP).

Methods: MRI of 244 CP patients, recruited between 2007 and 2019 in KRANIOPHARYNGEOM 2007, were reviewed for CI. Risk factors for CI and outcome after CI were analyzed.

Results: Twenty-eight of 244 patients (11%) presented with CI based on reference assessment of MRI. One CI occurred before initial surgery and one case of CI after release of intracystic pressure by a cyst catheter. 26 of 28 CI were detected after surgical tumor resection at a median postoperative interval of one day (range: 0.5-53 days). Vascular lesions during surgical procedures were documented in 7 cases with CI. There was a trend ($p=0.094$) towards higher initial presurgical tumor volume in CI patients compared with non-CI patients. No relevant differences with regard to surgical approaches were found. In all 12 irradiated patients, CI occurred before irradiation. Multivariable analyses showed that hydrocephalus and gross-total resection at the time of primary diagnosis/surgery both were risk factors for CI. PFS was lower after CI (median survival=1.16 years) when compared with the subgroup of patients without CI (median survival>5.62 years). After CI, quality of life (PEDQOL) and functional capacity (FMH) were impaired.

Conclusions: CI occurs in 11% of CP cases. Tumor size, degree of resection and increased intracranial pressure are risk factors, which should be considered in the planning of surgical procedures for prevention of CI.

FC8.5

Bardet-Biedl Syndrome: A retrospective study of progression through puberty

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Introduction: Bardet-Biedl syndrome (BBS) is a rare, pleiotropic, autosomal recessive disorder, with prevalence between 1 in 100,000 – 160,000 in Europe and the USA. It is characterised by 6 cardinal features: rod-cone dystrophy, truncal obesity, cognitive impairment, hypogonadism and genitourinary anomalies, post-axial polydactyly and renal dysfunction, as well as a plethora of secondary features spanning multiple body systems. BBS belongs to a family of inherited ciliopathies, which manifest secondary to genetically acquired anomalies in the proteins responsible for the maintenance of primary ciliary integrity - these result from mutations in a constellation of at least 21 identified genes, referred to as BBS genes. Hypogonadism is one of the hallmarks of BBS. Historically patients have been thought to present with absent or delayed puberty, resulting in close monitoring of pubertal development, and the use of hormone replacement therapy (HRT) to induce and maintain pubertal progression in some cases.

Objective: To review historical cases to ascertain whether children with BBS spontaneously entered and progressed through puberty normally, without the use of HRT.

Method: A retrospective 10-year review was conducted of paediatric patients diagnosed with BBS and managed in a specialist tertiary/quaternary UK Centre. The cohort of BBS patients was retrieved from a secure database, managed and developed by Certus Technology Associates. Data was also collected from Electronic Patient Records.

Results: 113 patients diagnosed with BBS presented to our Centre from 2010 - 2019; 68 were male. Their age at presentation was between 1.1 and 18 years (median 9.4 years). Three male patients had received testosterone treatment briefly during childhood and all later spontaneously entered puberty. No female patients have received HRT to date. All patients in this cohort entered puberty spontaneously; only 1 male had delayed puberty, with onset at the age of 15.4 years. Delayed puberty was not seen in any of the females. Of this cohort 27% have completed puberty to date.

Conclusion: Although the literature states that patients with BBS are at risk of delayed puberty and likely to require pubertal induction, our data shows that 99% of our studied cohort entered puberty spontaneously, without delay. Ongoing follow up and surveillance are needed to ensure that there is no evidence of pubertal arrest and to ascertain HRT requirements in adulthood. Further data regarding fertility outcomes are also needed.

FC8.6

Efficacy and Safety of Corifollitropin Alfa in Combination with Human Chorionic Gonadotropin for Initiation or Restoration of Puberty in Adolescent Males Aged 14 to < 18 Years with Hypogonadotropic Hypogonadism

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Background: Combinations of follicle-stimulating hormone (FSH) and human chorionic gonadotropin (hCG) have been successful in treating males with hypogonadotropic hypogonadism (HH). The aim of this study was to investigate the efficacy and safety of corifollitropin alfa (CFA), a long-acting FSH analog, combined with hCG to induce testicular growth and pubertal development in adolescent males with HH.

Methods: This was a 64-week, multi-center, open label, single-arm study of CFA in males 14 to <18 years of age with HH (n=17). After a 12-week priming period with CFA (100 µg if weight ≤60 kg, or 150 µg if weight >60 kg) given subcutaneously (SC) every other week (EOW), participants entered a 52-week combined treatment period with CFA EOW + SC hCG twice-weekly (dose adjusted between 500 IU and 5,000 IU to keep total testosterone [T] and estradiol levels within acceptable ranges). The primary efficacy endpoint was change from baseline at Week 64 (overall treatment period) in testicular volume (TV), measured as the sum of volumes of left and right testes by ultrasound. Efficacy analyses were based on the Full Analysis Set population (n=13), which included all participants who had a baseline and at least 1 post-baseline TV measurement, had LH levels ≤3 IU/L, had received treatment for at least 12 weeks with CFA followed by at least 24 weeks of CFA + hCG, and had ≤4 weeks between the last dose of CFA and the last endpoint measurement. Safety was evaluated by the presence of anti-CFA antibodies and the occurrence of adverse events.

Results: In the CFA priming period, mean TV increased (geometric mean [95% CI] fold increase from baseline at Week 12: 1.83 [1.58, 2.13]) and continued to increase during the combined treatment period (geometric mean [95%CI] fold increase from baseline at Week 64: 9.43 [7.44, 11.97]). Increases in serum T were noted and participants progressed through puberty (assessed by Tanner stages and growth velocity). Changes in serum inhibin-B and anti-Müllerian hormone levels were consistent with the initiation and progression of puberty. Treatment was generally well tolerated. No participant developed anti-CFA antibodies.

Conclusions: In adolescent males with HH, treatment with CFA (alone for 12 weeks and then combined with hCG from

Weeks 12 to 64) was generally well tolerated and induced testicular growth and pubertal development.

Growth Hormone and IGFs

FC9.1

How to interpret growth hormone stimulation test results in children and adolescents with overweight and obesity? A systematic review and meta-analysis and evidence-based proposal for weight-status adjusted cut-offs

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Background: Peak stimulated growth hormone (GH) levels are known to decrease with increasing BMI, possibly leading to over-diagnosis of GH deficiency (GHD) in children with overweight and obesity. However, current guidelines do not provide guidance how to interpret peak GH values of these children. The aim of this systematic review and meta-analysis was to study the effect of BMI standard deviation score (SDS) on stimulated peak GH values in children, to identify potential moderators of this association, and to quantify to which extent peak GH in children with obesity is decreased.

Methods: This systematic review was performed in accordance with PRISMA guidelines. Medline, Embase, Cochrane, Web-of-Science, and Google Scholar were searched for studies reporting impact of weight status on peak GH in children. Where possible, individual participant data was extracted or obtained from authors. Primary outcome was the association between peak GH and BMI SDS. The pooled correlation coefficient, 95% confidence interval (CI) and heterogeneity statistic I^2 were calculated under a multi-level, random effects model and exploratory moderator analyses and meta-regressions were performed. For the individual participant dataset, linear mixed-models regression analysis was performed with $\ln(\text{peakGH})$ as outcome, accounting for used GH stimulation agent.

Results: Fifty-eight studies were included, providing data on n=5135 children (576 with individual participant data). A pooled correlation of -0.32 (95% CI -0.41 to -0.23, n=2434 patients, k=29 cohorts, $I^2=75.2\%$) was found. In meta-regressions, larger proportions of males included were associated with weaker negative correlations (p=0.04). Pubertal status, presence of syndromic obesity, mean age and BMI SDS did not moderate the pooled r (all p>0.05).

Individual participant data analysis revealed a beta of -0.123 (95% CI -0.160 to -0.086, $p < 0.0001$), i.e., per 1 point increase in BMI SDS, peak GH decreases by 11.6% (95% CI 8.3 to 14.8%).

Conclusions: To our knowledge, this is the first systematic review and meta-analysis to investigate and quantify the impact of BMI SDS on peak GH values in children. Importantly, this relation is already present in the normal range of BMI SDS and could lead to overdiagnosis of GHD in children with overweight and obesity. With ever-rising prevalence of pediatric obesity, BMI-specific cut-off values for GH stimulation tests in children are needed. Based on this meta-analysis, we suggest weight status-adjusted cut-offs for children with overweight and obesity of 9.3 $\mu\text{g/L}$ and 8.6 $\mu\text{g/L}$, respectively, in stimulation tests that have a normal weight cut-off of 10 $\mu\text{g/L}$.

FC9.2

A simple model with height and age at start of treatment with recombinant human growth hormone can accurately predict future growth in children with growth disorders

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Background: A growth prediction model would not only allow patients with growth disorders the opportunity to see the expected effect of their recombinant human growth hormone (r-hGH) treatment, but also support healthcare professionals to individualise treatment to optimise growth outcomes.

Aim: To develop a growth prediction model in children with growth disorders.

Patients and Methods: Height and clinical/background characteristics from children receiving r-hGH during the easypod™ connect observational study (ECOS)1 were used to develop the model. For these children, height measurements from the easypod™ connect ecosystem were also included. Inclusion criteria were growth hormone deficiency (GHD), small for gestational age (SGA) or Turner syndrome (TS), age 2-18 years, age at treatment start 2-15 years, height standard deviation score (HSDS) at start < -1 , ≥ 1 height measurement between 0.5-3.5 years' treatment and treatment-naïve. A linear mixed-effects baseline model was applied, with HSDS between 0.5-3.5 years (y) as the dependent variable, and the main effects and interaction between the cubic polynomial of treatment duration and HSDS and age at start as fixed effects. Additional factors known at treatment start (e.g. sex) were then included in the model, which was validated using height measurements from patients from easypod™ connect who were not included in the ECOS study.

Results: In total, 1,212 children (885 with GHD, 243 with SGA, 84 with TS) with 7,485 measurements were available for model development. HSDS and age at start were highly significant in the

baseline model ($p < 0.001$). The proportion of variance explained was 71%. Other significant factors ($p < 0.01$) were sex, corrected target HSDS, r-hGH dose (mg/kg/week) at start, disorder (TS vs SGA and GHD), puberty status (Tanner stage 1 vs > 1) at start, birthweight SDS, and region (Western Europe, Asia/Oceania combined, Eastern Europe, Latin America and Caribbean, North America), but the proportion of explained variance only slightly improved to 72%. In the baseline model, predicted minus actual HSDS were 0.3 SD (1.9cm) at 1y, 0.5 SD (3.0cm) at 2y and 0.6 SD at 3y (3.9cm) after treatment start. Comparative figures were 0.3 SD (1.2cm) at 1y, 0.4 SD (3.2cm) at 2y and 0.5 SD at 3y (3.2cm) for 725 non-ECOS patients from easypod™ connect.

Conclusion: We developed a simple model, with age and height at treatment start, that accurately predicts future growth at any time between 0.5-3y after treatment start and at any starting age between 2-15y.

Reference

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FC9.3

Once-weekly somapacitan versus daily growth hormone in growth hormone deficiency: 3-year efficacy and safety results from REAL 3, a randomised controlled phase 2 trial

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Growth hormone (GH) replacement therapy currently requires daily subcutaneous injections. Somapacitan is a long-acting GH-derivative in development for once-weekly use in children with GH deficiency (GHD). A phase 2, multinational, randomised, open-label, controlled trial (NCT02616562) investigated the efficacy and safety of somapacitan compared with daily GH (Norditropin®).

GH-treatment-naïve prepubertal children with GHD received 0.04 (n=16), 0.08 (n=15) or 0.16 mg/kg/week (n=14) somapacitan, or daily GH 0.034 mg/kg/day (0.24 mg/kg/week; n=14) for 1 year, followed by a 2-year safety extension with all patients on somapacitan (n=45) receiving 0.16 mg/kg/week, while daily GH dose was unaltered. Safety endpoints comprised frequency of adverse events (AEs). The 1-year and 2-year results have been reported previously. Here, we report the efficacy and safety of somapacitan after 3 years of treatment.

At year 3, mean (SD) height velocity (HV) was 8.9 (1.7), 7.8 (1.5) and 8.4 (1.7) cm/year for 0.04/0.16 mg/kg/week, 0.08/0.16 mg/kg/week and 0.16/0.16 mg/kg/week somapacitan, respectively, vs 7.6 (2.0) cm/year for daily GH. Change in mean (SD) height

standard deviation score (SDS) from baseline to 3 years was 2.39 (1.00), 2.37 (0.97) and 2.67 (1.42) for somapacitan, respectively, vs 2.10 (0.85) for daily GH. The observed HV results for the somapacitan groups and daily GH arm in the third year, were similar. Change in insulin-like growth factor-I SDS from baseline to year 3 was 3.26 (1.04), 3.52 (1.43) and 3.66 (1.29) for somapacitan, respectively, vs 3.40 (1.58) for daily GH.

Number of AEs (% of patients) was as follows: somapacitan 0.04/0.16 mg/kg/week, 72 (75.0%); 0.08/0.16 mg/kg/week, 126 (93.3%); 0.16/0.16 mg/kg/week, 120 (100%); and daily GH, 95 (100%). In all treatment groups, the rate of AEs per 100 patient-years of exposure was lower in the 2-year safety extension than the first year. The most common AEs across the pooled somapacitan groups were pyrexia (40% for somapacitan and 14% for daily GH), influenza (20% and 21%), nasopharyngitis (16% and 21%), vomiting (13% and 7%), constipation (11% and 0%), allergic rhinitis (11% and 21%), otitis media (11% and 7%), tonsillitis (11% and 0%) and gastroenteritis (11% and 14%). Most AEs were mild to moderate and unlikely to be treatment related.

These 3-year data support the efficacy results observed in the first and second year of somapacitan treatment of GHD; no new safety signals were observed.

FC9.4

Optimising adherence using a connected injection device can improve growth outcomes: Evidence from real-world data on 11 million injections in 20,000 patients with growth disorders

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Background: For early identification of patients requiring adherence support, objective, real-time adherence data are needed. The easypod™ electromechanical injection device, in combination with the easypod™ connect ecosystem, electronically records and transmits, in real time, accurate records of the date, time and dose injected for patients receiving recombinant human growth hormone (r-hGH) to treat growth disorders. Healthcare professionals can use data extracted from easypod™ connect to monitor patient adherence and growth outcomes, which, in recent years, has been augmented by digital health solutions.

Aim: To evaluate adherence rates over time and growth outcomes by level of adherence using data from the easypod™ connect ecosystem.

Patients and Methods: Adherence and height data from 2007 to the end of 2020 were extracted from easypod™ connect. Height data for patients aged ≤18 years with ≥2 recorded growth measurements during treatment were included. Regional adherence rates were evaluated annually between 2010 and 2020. Linear

interpolation between height measurements was applied to calculate monthly Height Standard Deviation Scores (HSDS). Adherence overall and between height measurements were categorised as high (≥85% of prescribed doses administered), intermediate (>56 to <85%) and low (≤56%). Multi-level linear regression techniques were applied to study the effect of adherence level on ΔHSDS.

Results: Adherence data were available for 20,264 patients from 38 countries who transmitted data from 11,494,170 injections to the ecosystem. In total, 2,215 patients with 12,943 height measurements were analysed. The proportion of high adherence increased over time in European (76% in 2010; 82-84% in 2015-2019; 86% in 2020), North-American (Canadian) (65% in 2010; 68% in 2015; 88% in 2019-2020) and Asian (58-62% in 2014-2015 [insufficient data before 2014]; 68-73% in 2016-2020) patients. No consistent change in adherence was found among Latin-American and Caribbean patients. Adherence level had a statistically significant effect on ΔHSDS ($p < 0.001$). Mean ΔHSDS were 0.4, 0.7, 1.0 and 1.1 after 12, 24, 36 and 48 months' treatment, respectively, in patients with high monthly adherence, 0.3, 0.6, 0.8 and 0.9 in patients with intermediate monthly adherence and 0.2, 0.5, 0.6 and 0.7 in patients with low monthly adherence.

Conclusion: Data extracted from easypod™ connect showed high adherence rates and, for most regions, a positive trend in adherence to r-hGH therapy over time. A higher level of adherence resulted in a higher rate of catch-up growth, and its cumulative effect increased over time. The easypod™ connected injection device has the potential to optimise adherence and growth outcomes.

FC9.5

Dynamic Changes in Growth and IGF-I During the First Year of Life; A Longitudinal Study of 233 healthy Danish Infants

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Background: Growth during infancy is a continuation of the rapid fetal growth and its regulation is complex and multifactorial. It is well-established that insulin-like growth factor-I (IGF-I) and its regulators (e.g. IGF binding proteins (IGFBP-3) and pregnancy-associated plasma protein-A2 (PAPP-A2)) are important for prenatal and postnatal growth; however, their significance for growth during infancy is not fully explored.

Aims: The aim of this study was to evaluate length velocity, weight velocity and IGF-I concentrations and to explore the association between length and weight velocities and repeated IGF-I measurements in a large cohort of healthy infants followed prospectively from birth throughout first year of life.

Method: 233 infants (114 girls and 119 boys) participated in the longitudinal COPENHAGEN Minipuberty Study. We examined the infants six times during the first year of life. Length, weight and IGF-I were measured, and length and weight velocities were calculated. The infants were genotyped for *PAPPA2* (rs1325598).

Results: Length and weight velocities were high after birth, declined gradually and stabilized around 7th month of age in both boys and girls, but with markedly higher velocities and steeper declines in boys than in girls. At birth, IGF-I concentrations were higher in girls compared with boys (median concentration 78.7 and 69.5 µg/l, respectively, $p=0.05$), and increased significantly from birth to 10 days in boys (mean difference 24.8 ± 34.05 SD µg/l, $p<0.001$), but not in girls. Hereafter, IGF-I concentration increased significantly throughout the entire first year of life. In a univariate analysis, both mean length velocity (standard deviation score (SDS)) and mean weight velocity (SDS) were positively associated with mean IGF-I (SDS) ($\beta=0.12$ (95% CI, -0.0001-0.24), $p=0.05$ and $\beta=0.25$ (95% CI, -0.14-0.08), $p<0.001$). However, in a multiple regression analysis, only mean weight velocity (SDS) remained associated with IGF-I after adjusting for confounding factors (feeding pattern, birth weight, target height, body fat %, and *PAPPA2* genotype) ($\beta=0.19$ (95% CI, 0.05-0.33), $p=0.01$).

Conclusion: We present individual growth trajectories during the first year of life in 233 Danish infants. Weight velocity, but not length velocity, was positively associated with serum IGF-I concentration, but not *PAPPA2* genotype. This indicates that IGF-I promotes an overall gain in weight rather than length during first year of life.

FC9.6

Impact of pre-transplant serum-IGF-1 on hematopoietic stem cell transplantation outcome in pediatric cancer patients

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Background: Hematopoietic stem cell transplantation (HSCT) is associated with severe medical complications and variable outcome depending on the recipient's disease stage and health condition. As serum-IGF-1 is decreased in patients with severe illness, after major surgery, in malnutrition, and other conditions that cause catabolic metabolism, it may serve as predictive biomarker for transplant outcome.

Individuals and Methods: Based on patient records, laboratory files, and follow-up data from the German Childhood Cancer Registry, we evaluated the impact of pre-transplant serum-IGF-1 on both survival and adverse events in 587 pediatric cancer patients, who underwent autologous or allogeneic HSCT (in an age < 19 years) in 1987-2014 at the University Children's Hospital Tübingen, Germany. Serum IGF-1 was measured by an in-house

RIA (mean interassay CV 8.9%), which remained the same over the entire observation period.

Results: Mean pre-transplant IGF-1 ($n = 498$) was low: -1.67 SDS (SD, 1.54). Completeness of follow-up three and ten years post HSCT was 96 % and 83 % respectively. The ten-year overall survival was 44.8 % (95 % confidence interval [CI], 40.6-48.9). From IGF-1 SDS Quartiles 1 to 4, there was a significant decline of transplant-related mortality ($p = 0.0265$), veno-occlusive disease (12; 12; 1; 3 %; $p < 0.001$) and thrombotic microangiopathy (5; 2; 0; 0 %; $p = 0.004$). IGF-1 decile 1 showed a significantly poorer outcome ($p=0.042$) with lower median (12 versus 68 months) and ten-year overall survival (37 % versus 52 %) when compared to decile 2-10.

Conclusions: This study indicates pre-transplant serum-IGF-1 as a predictor of survival and selected vascular adverse events after HSCT that may have diagnostic and therapeutic relevance in pediatric cancer care.

Thyroid

FC10.1

Natural history of congenital hypothyroidism in the last two decades: what is changing? Experience of a single tertiary Italian paediatric centre

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Background and Aim: Congenital hypothyroidism (CH) is a well-known condition. Nevertheless, recent questions in clinical practice, especially in neonatal intensive care setting, prompted us to review the natural history of CH in our cohort.

Methods: This is a retrospective, observational study collecting anamnestic, anthropometric (height SDS, BMI SDS), diagnostic (TSH, fT4, thyroid ultrasound) and therapeutic data (dose of levothyroxine) in all children diagnosed of CH through national screening from January 2000 to July 2020 at our paediatric department. Data were collected at birth (T0), at 3 years old (T1), at onset of puberty (T2) and at final height (T3). Enrolled patients were retrospectively classified in persistent CH (pCH) or transient CH (tCH) according to clinical and biochemical subsequent trend. Statistical analysis was carried out on STATISTICA (StatSoft Inc, Tulsa, OK, USA) through Mann-Whitney U and Friedman ANOVA tests.

Results: Among 78 enrolled patients (51% females, 71% Caucasian), CH was permanent in 73% (9% thyroid agenesis, 19% ectopic gland, 9% hypoplastic gland, 63% gland in situ). At diagnosis, biochemical and therapeutic features were more severe in

pCH than in tCH (initial TSH 126.18 ± 181.68 vs. 43.25 ± 29.57 μ IU/ml, $p = 0.04$; starting levothyroxine dose 8.62 ± 8.80 vs. 5.73 ± 2.52 mcgr/kg/die, $p = 0.04$). Longitudinal analysis documented normal growth in pCH along follow-up (height SDS: T0 0.25 ± 1.39 , T1 -0.35 ± 1.06 , T2 0.10 ± 1.23 , T3 -0.05 ± 1.20 , $p = 0.82$, $X^2 = 0.90$). In pHC, 10.5% was preterm, while this rate increased to 28.6% in tCH group ($p = 0.04$). In pHC, at birth, preterm babies showed lower levels of TSH than ones at term (34.85 ± 20.86 vs. 131.08 ± 191.73 μ IU/ml, $p = 0.04$), an increased rate of gland abnormalities (50% vs. 29%) and the need of higher initial dose of levothyroxine (14.75 ± 24.29 vs. 6.83 ± 3.78 mcgr/kg/die, $p = 0.04$).

Conclusions: Our data confirm the increase of pCH with in situ gland than historically described and that an appropriate therapy ensures long-term normal growth. At birth, TSH levels and the initial dose of levothyroxine seem to predict pCH. Nevertheless, considering the increasing number of preterm births, our data underline the need to better describe pCH in this category of patients, taking into consideration their immaturity of both hypothalamic-pituitary-thyroid axis and biosynthetic functions, their nutritional deficiencies and increased tissue metabolism and the potential effect of concomitant therapies.

FC10.2

Prevalence and outcome of Congenital Central Hypothyroidism: A Multicenter Study

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Background: More than half of newborns with central congenital hypothyroidism (C-CH) have moderate-to-severe hypothyroidism in the neonatal phase, requiring immediate thyroxine

therapy to prevent brain damage. The Israeli newborn screening for CH is based on the measurement of total T4 (TT4) followed by TSH measurement. However, when TSH is within the normal range the physicians are not informed of the results and therefore the diagnosis of C-CH and initiation of L-T4 therapy are significantly delayed. This study aimed to assess the prevalence of C-CH in Israel and to characterize clinical features, neonatal screening results, the outcomes of children with C-CH.

Methods: In this multicenter, nationwide retrospective study data on 96 subjects (54 males) diagnosed with C-CH were collected from medical records from 9 Pediatric Endocrine Hospital Centers in Israel. Neonatal screening results were retrospectively retrieved from the computerized records of the National Newborn Screening Program between 2008 to 2021.

Results: The estimated prevalence of C-CH in the screened and studied population was 1:52000 live births and in the Northern region of Israel, where the consanguinity rate is high, the prevalence was 1:22000 live births. Seventy nine (82%) had combined pituitary hormone deficiencies (CPHD). The remaining 17 (18%) subjects had Isolated C-CH. Median and IQR (interquartile range) age at initial endocrine evaluation was 51(8-575) days. Median TSH and FT4 levels were 3.19 (1.78 - 5.25) mIU/l, and 9.00 (6.84 - 9.97) pmol/l respectively. At diagnosis 66% of patients had FT4 levels below 10 pmol/l. Neonatal screening results were available for 44 subjects with median TSH level 3.83 (2.56 - 6.69) (normal range for newborns (<20 mIU/l)) and TT4, for in term patients, was 6.7 percentile (6.68 (5.06 - 9.05)) mcg/dl. The diagnosis in the newborn period was based on signs and symptoms of hypopituitarism (40.8%), micropenis (23.5% of males). Growth failure (30%) and neurodevelopmental delay (7.8%) were the main reasons for diagnosis during infancy. Significant number of children 36 (37%) with CPHD and Isolated C-CH had neurodevelopmental sequelae included: mental retardation (18% and 7.7%); learning difficulties (27% and 23%), delayed speech (32% and 50%) and motor clumsiness (25% and 23%).

Conclusions: 1. Despite efforts to improve detection of all forms of congenital hypothyroidism with newborn screening, we found a significant delay in the diagnosis of C-CH. 2. At diagnosis, over half of the patients with C-CH had severe to moderate hypothyroidism, and a significant number of patients suffered from neurodevelopmental sequelae.

FC10.3

Genetic analyses in patients having congenital hypothyroidism with gland-in-situ by next-generation sequencing

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Introduction: Primary Congenital Hypothyroidism (CH) is an abnormal function of the thyroid gland present at birth. Anomalies of thyroid function are usually classified between thyroid dysgenesis, corresponding to an abnormal embryological development of the thyroid, and CH with gland-in-situ (GIS), resulting from mutations in genes involved in thyroid hormone synthesis. We report 105 patients with CH with GIS that have been referred to Angers University Hospital reference center for rare diseases of thyroid and hormone receptivity for genetic testing by next-generation sequencing (NGS).

Methods: 105 patients having a CH with GIS had a NGS containing 48 genes involved in thyroid development and metabolism, including *DUOX1*, *DUOX1*, *DUOX2*, *DUOX2*, *FOXE1*, *GNAS*, *HHEX*, *IYD*, *NKX2-1*, *NKX2-5*, *PAX8*, *SLC26A4* (*Pendrin*), *SLC5A5* (*NIS*), *TBX1*, *TG*, *TPO*, and *TSHR*. Patients were sorted in resolved, probably resolved or partially resolved genetic cases according to the gene involved (recessive or dominant), the classification of variants (pathogenic, likely pathogenic or of uncertain significance according to the guidelines of the American College of Medical Genetics) and the potential familial segregation.

Results: Genetic testing identified 99 variants in 10 genes: *DUOX1*, *DUOX2*, *DUOX2*, *NKX2-1*, *PAX8*, *SLC26A4*, *SLC5A5*, *TG*, *TPO* and *TSHR*. These variants allowed to solve 29 genetic cases (28%), to have a probable resolution for 20 of them (19%) and to partially solve 22 cases (21%). Among patients having a neonatal TSH ≥ 100 mIU/L ($n=23$), 74% were probably solved or solved cases, whereas when TSH was < 40 mIU/L ($n=28$), only 5 patients (18%) were probably solved or solved cases. Eight patients carrying heterozygous variants on 2 different genes, they were categorized as partially solved cases (digenism?).

Conclusion: We can recommend NGS sequencing for every patient having CH with GIS. The study of environmental factors would be interesting in CH with GIS having neonatal TSH < 40 mIU/L. The transient or permanent nature of these CH remains to be established.

FC10.4

Towards a novel genetic model for Congenital Hypothyroidism due to thyroid dysgenesis

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Background: Congenital hypothyroidism (CH) affects one in 3000 children at birth. In 65% of cases, CH is due to thyroid dysgenesis (CHDT). For CHDT, there is a family component and therefore genetic. Over the past 20 years, disease-causing mutations in 10 genes have been implicated in CHDT cases (*NKX2-1/TTF1*, *FOXE1/TTF2*, *NKX2-5*, *PAX8*, *GLIS3*, *NTN1/Netrin-1*, *JAG1*, *BOREALIN/CDCA8*, *TUBB1* and *TSHR*). In the vast majority of cases, the inheritance model is autosomal dominant. However, less than 10% of all CHDT patients have a mutation in one of these genes. Except for the 10 genes above, in our knowledge, other genes are involved in the development of the thyroid in mice, zebrafish or *in vitro*, which prompted us to explore genetic aspects of these genes in humans.

Aim of the Study: To perform both a genetic inventory and genes interactions of all the known genes involved in the thyroid development by searching for molecular variants of these genes in a group of patients with a very well-described CHDT.

Methods: Patients were recruited through HYPOTYGEN Programme Hospitalier de Recherche Clinique (PHRC). HYPOTYGEN study is a multi-center cross-sectional clinical trial which aims to describe the population with CHDT. 482 patients with CHDT were collected and DNA samples from more than 318 CHDT patients have been sequenced through a custom-targeted NGS panel (n=79), which were compared with 709 controls. Then, statistical analysis were performed to compare these two groups.

Results: We confirmed that patients with CHDT have a disease-causing mutation in one of the 10 known genes in 7.9% of cases. By comparing the sequencing results in the group of CHDT patients *versus* controls, we found variants in genes involved in the development of the thyroid, not yet involved in humans, i.e. *EDN1*, *EYA1*, *CHRD*, *ISL1*. However, the results are more complex than expected. We found, in a very interesting way, an oligogenism in the CHDT cohort as compared to the controls ($P<0.01$). CHDT have a more complex origin than that described so far and the accumulation of our knowledge allows us to refine the genetic diagnosis of CHDT.

Conclusion: Beyond the monogenic model, we found an oligogenic one that explain 6.2% of the CHDT patients. The main challenge in the next years will be to enhance our understanding in the pathogenesis of CHDT by using a new paradigm, the oligogenism model on known genes.

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FC10.5

Adjuvant Rituximab – exploratory trial in young people with Graves' disease

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Objective: Remission rates in young people with Graves' hyperthyroidism are 25% or less after a 2-yr course of thionamide antithyroid drug (ATD). Immunomodulatory agents could potentially improve outcome by facilitating immune tolerance. We wanted to explore whether rituximab, a B lymphocyte depleting

agent, would increase remission rates when administered with a short course of ATD.

Design: This was an investigator-initiated open label multi-centre single arm phase 2 trial in young people (12-20 years) with Graves' hyperthyroidism. The trial used an A'Hern design to distinguish an encouraging remission rate of 40% from an unacceptable rate of 20%, with power of 80% and Type I error of 10%. Participants presenting with Graves' hyperthyroidism received a single 500mg dose of rituximab (RTX) followed by up to 12 months of ATD titrated according to thyroid function. The primary end-point was relapse at 24 months (12 months without ATD) as judged by suppressed serum TSH and raised FT3; or they had restarted ATD between months 12 and 24; or they had thyroid surgery or radioiodine therapy at any time following RTX.

Results: Twenty-seven participants were recruited from 6 UK centres. All completed the trial and there were no serious side effects linked to treatment. The daily ATD dose at 12 months was 5mg or less in 20/27 participants. 13 of the 27 participants were in remission at 24 months (48%, 90% one-sided confidence interval 35%, 100%); this number exceeded the critical value (9) for the A'Hern design and provided evidence that the remission rate exceeded 40%. Two of the 13 participants in remission had low TSH and elevated thyroid receptor antibody titre and were considered at high risk of relapse. B lymphocyte count at 28 weeks, expressed as a percentage of baseline value, was related to likelihood of remission but there was no evidence of a difference between remission/relapse groups in terms of total ATD dose received or time to non-suppressed TSH.

Conclusions: This trial indicates that adjuvant rituximab, administered with a 12 month course of ATD, may increase the likelihood of remission in young people with Graves' hyperthyroidism. B cell count at 6 months may be a pointer towards a favourable outcome. This data suggests that a formal randomised trial of adjuvant rituximab in young people with Graves' hyperthyroidism is warranted.

FC10.6

Clinical features and long-term follow up of childhood papillary thyroid cancer (PTC): a single reference-center experience

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Background: Thyroid cancer before 20 years of age constitutes less than 2% of thyroid malignancies. Adult guidelines have been used in evaluation and follow-up of children until 2015. Features

and long-term results of more children with PTC are needed to improve the ATA guideline for children. The aim of this study is to evaluate children with PTC in the last 15 years in a single reference-center, and assess the convenience of ATA 2015 guideline in practice.

Methods: 66 cases with PTC (F/M:48/18) are analyzed, retrospectively. Clinical features, treatment and their impact on prognosis are examined. Patients with >1.5 years follow-up were stratified for risk using the latest ATA guideline for prognosis evaluation.

Results: Median age at diagnosis was 12.2 years, and 30% were <10 years old. Multifocal, bilateral tumor, and lymph node metastases (LNM) were present in 58, 37, and 57.5% of patients, respectively. Among 38 patients with LNM, 24 (63%) had only LNM, the remaining had also local invasion and/or distant metastasis. LN and lung metastasis at diagnosis were more frequent in patients with large, bilateral and multifocal tumors. Total resection was performed in all children but one. LN dissection (LND) was performed in 68% (37% central±lateral, 31% berry picking). 8 patients underwent re-LND and 1 patient residual tumor excision after postoperative ¹³¹I whole body scanning, stimulated thyroglobulin and neck ultrasound. All patients received radioactive iodine treatment (30-150 mCi). 46 patients were followed for >1.5 years, 34 (73%) were in remission, 8 (17%) had persistent and 4 (10%) had recurrent disease. 88% (15/17) with solitary tumor nodules and 65% (19/29) with multifocal tumors achieved remission (p=0.08). Achievement of remission according to ATA 2015 risk stratification revealed that 95% (19/20) of low-risk, 62% (5/8) of moderate-risk and 55% (10/18) of high-risk went into remission, all after RAI treatment. In the low-risk group post-operative screen with RAI showed persistent local disease in 60%. Among patients with moderate/high-risk PTC, remission rate was higher in patients with solitary tumor nodule in comparison to multifocal tumor (75% vs 54%).

Conclusion: Multifocality decreases remission rate, thus it should be included in risk assessment of pediatric cases with PTC. It seems post-operative RAI screen and treatment is still crucial in achievement of remission in low-risk PTC.

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ePoster Presentations

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ePoster Category 1

Adrenal A

P1-1

Optimizing the timing of highest hydrocortisone dose in children and adolescents with 21-hydroxylase deficiency

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Context: Children with 21-hydroxylase deficiency (21OHD) require chronic glucocorticoid administration to substitute glucocorticoids and suppress adrenocorticotrophic hormone-induced hyperandrogenemia. There is still no evidence about the best

timing of the highest hydrocortisone (HC) dose. Administration of the highest dose in the morning aims to mimic the physiological rhythm of cortisol, while a high dose late in the evening may inhibit the early-morning increase in androgens more effectively.

Objective: The primary aim was to compare two standard HC timing strategies, either the highest dosage in the morning or the highest dosage in the evening, with respect to hormonal status throughout the day of children and adolescents with 21OHD. The secondary objective was to evaluate these treatment regimens with respect to nocturnal blood pressure, and sleep- and activity scores.

Design: A six-week cross-over study was performed.

Patients and Interventions: Thirty-nine children and adolescents (age 4-19 years) with 21OHD were treated for three weeks with highest HC dose in the morning, followed by three weeks with highest dose in the evening (n=21), or the other way around (n=18). During the last two consecutive days of each treatment period, patients collected saliva at 5.00 am; 7.00 am; 3.00 pm; and 11.00 pm. Androstenedione (A4) and 17-hydroxyprogesterone (17OHP) levels in saliva were quantified using liquid chromatography-mass spectrometry. Overnight blood pressure was measured in the last week of each treatment period and sleeping and activity scores were reported for each day during the entire six-week period.

Results: Administration of the highest dose in the evening resulted in significantly lower 17OHP levels in the early morning (5.00 am) but not at 7.00 am, whereas the highest dose in the morning resulted in significantly lower 17OHP and A4 levels in the afternoon. Interestingly, a persistent circadian rhythm of 17OHP and A4 was observed during both treatment regimens. No substantial differences in overnight blood pressure, activity scores, or sleeping scores were found between the two treatment regimens.

Conclusion: The two treatment dose regimens were comparable with respect to overall daily hormonal control, nocturnal blood pressure, and subjective activity and sleep scores. A high-evening-dose regimen resulted in more effective inhibition of the 17OHP rise in the early morning, whereas a high-morning-dose regimen resulted in more effective 17OHP and A4 inhibition in the afternoon. We suggest to individually optimize dose distribution and recommend monitoring disease control at multiple timepoints a day, as single measurements do not reflect hormonal status throughout the day.

P1-2

Adrenocortical hormone profiles do not predict the molecular etiology in non-CAH primary adrenal insufficiency

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Background: Primary adrenal insufficiency other than congenital adrenal hyperplasia (non-CAH PAI) is very uncommon in children but associated with a variety of molecular defects. Biosynthesis of adrenocortical hormones is reduced although the relation of steroid profiles with underlying molecular etiology is not yet studied.

Objective: Investigation of clinical and steroid hormone profiles of a multicenter cohort of children with non-CAH PAI.

Design: Patients with CAH, adrenoleukodystrophy, autoimmune adrenal insufficiency or obvious syndromic PAI on clinical and biochemical assessment were excluded. Genetic analysis was performed using either targeted gene panel or whole-exome sequencing. Plasma adrenal steroids were quantified by liquid chromatography-mass spectrometry and compared to that of controls.

Setting: Sixteen tertiary pediatric endocrinology clinics.

Patients: Forty-one children (19 females, median age: 3 months, range: 0-8 years) with non-CAH PAI of unknown etiology.

Results: A genetic diagnosis was obtained in 29 (68%) patients by targeted gene panel. Further molecular diagnosis could not be achieved by WES. The range of etiologies was: *MC2R* (n=6), *StAR* (n=6), *NNT* (n=3), *NROB1* (n=3), *CYP11A1* (n=2), *MRAP* (n=2), *SGPL1* (n=2), *ABCD1* (n=1), *AIRE* (n=1), *AAAS* (n=1), *HSD3B2* (n=1). Steroid profiling demonstrated low levels in all adrenocortical steroid hormones irrespective of age and not varied among the genetic etiologies except two patients with new-onset symptoms of PAI due to homozygous c.518T>A(p.Leu173Gln) *SGPL1*, and hemizygous c.1772G>T(p.Arg591Leu) *ABCD1* defects, and another patient with non-classic non-CAH PAI due to homozygous c.1351C>T (p.Arg451Trp) variant in *CYP11A1*. Compared to age-matched healthy control group in whom steroid hormone concentrations are physiologically low, the patient group had even lower steroid concentrations, most significantly in cortisone, cortisol, and corticosterone ($p<0.0001$, area under the ROC curve: 0.96, 0.88, 0.87, respectively). Plasma cortisol<4 ng/mL, cortisone<11 ng/mL, and corticosterone<0.11 ng/mL had >95% specificity to segregate non-CAH PAI patients compared to control groups.

Conclusion: Adrenocortical hormone profiles are highly sensitive for the diagnosis of non-CAH PAI, while, in contrast to CAH, they are unlikely to point out a specific molecular diagnosis. Targeted gene panel sequencing is an undisputed optimal approach in the molecular diagnosis of non-CAH PAI with low cost and high efficacy, while little additional benefit is expected from whole-exome sequencing. Further progress can be made, mainly by more collaboration and exchanging knowledge for delineation of rare causes of primary adrenal insufficiency.

P1-3

Growth-Related Characteristics of Patients <18 Years of Age with Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency (21OHD): Real-World Evidence from the I-CAH Registry

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Background: Classic congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is a rare autosomal recessive condition characterized by cortisol deficiency and elevated ACTH secretion, resulting in excess androgen production. This exposure to excess androgens contributes to advanced skeletal maturation and reduced growth in puberty. Data from the I-CAH registry were analyzed to identify growth-related characteristics of children and adolescents with classic CAH.

Methods: The I-CAH registry was queried on 02-April-2021 using the following criteria: CYP21A enzyme deficiency; male or female, age <18 years; and ≥ 1 growth-related assessment. Data from all patient visits were analyzed descriptively by sex and age (0-<2, 2-5, 6-9, 10-13, 14-17 years). Since I-CAH data are longitudinal, patients who aged during registry enrollment were included in >1 subgroup. Using WHO growth chart data as reference, standard deviation scores (SDS) were analyzed for height for chronological age (CA) and height for bone age (BA).

Results: Analyses included 431 patients (ages 0-17 years, female=57%, male=43%). The number of patients/visits, bone age, and growth characteristics (median SDS) by age are presented in the table. Height for CA indicated a trend for shorter height relative to age, with males 14-17 years having more pronounced height deficits than females. Mean BA was advanced by 7.2 months compared to CA (SD=36.6 months, 95% CI=-10.1 to -4.3 months [$p<0.0001$]), which was less pronounced in females (4.2 months) than males (11.3 months).

Conclusions: This is the first study to examine growth-related characteristics using data from the entire I-CAH registry. Exploratory analyses of this dataset indicate that children/adolescents with classic CAH are shorter relative to CA even before 10 years of age, despite having an advanced BA, which further reduces their height potential and highlights the importance of proper glucocorticoid and disease management during pubertal growth.

	Patients With Classic CAH by Age, Years					
	All	0-<2	2-5	6-9	10-13	14-17
Median CA, overall (years)	3.2	1.1	3.3	7.8	11.8	15.9
Height for CA, #patients/visits	431/4029	332/1349	314/1435	136/598	98/371	77/276
Median SDS, overall	-1.24	-3.53	-1.08	-0.15	-0.30	-0.61
Median SDS, females	-1.20	-3.32	-1.07	-0.35	-0.53	-0.44
Median SDS, males	-1.33	-3.80	-1.12	0.43	0.36	-1.50
Median BA, overall (years)	8.0	1.0	3.0	10.0	12.0	14.0
Height for BA, #patients/visits	197/594	38/35	144/238	73/174	58/115	27/32
Median SDS, overall	-0.50	2.21	0.28	-1.25	-0.94	-0.71
Median SDS, females	-0.40	2.91	0.24	-1.14	-0.75	0.01
Median SDS, males	-0.55	2.21	0.42	-1.83	-1.29	-0.97

P1-4

Depression among insured children and young adults in the United States with congenital adrenal hyperplasia

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Background: Individuals with congenital adrenal hyperplasia (CAH), a form of adrenal insufficiency, are exposed to daily non-physiologic, non-circadian cortisol profiles due to both the disease and therapeutic limitations. Dysfunction in the hypothalamic-pituitary-adrenal axis is strongly associated with depressive disorders. However, little is known about the prevalence of depression among children and young adults with CAH. We investigated the prevalence of depressive disorders in a large administrative sample of insured children and young adults with CAH as compared to their peers without CAH in the United States.

Methods: We used the Treatment Pathways® interface to analyze claims data for individuals enrolled in employer-sponsored health insurance plans. We reviewed claims between October 1, 2015 and December 31, 2019 for subjects between the ages of 4 and 25 years. CAH prevalence was measured as the percentage of subjects with ≥2 claims with E25.0 ICD-10 codes for CAH and ≥2 glucocorticoid prescriptions filled during the study period. Depression prevalence was measured as the percentage of subjects with ≥2 outpatient claims or ≥1 inpatient claim with an ICD-10 code for a depressive disorder. We compared the prevalence of diagnosed depressive disorders in subjects with and without treated CAH, both overall and stratified by age group (4-11 years, 12-17 years, and 18-25 years). A combined adolescent and young adult group (12-25 years) was used to stratify by gender.

Results: The study period prevalence of CAH for individuals aged 4-25 years was 1/11,660 (n=1,056). Among those with CAH, there was a higher unadjusted prevalence of depression (7.8%, n = 82, prevalence ratio (PR) = 1.57, 95% confidence interval (CI): 1.28-1.94, p<0.001) as compared to their peers without CAH (4.9%, n = 607,692). The prevalence of depression was higher among those with CAH across all age groups; however, this difference reached statistical significance only in the young adult group (12.6% vs. 6.9%, PR = 1.57, 95%CI: 1.28-1.94, p<0.001). The prevalence was also significantly higher among both males (PR = 2.24, 95%CI: 1.62-3.09, p<0.001) and females (PR = 1.34, 95%CI: 1.04-1.74, p<0.05) in the combined adolescent and young adult group with CAH.

Conclusions: Using a large administrative sample of privately insured children and young adults in the United States, we found that the prevalence of depression was significantly higher among those with CAH. Enhanced screening for symptoms of depression among the pediatric and young adult population with CAH may be warranted if these associations are confirmed in further research.

P1-5

Alterations in resting-state functional connectivity in patients with congenital adrenal hyperplasia

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Background: Patients with congenital adrenal hyperplasia (CAH) are treated with life-long glucocorticoid (GC) replacement therapy. Negative effects on cognition, brain structure and function during working memory tasks have been identified. To date, no studies on functional connectivity during rest have been performed in patients with CAH. One study conducted on patients with Cushing's syndrome, another disorder of cortisol imbalance, suggests that long-term cortisol excess results in increased connectivity within the default-mode network (DMN), in particular medial temporal lobe and prefrontal cortex. Interestingly, the precuneus, which was reduced in volume in our study in CAH patients

(Van't Westeinde et al. 2019) is functionally connected to both the fronto-parietal and the default mode network. Thus, altered structure, as a result of prolonged cortisol imbalance, might result in altered connectivity of both working memory and default mode network.

Objective: To investigate resting-state functional connectivity in patients with CAH compared with healthy untreated controls and the association between functional connectivity in our region of interest (ROI) and disease severity, dose of GC and visuo-spatial working memory.

Design, Setting and Participants: Thirty-one patients with CAH (18 females) and 38 healthy controls (24 females), aged 16-33 years, from a single research institute, underwent functional magnetic resonance imaging of the brain during rest. Two patients in the CAH group had non-classic (NC) CAH, 13 had simple-virilising (SV) CAH and 16 had salt-wasting (SW) CAH.

Results: Patients with CAH showed increased functional connectivity in the precuneus compared with controls. However, activity was not associated with executive functions. Analyses in this ROI indicated a significant quadratic association between genotype, phenotype and functional connectivity. Patients with the null genotype showed reduced functional connectivity, whereas patients with non-null and simple virilising genotypes exhibited increased functional connectivity in the precuneus.

Conclusion: Patients with CAH demonstrated altered functional connectivity during rest in the precuneus. Such a change may reflect a functional reorganisation in response to the CAH disease. The change in functional connectivity may depend on the severity of CAH.

P1-6

International practice of therapy monitoring in congenital adrenal hyperplasia – Real World data from the I-CAH registry

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Aim: Recommendations for the management of Congenital Adrenal Hyperplasia (CAH) outline a target 17-OH Progesterone (17OHP) of 12–36 nmol/l, but do not specify target concentrations for Androstenedione (D4). We aimed to study the temporal variations of these biomarkers in patients from different geographical regions.

Method: This retrospective multi-centre study, including 21 centres (14 countries), analysed serum biomarker data from the International-CAH Registry. Data was available from 345 patients (52% females) under 18 years (median age 4.3 years IQR (Interquartile Range) 3.1 to 9.2 years) with classic 21-hydroxylase deficiency under follow-up between 2000 to 2020.

Results: Analysing each patient's most recent biomarkers, median 17OHP for males was 33.0 nmol/l (n=160, IQR: 6.0, 93.2), 17.5% values within and 49.4% above target. For females, median 17OHP was 40.0 nmol/l (n=180, IQR: 3.0, 120.3), no different to males ($p>0.05$), 14.4% within and 50.6% above target. 17OHP did not vary with age, but D4 increased by 0.95 nmol/l per year of age in males (intercept = -1.61, $R^2 = 0.17$, $p<0.001$) and 0.57 nmol/l per year of age in females (intercept = 2.0, $R^2 = 0.06$, $p=0.003$). In children under 12 years, median D4 in males and females was 0 nmol/l (n=127, IQR: 0, 2.0) and 0 nmol/l (n=116, IQR: 0, 2.0), respectively, whereas in those over 12 years, median D4 in males and females was 10.2 nmol/l (n=22 IQR: 4.0, 24.4) and 11.0 nmol/l (n=33 IQR: 3.9, 18.0), respectively. There was no difference in median 17OHP or D4 concentrations in the last 20 years (comparison of 5 year periods, $p>0.05$). Comparing centres with over 10 readings available, there were differences in median 17OHP in both sexes, ranging from 0.7 nmol/l (IQR: 0.03, 40.7) up to 104.4 nmol/l (IQR: 47.7, 242.1), ($p<0.01$), but no significant difference between D4 readings in those under or over 12 years ($p>0.05$). Where paired readings were available, 17OHP correlated with D4 in both male patients ($R^2=0.18$, $p<0.001$) and female patients ($R^2=0.21$, $p<0.001$)

Conclusions: Data from the I-CAH Registry show large variability in 17OHP and D4, with 17OHP most commonly above target range and D4 concentrations varying with age, and significant variability in 17OHP between centres. Concordance between the biomarkers suggests both have utility in disease monitoring. Further research is needed to establish optimal age- and sex-specific D4 targets in patients with CAH, to develop strategies for using these biomarkers in combination as monitoring tools, and to work towards standardising treatment to reduce unwarranted variation.

P1-7

Brain activity during working memory in congenital adrenal hyperplasia

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Objective: Congenital Adrenal Hyperplasia (CAH) requires life-long replacement of cortisol. However, this long-term GC-treatment could change the developmental trajectory of the brain and predispose patients to problems with cognition and mood regulation. Previously, we have found impairments in working memory in patients with CAH, as well as alterations in brain structure in regions of the central executive network (CEN). These changes could be associated with differences in brain function during working memory. The present study therefore sought to compare working memory related brain activity between patients and healthy controls.

Methods: 29 patients with CAH (17 female) and 40 Controls (24 female), aged 16–33 years, underwent MRI 3T scanning while performing a verbal and visuo-spatial working memory task. Functional MRI images were analyzed with FSL FEAT to compare brain activity during the encoding and decoding phases of working memory between patients and healthy controls. In addition, interactions between group and sex on brain activity were assessed.

Results: On the whole group level, no differences in brain activity were found between patients and controls. However, there was an interaction with sex, during the decoding phase of visuo-spatial working memory. Males with CAH showed stronger activity in regions of the left parieto-occipital network, while females with CAH showed reduced activity in these areas. These regions are known to be involved in the processing of visuo-spatial information. However, activity changes were not associated with working memory performance or structure of regions of the CEN.

Conclusion: Overall, the brains of patients with CAH seemed to be able to compensate to healthy activity levels during working memory, despite thinner cortices in the working memory network. However, hubs of the left dorsal-visual stream might be more sensitive for GC-disturbances in a sex-dependent manner. Future studies are needed to investigate sex-differences in brain activity in patients with CAH, and treatment optimization strategies to optimize brain function.

Long-Term Cardiometabolic Morbidity in Young Adults with Classic 21-Hydroxylase Deficiency Congenital Adrenal Hyperplasia

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Background: Congenital adrenal hyperplasia (CAH) and long-term glucocorticoid treatment may be associated with an increased risk of developing cardiometabolic sequelae such as abnormal glucose homeostasis, hyperlipidaemia, hypertension, cardiovascular (CV) disease, obesity and osteoporosis.

Objectives: To study the current practice amongst expert centres for assessing cardiometabolic outcomes in adult patients with 21-hydroxylase CAH and to assess the prevalence of cardiometabolic morbidity.

Methods: Data were collected using a structured questionnaire sent to 46 centres managing adults with CAH within three overlapping networks: International Congenital Adrenal Hyperplasia (I-CAH) Registry, CaH Adult Study Executive (CaHASE) Consortium UK and European Reference Network on Rare Endocrine Conditions (Endo-ERN). Information collected included current therapy and surveillance practice of adults with CAH with emphasis on cardiometabolic conditions.

Results: Thirty-one (67%) centres from 15 countries completed the survey. Thirty (97%) centres screened patients for hypertension by measuring blood pressure during clinical routine examination. Thirty (97%) screened for obesity by mainly using BMI (87%) and weight (81%). Twenty-six (84%) centres screened for abnormal glucose homeostasis by mainly using Hb1Ac (61%) and fasting plasma glucose (42%). Twenty-five (81%) centres screened for osteoporosis mainly by using DXA scans (74%). Twenty (65%) centres screened for hyperlipidaemia using fasting lipids. Five (19%) routinely screened patients for other CV disease. Out of 255 adults with a median age of 32 yrs (range, 19,94) from 13 centres, 93 (36%) had obesity/overweight, 58 (23%) osteoporosis/osteopenia, 50 (20%) hyperlipidaemia, 20 (8%)

T2DM/hyperinsulinaemia, 18 (7%) hypertension and 10 (4%) CV disease. Of these 255, 78 (30%) were receiving therapy for cardio-metabolic morbidity and, of these, 17 (7%) were treated for 2 or more comorbidities. Of the total affected by each comorbidity, the number of patients who received therapy for obesity/ overweight, osteoporosis/osteopenia, hyperlipidaemia, hypertension, CV disease and T2DM/ hyperinsulinaemia was 3 (3%), 43 (74%), 17 (34%), 10 (56%), 8 (80%) and 18 (90%), respectively. The median age at start of therapy for obesity/overweight, osteoporosis/osteopenia, hyperlipidaemia, hypertension/CV disease and T2DM/ hyperinsulinaemia was 27 yrs (17,55), 34 (18,63), 55 (19,79), 57 (39,72) and 27 (14,78), respectively. For some conditions such as hypertension there was a wide range of drugs used (8 drugs in 18 patients).

Conclusions: Cardiometabolic morbidities are not uncommon in adults with CAH. There is a need for greater standardisation of the screening for these morbidities from early adulthood and there is a need to explore optimal therapy through routine collection of standardised data.

P1-9

Backdoor Pathway hormones and 11-oxygenated Androgens are elevated in Patients with 21-hydroxylase deficiency

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Background: Patients with 21-Hydroxylase deficiency (21OHD) present increased levels of cytochrome P450 21-hydroxylase substrates, like progesterone and 17 α -hydroxyprogesterone. Previous studies could show that these hormones are involved in the production of androgens via the backdoor pathway. As a second source of androgens, 11-oxyandrogens derived from the human adrenal glands are recognized as being major androgens. Specifically, 11-oxyandrogens are active androgens in many patients with 21-hydroxylase deficiency.

Methods and Patients: We developed an LC-MS/MS method for the determination of 5 α -pregnane-3 α ,17 α -diol-20-one (pdol), androstenediol, androsterone, dihydrotestosterone (DHT), androstenedione, testosterone, 17-hydroxyprogesterone (17OHP), 11-ketotestosterone (11KT), 11-ketoandrostenedione (11A4), 11-ketodihydrotestosterone (11KDHT) for plasma and serum. We compared the steroid profiles of 56 treatment-naïve 21-OHD patients (25 males, 31 females, aged 0-19 years) and 63 age-matched control subjects.

Results: 21-OHD patients had significantly higher concentrations for 11KT, 11A4 ($p < 0.001$, respectively). We also found higher concentrations for pdol ($p < 0.0001$) and androsterone in males ($p = 0.001689$). We revealed a strong correlation of 11KA4 ($r = -0.87$, $p = 0.001$) and 11KT ($r = -0.83$, $p = 0.001$) with the functional severity according to the underlying CYP21A2 genotype.

Conclusion: We developed a reliable LC-MS/MS assay for an extended "androgen profile" representing ten steroids covering androgen biosynthesis of the classical, the so called "backdoor" pathway and the 11-oxyandrogens. In our cohort, we could demonstrate that 11-oxyandrogens are elevated in 21OHD patients.

P1-10

Glucose regulation in children with primary adrenal insufficiency: preliminary data

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Background: During treatment of adrenal insufficiency (AI) with hydrocortisone (HC), cortisol concentrations are supra-physiological following doses, and low before doses. We speculated that this cortisol profile may result in periods of hyperglycaemia and hypoglycaemia. We describe glucose profiles in the first 18 children recruited to a study of metabolic and cardiovascular profiles in AI.

Methods: Children with primary AI, treated with HC underwent continuous glucose monitoring (CGM) for 7 days using the Dexcom G6 device, blinded to participants. Data were interpreted using published data from 57 healthy children [1] and are shown in table 1.

Results: Eighteen children (9M, two Addison's disease, 16 congenital adrenal hyperplasia (CAH)), aged 8.1yrs (range 2-16) participated. Mean HC dose was 10.8mg/m²/day (5.6-22.5), height SDS -0.07 (-2.03-2.59) and body mass index (BMI) SDS 0.70 (-0.7-3.7). Total number of glucose measurements was 1846 (688-2017). One child could not tolerate CGM.

Table 1. Table showing glucose data compared to healthy controls [1].

Hypoglycaemia: Three out of eighteen children had glucose measurements < 3 mmol/L for 1-2% of readings. In one child, glucose was < 3 mmol/L on 2% of readings and < 4 mmol/L for 11% of readings. Their BMI SDS was 0.6 and HC dose 9.2mg/m²/day.

Hyperglycaemia: Four out of eighteen children had glucose measurements > 10 mmol/L for 1-2% of readings, and > 14 mmol/L for 1% of readings in one. HC doses in these children were 7.8-9.4 mg/m²/day and BMI SDS -0.7-0.7. Hyperglycaemia was more likely following morning and evening doses of hydrocortisone.

Parameter	Grace study (n = 17)	Reference data 6 to <12y (n = 27)	Reference data 12 to <18y (n = 30)
Mean glucose (1SD)	6.05 (± 0.51)	5.50 (± 0.39)	5.40 (± 0.39)
Standard deviation of measurements	1.01 (± 0.47)	0.89 (± 0.39)	0.83 (± 0.33)
% of time < 3mmol/L (median, IQR)	0.00 (0.00-0.24)	0.00 (0.00-0.20)	0.00 (0.00-0.40)
% of time >10mmol/L	1.26 (0.00-1.52)	0.00 (0.00-0.10)	0.00 (0.00-0.00)

Conclusion: To our knowledge, these are the first data describing glucose profiles in children with primary AI. These preliminary data suggest both hypoglycaemia and hyperglycaemia may occur more commonly than in healthy children, with an overall trend for higher mean glucose concentrations. Disturbance in glucose metabolism may contribute to differences in cognitive function reported in childhood (hypoglycaemia), and impaired quality of life, metabolic and cardiovascular disease reported in adults (hyperglycaemia, increased glycaemic excursions).

Reference

1. Shah, V.N., et al., *Continuous Glucose Monitoring Profiles in Healthy Nondiabetic Participants: A Multicenter Prospective Study*. J Clin Endocrinol Metab, 2019. **104**(10): p. 4356-4364.

Bone A

P1-11

Bone and endocrine monitoring in boys with Duchenne Muscular Dystrophy

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Background: In 2020, a UK wide collaborative project between clinicians and patient organisations (Funding from Duchenne UK) called DMD Care UK was launched. The project aims to define the care standards which should be implemented as a

priority in all UK centres. Adapting recommendations from the 2018 international care consensus, items were highlighted and used as standards for this audit in one tertiary centre. The standards are that all boys with DMD

- Should be on vitamin D supplementation.
- Should have vitamin D levels checked every 12 months.
- Should have lateral spine imaging to identify vertebral fracture every 12 months
- On glucocorticoid therapy should have access to hydrocortisone for injection during severe acute and/or vomiting illness
- Should have pubertal assessment if aged 12 years or older.

Methods: All boys with DMD under routine clinical follow-up of the neuromuscular team in Glasgow in 2019 were identified from a departmental database. Results were presented as median (range).

Results: A total of 49 patients were identified. Forty were on GC therapy; 4/9 not on GC were GC naïve. Median age of the boys was 11.5 years (3.0, 17.4). Forty-seven of 49 (96%) were prescribed vitamin D supplementation [Target 100%]. The two who were not on vitamin D supplementation were recently diagnosed. Thirty-eight of 49 (78%) had vitamin D levels measured in 2019. Excluding the 4 GC naïve boys (who were only diagnosed in < 12 months from the last clinic visit in 2019), 23/45 (51%) had vitamin D levels measured in 2019 and 12 months prior [Target 80%]. Thirty-six out of 49 (74%) had lateral thoracolumbar spine x-ray performed in 2019. Similarly, excluding the 4 GC naïve boys, 15/45 (33%) had lateral thoracolumbar spine x-ray performed in 2019 and 12 months prior [Target 80%]. Of the 40 on GC therapy, 39 (98%) has access to injectable hydrocortisone for use out of the hospital for severe and/or vomiting illness [Target 100%]. All 39 patients had receive training on injecting hydrocortisone. Of the 21 boys who were 12 years or older, all 21 boys (100%) had at least one documented assessment of puberty [Target 80%].

Conclusion: This single-centre audit of endocrine and bone monitoring in DMD showed variable degree of adherence to current international and national guidance. The audit standards and target can now be used for collecting clinical outcomes wider in the UK. Such plans are in discussion but require buy-in from numerous stakeholders.

P1-12

Real-world clinical profiles of children with hypophosphatasia (HPP) from the Global HPP Registry

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Hypophosphatasia (HPP) is a rare, inherited metabolic disease caused by deficient activity of tissue non-specific alkaline phosphatase (TNSALP). In children, HPP has a heterogeneous clinical presentation, frequently with nonspecific musculoskeletal and systemic manifestations, often leading to misdiagnoses and substantial delays in diagnosis. Data from 323 children with confirmed HPP diagnosis (aged <18 years, ALP activity below the reference range and/or *ALPL* mutation) enrolled in the Global HPP Registry were analyzed (1) to better understand the most common clinical profiles of children with HPP and (2) to evaluate the potential differences in baseline signs and symptoms prior to the decision to start treatment with the enzyme replacement therapy (ERT) asfotase alfa.

In the whole cohort, the median age at enrollment was 5.4 years and 52.6% were girls. Based on medical history, dental issues constituted the most frequent symptoms (56.0%; mostly early loss of primary teeth). Skeletal manifestations, including bone deformity, rickets, and other signs/symptoms, were observed in 45.2% of children. A subset of patients reported failure to thrive (21.1%) and muscle weakness (20.7%). Only a small proportion of patients reported recurrent fractures or pseudofractures (7.4%).

Of 323 children, 151 received ERT, while 172 did not. Untreated patients had a median of 2 HPP signs and symptoms, predominantly dental manifestations. In contrast, patients who eventually received ERT had a median of 4 HPP signs and symptoms at baseline, and had a proportionally higher frequency of bone deformity, rickets, failure to thrive, muscle pain and weakness, and gross motor impairment compared with untreated patients.

These results establish real-world clinical profiles of children with HPP. At baseline, dental manifestations were frequent in both groups of patients, and the predominant in those not receiving ERT whereas skeletal manifestations were the most important ones in the group receiving ERT. Baseline medical history, however, documented systemic manifestations of HPP in both the ERT treated and untreated groups including muscle pain, muscle weakness, and abnormal gait. These findings highlight the importance of considering non-skeletal manifestations as part of the clinical spectrum of HPP and in the initiation of ERT.

P1-13

Characterisation and phenotype-genotype associations of a large cohort of patients with pseudohypoparathyroidism type 1A and 1B

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Background and Objective: Pseudohypoparathyroidism (PHP) is a heterogeneous condition, principally causing parathyroid hormone (PTH) resistance. PHP1a is also associated with Albright's hereditary osteodystrophy (AHO), resulting from heterozygous inactivating mutations on the maternally derived *GNAS* allele. PHP1b is associated with methylation defects affecting the upstream overlapping *GNAS* imprinted gene cluster which may be sporadic, or familial, when usually associated with a maternally inherited intragenic STX16 deletion.

We characterised the phenotype of PHP patients at two UK tertiary care centres and investigated phenotype-genotype correlations.

Method: Retrospective review of case notes for patients with PHP at two UK tertiary care centres.

Results: 55 patients, from 41 kindreds, were identified; 32 with PHP1a, 23 with PHP1b.

The PHP1a cohort (56% female, 69% White), currently aged 16.7+/-10.6 years, presented at age 3.9+/-6.1 years; the majority with hypothyroidism (n=11, half as neonates), familial testing (n=6), AHO (n=5) or hypocalcaemia (n=5). 94% have TSH resistance/hypothyroidism and 72% PTH resistance. Additionally, 6 have GHRH resistance, 1 had precocious puberty and 2 were treated for delayed puberty. Of 20 patients older than 12 years, 40% have type 2 diabetes or severe insulin insensitivity (average weight 1.66 SDS); another patient has acanthosis nigricans.

Of 32 patients with PHP1a, 14 have *GNAS* missense variants and are shorter (p=0.002) but of similar weight SDS (p=0.2) to those with other variants; fewer have PTH resistance (36% vs 100%, p=0.0006); they presented later and fewer have ossifications. Two patients with splicing/frameshift mutations have progressive osseous heteroplasia (POH).

The PHP1b cohort (52% female, 39% White), currently aged 17.1+/-7.5 years, presented later at 8.2+/-4.3 years (p<0.05); two thirds with hypocalcaemia. They are taller than those with PHP1a (p<0.0005), with no difference in weight SDS. PTH resistance is more frequent (91%). 35% have TSH resistance. 10 patients with STX16 deletions and methylation defects only in *GNAS* exon 1A/B are heavier (p=0.006) than those with sporadic methylation defects. Similar numbers are on alfacalcidol and levothyroxine.

Discussion: This is one of the largest PHP cohorts reported to date and presents several notable findings. A large proportion of PHP1a patients have T2D or insulin insensitivity, even without

obesity. POH is not confined to paternally derived *GNAS* mutations and can be associated with PHP1a. Missense variants may cause a milder phenotype, and more likely to be associated with hypothyroidism without PTH resistance. One third of our PHP1b patients have TSH resistance, with little phenotypic difference between sporadic and familial gene abnormalities.

P1-14

Tumor induced osteomalacia, a rare and complex condition with more treatment options, exemplified in two patients

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Background: Tumor induced osteomalacia (TIO) is clinically characterized by bowed, short and painful legs in children and bone pain if onset in adolescent or adult life. Paraclinical, TIO is characterized by hypophosphatemia, low levels of 1.25-OH₂-vitamin D (1.25 OH₂D), and elevated levels of fibroblast growth factor 23 (FGF23). TIO is due to tumor secretion of FGF23, which inhibits phosphate re-absorption in the proximal renal tubules and the hydroxylation of 25 OH vitamin D to 1.25 OH₂D. The FGF23 tumors are of bone or mesenchymal origin.

Objective: To present the diverse phenotype and treatment options of TIO, we describe the diagnostics and treatment in two children with TIO.

Method: Patient one, a girl, was referred for severe rickets aged 2½ years old. She had a large diffuse hemangioma on the left side of the neck involving all tissue layers and with protrusion into the left oropharynx. Patient two, a girl, had been followed for mental retardation and epilepsy of unknown origin, and was referred for leg pain and hypophosphatemia aged fourteen years old. Both patients had healthy, Caucasian, and unrelated parents.

Results: Both patients had low plasma phosphate and 1.25 OH₂D, elevated alkaline phosphatase and urine phosphate excretion, and a 10-fold increase in plasma FGF23. A blood sample taken directly from the haemangioma of patient one revealed a 25-fold increase in FGF23. Direct sequencing of the *PHEX* and *FGF23* genes of both patients did not show gene variants. Magnetic resonance (MR) angiography in patient one showed a 6x5x4 cm³ haemangiomatous tumor with intraosseous venous malformation in the left skull base and communication with the middle cerebral vein. Due to tumor size and location, surgery was not an option. A treatment trial with intravascular bleomycin sclerotherapy did not reduce tumor size. Treatment was alphacalcidol and phosphate supplementation for 15 years. In January 2020 treatment was changed to burosumab (a FGF23 antibody), 1.4 mg per kg every 4 weeks which resulted in normal 1.25OH₂D and near normal plasma phosphate and FGF23. PET/CT and MRI in patient two revealed an osteolytic tumor of 2.3x3.1x3.6 cm³ in the left scapula. Tumor was surgically removed, leg pain disappeared, and all paraclinical data normalised.

Conclusion: TIO is a very rare condition, and the tumor may be difficult to localize. Treatment is easy if removal of the tumor by surgery is possible. If the tumor is in-operable the FGF23 antibody burosumab today may be an effective treatment option.

P1-15

Vitamin D status and guidelines in Paediatric Inflammatory Multisystem Syndrome Temporarily associated with SARS-CoV-2 (PIMS-TS)

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Introduction: Paediatric Inflammatory Multisystem Syndrome Temporarily associated with SARS-CoV-2 (PIMS-TS) was first reported by our hospital in the UK. Vitamin D₃ (25(OH)D) has important roles in cardiac function, immunomodulation, and inflammation. It therefore may be an important biomarker for severity in PIMS-TS, however 25(OH)D status and treatment guidance in PIMS-TS are lacking. We report serum 25(OH)D levels on admission and associations with disease severity. We outline our initial treatment strategy and subsequent modification to obtain a rapid and safe correction of serum levels of 25(OH)D to optimal levels (>75 nmol/L).

Methods: Retrospective data analysis of children aged 1-18 years with PIMS-TS admitted to a tertiary paediatric hospital in London between 16 April 2020 and 31 January 2021. Baseline 25(OH)D serum levels were measured prior to treatment with cholecalciferol and associations with indicators of severity were assessed. Early in the pandemic a single dose of 100,000 IU cholecalciferol was administered on admission, but on subsequent review this was modified to 200,000 IU. Post-treatment 25(OH)D serum levels were taken to assess efficacy.

Results: The median age of the cohort (n=109) was 8.9 years, 68 (62.4%) were male, and 53 (48.6%) were of black or Asian race. Median baseline 25(OH)D level was 36 nmol/L and levels <50 nmol/L were present in 69% children (75/109). Associations with lower baseline levels included: markers of inflammation (p<0.001) including ferritin (426mcg/L IQR 227-861), D-Dimer (2.3mg/L IQR 1.5-6.7), and lymphocyte count (1.3x10⁹/L IQR 0.7-2.4); paediatric intensive care unit admission (p<0.001); and fractional shortening on echocardiography <29% (p<0.001). There was no significant difference in the baseline 25(OH)D levels between the 100,000 IU and 200,000 IU treatment groups but the post-dose levels were >75 nmol/L in 30% (8/27) and 89% (17/19) children, respectively. No adverse effects of supplementation were reported.

Conclusions: PIMS-TS is associated with low 25(OH)D levels and a high proportion of children had vitamin D deficiency on presentation which could be effectively treated with a single dose 200,000 IU cholecalciferol. Serum 25(OH)D levels are a valuable biomarker of severity, but further studies are needed to establish if effective supplementation can modify outcomes.

P1-16

Leptin to adiponectin ratio at the age of 12 is negatively associated with lumbar spine bone mineral apparent density independently of body fat mass in 18-year old males

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Background: Inconsistent associations of leptin and adiponectin with bone mineral characteristics in puberty and adolescence have been reported.

Aim: To examine associations between leptin to adiponectin ratio (LAR) in puberty and bone mineral characteristics at 18 years of age and increase of bone mineral characteristics until 18 years of age.

Materials and Methods: 88 boys were investigated with a mean age of 12.1±0.7 (T1), 14.0±0.7 (T2) and 18.0±0.7 (T3). Serum leptin and adiponectin were measured at all time points and LAR was calculated. Bone mineral density (BMD) and bone mineral content (BMC) were measured for total body (TB) and lumbar spine (LS) at T1 and T3, bone mineral apparent density (BMAD) was calculated. As different brands of DEXA machines were used at T1 and T3, we calculated standard deviation scores (SDS) from present samples at T1 and T3 and their change (Δ). Partial correlation analyses was performed with body fat percentage, testosterone, HOMA-IR and physical activity as covariates.

Results: Significant negative correlation was found between mean pubertal LAR and LS BMD at T3 ($r = -0.311$; $P < 0.05$) and LS BMAD at T3 ($r = -0.405$; $P < 0.05$). Moreover, pubertal LAR correlated significantly with Δ LS BMD SDS ($r = -0.397$; $P < 0.05$) and Δ LS BMAD SDS ($r = -0.415$; $P < 0.05$).

Conclusion: LAR in puberty is negatively associated with LS BMD and LS BMAD at the age of 18 years and with subsequent increase in relative LS BMD and LS BMAD by the age 18 years.

Objective: To determine the clinical spectrum of HOMG1 due to *TRPM6* mutation at a tertiary centre.

Case Series: Seven patients (all male) from six different families of hypomagnesemia type 1 due to homozygous *TRPM6* mutation (parents' carrier) were reported over last 1 years. Four different variants of *TRPM6* mutation were identified and 3 of them were never reported before (novel).

Most common *TRPM6* variant identified was c.2538G>T p.(=) (4/7 cases, 3 families). This variant is predicted not to change amino acid sequence, but this substitution is near the highly conserve donor splice site and is classified as likely pathogenic. There was one case with *TRPM6* variant c.3514C>T p.(Arg1172*), one with c.2162C>G p.(Ser721*), and one with c.1420C>T p.(Arg474*), all creating premature stop codon.

Five cases (4 families) had history of sibling deaths due to unexplained hypocalcemia fits and two cases were the first born. Irritability and excessive cry were the first symptoms (Day 9 to 1 month) followed by intractable seizures at mean age of 2.2 (1.5-3) months. Six cases presented to tertiary care between 3- 6 months, and one is delayed presentation at 3 years (taking on and off calcium and magnesium supplementation). All patients were on anti-convulsants at the time of presentation.

Initial bone profile in all cases revealed low magnesium (0.4-1.1 mg/dl), low or low normal calcium (5.2-8.1 mg/dl), normal phosphate (5.2-6.8 mg/dl), normal or raised alkaline phosphatase (187-487 IU), low normal PTH (16-21.6 pg/ml), normal 25 OH D level, normal urine calcium to creatinine ratio (< 0.20) and low fractional excretion of Mg ($< 2\%$ - intestinal loss). All were started on daily oral magnesium supplementation with dose of 200 mg/kg/day which was gradually increased to 336(240-400) mg/kg/day to achieve a normal magnesium level.

Five cases were fit free (4 off anticonvulsants and 1 on tapering dose), however, 2 were having subtle seizures and still on anticonvulsants. Three patients were developmentally normal and 4 were having mild developmental delay.

Conclusion: Hypomagnesemia type 1 due to *TRPM6* mutation is a rare condition. Early diagnosis and prompt treatment lead to favorable outcome. We are reporting 7 cases of *TRPM6* mutation due to 4 different variants (3 were novel), presented with intractable seizures and responded well to oral magnesium supplementation.

P1-17

Clinical Spectrum of Hypomagnesemia type 1 (HOMG1) due to Novel TRPM6 mutations

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Background: Hypomagnesemia type 1 (HOMG1) is a rare autosomal recessive condition due to *TRPM6* mutation, leading to decrease intestinal magnesium absorption.

P1-18

A rare cause of hypercalcemia: Congenital Lactase Deficiency

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Background: Congenital lactase deficiency (CLD) occurs as a result of loss of function of intestinal lactase-phlorizin hydrolase (LPH) encoded by LCT gene. Patients usually present with osmotic diarrhea in the first few days of life. Although the exact mechanism is not known, hypercalcemia is a common feature of CLD; with calcium levels up to 14 mg/dl and nephrocalcinosis have been reported. However, CLD is frequently overlooked in the differential diagnosis of hypercalcemia. Here, we present a patient admitted for dehydration and hypercalcemia in whom CLD was considered due to diarrhea and failure to thrive.

Case report: A two month-old girl presented with vomiting and failure to thrive. She was born at term with a birth weight of 3030 gr to first cousin parents. She had severe dehydration and her height, weight and head circumference were 55 cm (-1.25 SDS), 3.4 kg (-2.83 SDS) and 36 cm (-2.69 SDS), respectively. Hypercalcemia, hyponatremia and metabolic acidosis were detected on laboratory evaluation (Ca:17.3 mg/dl, Na:127 mEq/L, pH:7.22, HCO₃:10.6, I.Ca:9.1 mg/dl). Additionally, the patient had hypercalciuria (Urine ca:cr:1.05 mg/mg), and medullary nephrocalcinosis on renal ultrasound. Etiological evaluation for hypercalcemia was unrevealing except low 1.25(OH)₂D level (22 pg/ml). She was started on intravenous fluid and 1 mg/kg methylprednisolone was given once. Further history revealed that she had watery-foamy diarrhea starting shortly after birth despite being fed exclusively with breast milk. A malabsorption was considered and she was placed on lactose-free (LF) formula. Serum calcium, decreased to 13.6 mg/dl on the second day after hydration and methylprednisolone and returned to normal within a month of initiating LF formula. No further hypercalcemia was detected on follow-up. Her diarrhea and vomiting also ceased and the patient started to thrive well. On her last examination, when she was 7.5-year-old, her height and weight were 116.6 cm (-1.3 SDS) and 27 kg (0.71 SDS), respectively with normal biochemistry. Molecular genetic evaluation revealed absence of mutations related to the hypercalcemia but identified bi-allelic c.1364T>C (p.Ile455Thr) mutation in the LCT gene.

Conclusion: Cause-specific treatment in hypercalcemia prevent unnecessary nonspecific treatments (Bisphosphonates, calcitonin etc) as LF diet provided and maintained normocalcemia in our patient. CLD should be kept in mind in the differential diagnosis of hypercalcemia and history of diarrhea should be carefully sought in these patients.

P1-19

Acetazolamide treatment in a patient with pseudohypoparathyroidism with venous calcification

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Context: Type 1A pseudohypoparathyroidism (PHP-1A) is characterized by target organ resistance to PTH and Albright's hereditary osteodystrophy (AHO). Basal ganglia calcifications and subcutaneous ossifications can be seen in PHP-1A. Acetazolamide, a carbonic anhydrase inhibitor, causes metabolic acidosis by increasing bicarbonate excretion from the proximal renal tubule thereby diminish precipitation of calcium and phosphorus. Acetazolamide had been used for soft tissue calcifications in tumoral calcinosis cases, however not used in PHP-1A and vascular calcification previously. Here, we report the beneficial effect of acetazolamide treatment in a PHP-1A patient with the subcutaneous and intravascular calcifications.

Case Description: A female patient presented with short stature, fatigue and exercise-induced carpopedal spasms at the age of 11^{7/12} years. Diagnosis of PHP-1A was made based on hypocalcemia, hyperphosphatemia, elevated serum PTH and AHO features (Round face, short stature, short metacarpal bones) and calcifications in the basal ganglia). Her height was 127.6 cm (-3.37 SDS), weight was 30 kg (-1.81 SDS). The patient was treated with IV and oral calcium and calcitriol. During intravenous calcium therapy, extravasation of calcium occurred in left forearm and a small hematoma developed in the right antecubital area after phlebotomy. Three weeks later on follow-up examination, a palpable rigidity was detected along the extravasated vascular path on the left arm and a 2x1 cm solid nodule was palpable in the location of hematoma in the right antecubital area. X-ray of the arms demonstrated calcification in these areas. Venous doppler ultrasound examination was consistent with thrombophlebitis and intravascular calcifications in both arms. The patient was treated with antibiotics and low molecular weight heparin (LMWH) for thrombophlebitis. Acetazolamide (25 mg/kg/day) was started for calcifications which created mild metabolic acidosis (pH:7.30-7.35). LMWH was discontinued on 6 months and acetazolamide treatment was discontinued at 8 months of treatment when calcifications in both arms disappeared completely. No adverse effects were observed during treatment. Maternally inherited p.Arg999Thrfs*47 heterozygous mutation was detected in the GNAS gene.

Conclusions: This case represents the first successful use of Acetazolamide for soft tissue and vascular calcifications in PHP and provides new insight for treatment of ectopic calcifications in PHP.

A novel TRPM6 variant (c.3179T>A) causing familial hypomagnesemia with secondary hypocalcemia

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Familial hypomagnesemia with secondary hypocalcemia (FHS) is a rare autosomal recessive disorder (OMIM# 602014) caused by mutations in the gene encoding TRPM6 (Transient receptor potential melastatin 6) on chromosome 9q22. This channel causes epithelial absorption of magnesium in the colon and renal distal convoluted tubule. **Fewer than 100 cases have been reported in literature.**

A four year old girl had presented to us with tetany lasting for 30 minutes. Detailed history revealed that she had repeated episodes of convulsions, the first being when she was 3 days old, which was a generalized tonic - clonic convulsion lasting for around 2 minutes. Tetany like episodes consequently were observed at the age of 1 yr and 3 yrs. All the previous episodes subsided with intravenous calcium gluconate. She was developmentally normal and there was no family history of similar episodes or consanguinity.

A basic workup revealed hypocalcemia 7.1 mg/dl (8.8 -10.8 mg/dl) and hypomagnesemia 0.5 mg/dl (1.7-2.3 mg/dl). Fractional excretion of magnesium was <1.4% (NR: 2-4%). Serum PTH was normal 54.2 (12.0 – 65.0 pg/ml). Complete blood count, C- reactive protein, Serum electrolytes, arterial blood gases and renal function test were normal.

In view of the severe hypomagnesemia, magnesium sulphate infusion and intravenous calcium gluconate was started. On Day 2 of treatment serum magnesium levels increased to 1.4 mg/dl and serum calcium levels normalized.

Genetic Evaluation: Clinical Exome Sequencing was done which revealed a homozygous nonsense variation in exon 17 of the TRPM6 gene that results in a stop codon and premature truncation of the protein at codon 717.

Our case revealed a novel TRPM6 gene variant c.3179T>A (p.Arg717Ter). As far as we know this homozygous variant has not been reported in the 1000 genomes database and has a minor allele frequency of 0.0007% in the gnomAD database. The *in silico* prediction of the variant is damaging by MutationTaster2. We considered the variant found in the patient to be pathogenic, especially associated with the clinical manifestations at presentation.

She was discharged on 20mg/kg per day of oral magnesium supplements and at the end of a six month follow up maintains a magnesium level at the lower end of normal range. She remains normal clinically and developmentally.

Thus, although rare, FHS should be considered in any child presenting with refractory hypocalcemic seizures and severe hypomagnesemia, as early diagnosis and treatment can result in a normal physical and neurological development.

Diabetes A

Incidence of Type 1 Diabetes in Children and Adolescents during the Covid-19 Pandemic in Germany: Results from the DPV registry

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Objective: The aim of this study was to investigate the incidence of type 1 diabetes in children and adolescents during the Covid-19 pandemic in Germany compared to previous years.

Research Design and Methods: Based on data from the multicenter German Diabetes Prospective Follow-up Registry (DPV), we analyzed the incidence of type 1 diabetes per 100,000 patient years in children and adolescents in the year 2020. Using Poisson regression models, expected incidences for 2020 were estimated based on the data from 2011 to 2019, and compared to observed incidences in 2020 by estimating incidence rate ratios (IRRs) with its 95% confidence interval (CI).

Results: In 2020, 3,259 children and adolescents with new-onset type 1 diabetes in Germany were registered. The observed incidence in 2020 was significantly higher than the expected incidence (23.2 [95% CI, 22.4–24.0] vs. 21.0 [20.2–21.7]; IRR, 1.11 [1.05–1.16], p<0.001). Analysis by month showed that the increase in incidence was particularly pronounced in the months June and July (IRRs, 1.43 [95% CI, 1.09–1.87], p=0.002, and 1.51 [1.16–1.98], p<0.001, respectively).

Conclusions: This study found a significant increase in the incidence of type 1 diabetes in children during the Covid-19 pandemic year 2020 with the peak incidence delayed about three months after the first wave of the pandemic. The underlying causes are yet unknown. However, indirect effects of the pandemic are more likely to be the cause than direct ones.

P1-22

Early meal reporting enhances post-prandial glycaemic balance but remains underused in teenagers with artificial pancreas

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Background and Aims: In an artificial pancreas, the meal management depends on the meal size and time being reported to the system. Because of the delay of insulin action, it is recommended to declare a meal in advance to allow insulin to limit the glycaemic peak. We aim to assess if the post-prandial glycaemic balance improves as meals are reported in advance.

Clinical Dataset: As part of Diabeloop DBLUS clinical trial (NCT04190277), 37 teenagers (age [14-18]) with type 1 diabetes were equipped with an artificial pancreas close-loop (CL) during 12 weeks in real life conditions. Data include CGM and meal reports. We select patients with more than 80% of CL in total, and data of days with more than 70% CL.

Frequency: First, the frequency and time intervals of early meal reporting (EMR) events are computed for every patient. We consider a meal to be reported early if the reporting is done at least 5 min before the meal.

Based on the 822 selected meals, the 26 teenagers tend to rarely report their meal in advance, with a median frequency of 3.2% (min=0%, max=20.4%). The time interval between EMR and meal times is short, with a median of 10 min (min=5 min, max= 35min).

Impact: Then, we compare the glycaemic post-prandial balance after an EMR or a standard meal reporting (SMR), during a window of 1 hour after meals. We select the eight patients with at least two EMR and two SMR, leaving a dataset of 47 EMR and 214 SMR.

The meal size remains overall similar, with a median null variation over the individual median meal sizes (min=-10g, max = +13g). The median percentage of time in normal range ([70-140] mg/dL) of each patient globally increases with EMR, with a median increase of 8% (min = -10%, max=+63%) compared to SMR. The individual median average glycaemia during post-prandial periods generally decreases, with a median variation of -17 mg/dL (min = -87, max=+33) compared to SMR.

Conclusions: In this study, we show that teenagers who report meals in advance to their artificial pancreas benefit from a decrease of median glycaemic post-prandial peaks and an increase of the time in normal range. The possibility to report meals early could be encouraged by targeted patient education and customized reminders.

P1-23

Capillary blood sample collection at home for HbA1c measurements during the COVID-19 pandemic in children with diabetes mellitus

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Background: The COVID-19 pandemic has resulted in rapid implementation of tele-clinics; patients have frequently missed routine point-of-care HbA1c testing, vital for evaluating long-term glycaemic control. We evaluated the feasibility of remote HbA1c monitoring via self-collection of capillary blood samples at home, and examined clinical characteristics associated with engagement with this system.

Methods: Bio-Rad Haemoglobin Capillary Collection System (HCCS) was used. Relation between capillary and venous samples is linear ($r = 0.998$ $y = 1.0x + 0.0$ (manufacturer's manual). The kit's performance was tested at the Chemical Pathology Laboratory at Royal London Hospital.

100 participants were recruited from paediatric diabetes clinics at 2 sites in East London (age 4-19, Pre-Covid HbA1c: 29-120mmol/mol). Home kits for self-collection of capillary samples were mailed out with step-by-step instructions containing pictures and a video demonstration link, and a prepaid envelope for sample return. Feasibility was assessed by examining the rate of sample return and duration taken for lab to receive sample. A usability survey addressing the home collection process and experience with the kit was emailed to families who had been sent a home HbA1c kit, consisting of 7 questions on a 5-point Likert scale to assess ease of use and preferences around HbA1c monitoring.

Results: Completion rate was 58%. Mean time taken from kit being mailed out to sample analysis was 15.6 ± 9.8 days (median 13.5). Pre-covid HbA1c was higher in the group that failed to return a sample, as compared to the group that did (65.3 ± 20.1 vs 56.8 ± 14.7 mmol/mol, $p < 0.05$).

Overall, HbA1c remained relatively stable over the pandemic in the completion group (T1DM (n=41) HbA1c 60.1 ± 8.8 to 57.1 ± 8.8 , $p > 0.05$, T2DM (n=8) HbA1c 56.4 ± 28.8 to 52.4 ± 17.3 , $p > 0.05$). A higher proportion of non-T1DM patients had an increase in HbA1c over the pandemic (T1DM (n=41): 49%, T2DM (n=8): 63%, Other (n=5): 80%).

Usability scores were high: 96% found it easy to learn capillary blood sample collection, and 89% found this system very convenient.

Conclusion: Self-collection of capillary blood samples at home appears feasible to remotely assess HbA1c for patients with relatively stable glycaemic control and good engagement with their care. Routine telemedicine appointments could be suitable and convenient for these patients, if data from their devices are shared.

Future work should focus on improving processes to allow for HbA1c level to be available prior to the telemedicine appointment, and assessing and removing hurdles for engagement to increase completion.

P1-24

Resolution of feeding problems in patients with congenital hyperinsulinism

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Background: Congenital Hyperinsulinism (CHI) is the most common cause of recurrent and severe hypoglycaemia in childhood and can be broadly categorised into two subtypes. Diffuse CHI (CHI-D) involving all pancreatic cells is usually treated with medications and rarely subtotal pancreatectomy. Focal CHI (CHI-F) involves a solitary insulin hypersecreting pancreatic lesion and can be cured following surgical lesionectomy. Many patients with CHI-F and CHI-D undergo prolonged hospital admissions and require feeds delivered via nasogastric (NGT) or gastrostomy tubes or administration of parenteral nutrition (PN) to meet nutritional demands. Combined with potentially emetogenic medications, interruption of normal feeding milestones and the possible adverse effect of hyperinsulinism itself, infants are at high risk for the feeding problems frequently observed in severe CHI. We aimed to describe types and incidence of feeding problems in a longitudinal cohort of children with CHI and investigate factors predictive of resolution.

Methods: All patients with CHI admitted to a specialist centre during 2015-2016 were assessed for feeding problems at hospital admission and for three years following discharge, through a combination of specialist speech and language therapy review, parent-report and research telephone clinics.

Results: Twenty-five patients (18% of all patients admitted) with CHI were prospectively identified to have feeding problems related to sucking (n=6), swallowing (n=2), vomiting (n=20) and feed aversion (n=17). Sixteen (64%) patients required feeding support by NGT/gastrostomy tubes at diagnosis; tube feeding reduced to four (16%) patients by one year and three (12%) patients by three years. Feed aversion resolved slowly with a mean time to resolution of 240 days after discharge; in 15 patients followed up for three years, 6 (24%) continued to report significant feed aversion. The mean time (days) to resolution of feeding problems was lower in those who underwent lesionectomy (n=4) than in those who did not (30 vs 590, p=0.009) and significance persisted after adjustment for associated factors in Cox Regression analysis (p=0.015). No other clinical factors investigated (gene mutation status, neurodevelopmental problems, glucose infusion rate, use of

PN, NGT/gastrostomy, glucagon or octreotide) were predictive of faster resolution of feeding problems.

Conclusion: Feeding problems are frequent in patients with CHI and frequently require support over several years following discharge from hospital. Patients often require feeding via the non-oral route and this requirement may persist for years. Successful lesionectomy in focal CHI is the only factor that predicts a significantly shorter time to resolution of feeding problems.

P1-25

Longitudinal Auxological Recovery and Reduced Neurodevelopmental Problems in Hyperinsulinaemic Hypoglycaemia

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Background: Hypoglycaemia due to congenital hyperinsulinism (CHI) is the commonest cause of severe, recurrent hypoglycaemia in childhood. Previous follow up studies have focused on neurodevelopmental status which is noted to be delayed in as many as 48% of cases. There has been less emphasis on other long-term outcomes in patients with CHI. Given the requirement for high volume carbohydrate in most patients, there are concerns regarding the adverse effects on weight. However, there are no long-term studies describing feeding and auxology outcomes in children with CHI. We aimed to provide a description of auxological, feeding and neurodevelopmental outcomes in a longitudinal cohort to better understand the natural history and long-term outcomes of children with CHI.

Method: We reviewed medical records for all patients with confirmed CHI over a three-year period in a single specialist centre. Notes were reviewed for follow up data on auxology, feeding problems, medications and neurodevelopmental outcomes up to five years of age. Linear interpolation was used to impute missing values of height and weight data. Non-parametric tests were performed using SPSS 25.

Results: Seventy patients were recruited to the study. Mean weight at birth was -1.0 standard deviation scores (SDS) for age and sex (-3.2 for small for gestational age (SGA) patients and +0.4 for appropriate for gestational age (AGA) patients), while mean height at three months was -1.5 SDS. Both weight and height trended to the population mean over the follow-up period and by five years of age mean weight was -0.1 SDS and height +0.1 SDS.

Feeding difficulties, defined as the requirement for non-oral enteral feeding, were present in 12 patients (17%) at three months, reducing to two patients (3%) by five years. At age five years, 11 patients (15%) had neurodevelopmental delay and of these only one was severe. Earlier resolution of disease was predicted by lower maximum early diazoxide dose ($p=0.007$) and being born SGA ($p=0.009$) as expected.

Conclusion: We have provided the first description of auxological natural history data in a longitudinal cohort of patients with CHI. After five years, in spite of feeding difficulties and carbohydrate loading in early life, auxology parameters are reassuringly normal in follow-up. A lower than expected rate of neurodevelopmental delay could be attributed to prompt early treatment. Early maximum diazoxide dose and being born SGA can be used in discussions with families to prognosticate possible resolution of disease.

P1-26

Efficacy and Tolerability of GLP-1 Receptor Agonists in Children and Adolescents with Obesity

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Background: Rates of pediatric obesity are on a concerning upward trajectory globally, with the prevalence approaching 1 in 5 children and adolescents aged 2-19 years in the United States. As a direct consequence of this obesity surge, we will continue to experience a substantial adult cardiometabolic burden. Although public health measures to optimize lifestyle interventions and reduce culpable environmental exposures are the primary target for governments and societies, there remains a subset of children and adolescents whose obesity is resistant to this approach.

Objectives: To determine the cardiometabolic and gastrointestinal effects of incretin-based therapies in children with obesity.

Study Design: Web of Science, PubMed/MEDLINE, and Scopus databases from 01/01/1994-01/01/2021 for RCTs examining the cardiometabolic or gastrointestinal effects of incretin-based therapies (*i.e.*, GLP-1 receptor agonists and DPP-4 inhibitors) in children and adolescents with obesity. Data were extracted by two independent surveyors and a random effects model was applied to meta-analyze generic inverse variance outcomes. Primary outcomes were related to cardiometabolic profile, while secondary outcomes of interest were gastrointestinal-related treatment-emergent adverse events.

Results: Nine studies involving 574 participants were identified, of which three involved exenatide and six involved liraglutide. No studies of relevance involving DPP-4I were identified. GLP-1RA use caused a modest reduction in body weight (mean difference [MD] -1.50 [-2.50, -0.50] kg, I^2 : 64%), BMI (MD -1.24 [-1.71, -0.77] kg/m², I^2 : 0%), and BMI z-score (MD -0.14 [-0.23, -0.06], I^2 : 43%). Interestingly, lifestyle interventions proved to be complementary to these effects. Glycemic control was improved in children with proven insulin resistance (HbA1c MD -1.05 [-1.93, -0.18]%, I^2 : 76%). Although no lipid profile improvements were noted, a modest decrease in systolic blood pressure was detected

(MD -2.30 [-4.11, -0.49] mmHg; I^2 : 0%). Finally, analysis of gastrointestinal-related treatment-emergent adverse events revealed an increased rate of nausea (risk ratio 2.11 [1.44, 3.09]; I^2 : 0%), without significant increases in other gastrointestinal symptoms or pathology.

Conclusions: This meta-analysis indicates that GLP-1RAs are safe and effective in modestly reducing weight, HbA1c and systolic blood pressure in children and adolescents with obesity in a clinical setting, albeit with increased rates of nausea.

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P1-27

The SARS-CoV-2 Pandemic Is Associated With Increased Severity Of Presentation Of Childhood Onset Type 1 Diabetes Mellitus: A Multicentre Study Of The First COVID-19 Wave

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Objective: Children are usually mildly affected by Severe Acute Respiratory Syndrome Coronavirus 2 infection (SARS-CoV-2, COVID-19). However, the pandemic has impacted negatively on children with non-COVID-19 diseases. We aimed to determine the impact of the COVID-19 pandemic on the presentation of newly diagnosed childhood-onset type 1 diabetes.

Methods: This was a cross-sectional study conducted over a one-year period. We compared the severity of presentation of new-onset type 1 diabetes in children under the age of 18 presenting to a multi-centre paediatric diabetes network before (1st July 2019 to 22nd March 2020) and during (23rd March 2020 to 30th June 2020) the first wave of the COVID-19 pandemic in the United Kingdom.

Results: A total of 47 children presented during the one-year study period: 30 pre-pandemic and 17 during the first COVID-19 wave. The odds ratio (OR) of presenting with any diabetic ketoacidosis (DKA) and with severe DKA was greater during the first COVID-19 wave compared to the pre-pandemic period (OR 7.58 [95% Confidence Interval (CI) 1.9-29.7], $p=0.003$ and OR 8.0, [CI 1.7-36.8], $p=0.009$, respectively). During the first COVID-19 wave, older children were less likely to present in severe DKA (OR 0.77 per year increase in age, [CI=0.6-0.9], $p=0.018$). Children with a family history of type 1 diabetes were less likely to present in any DKA ($p=0.002$). HbA1c measurement at diagnosis was higher in children presenting during the first COVID-19 wave (12.9 vs 11.0%; 119 ± 5 vs 96 ± 5 mmol/mol, $p=0.008$).

Conclusion: The COVID-19 pandemic is associated with increased severity of presentation of childhood onset type 1 diabetes across multiple clinical and biochemical parameters. Young people with suspected new-onset type 1 diabetes should be referred for urgent clinical review. This is particularly true in view of the disruption to usual clinical care caused by the COVID-19 pandemic.

Glycemic control and changes in habits in patients with type 1 diabetes during the lockdown due to the COVID-19 pandemic

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Background: The SARS-CoV-2 pandemic has forced the authorities to impose a lockdown to minimize the risk of infection. This extreme and prolonged situation has caused changes in habits, dietary and glycemic control in children with type 1 diabetes (T1D). Continuous glucose monitoring (CGM) and Flash glucose monitoring (FGM) have allowed health care professionals to a remote control of the patients.

Aim: The aim of the study was to evaluate the effect of lockdown on routine and glycemic control in children with T1D.

Methods: A retrospective study on children under 18 years old with T1D using CGM or FGM in one centre (Barcelona, Spain) comparing 2 periods: 4 weeks before the start of the COVID-19 lockdown and 4 weeks during consecutive lockdown. They answered a questionnaire about their habits, T1D treatment and control. Sensor data from the two periods were compared.

Results: A total of 39 children were included (age 10.4 ± 3.6 , diabetes duration 4.3 ± 3.5 ages). Most of the children experienced changes in their routines especially in exercise habits and time spent with screens that were reversed and most of them reduced the number of meals per day.

Daily insulin doses changed in more than a half of children (56,4% basal and 69,2% bolus). Problems related with diabetes which needed medical assistance were resolved with a virtual visit.

No significant differences in glucose targets were found when comparing the two periods of time. Only coefficient of variation (CV) decreased from $36.4 \pm 5.8\%$ to $34.8 \pm 6.5\%$, ($p = 0.036$) comparing the two periods of time. No differences were found in time in range (49,3% to 48,55%) ($p = 0,5$), estimated HbA1c (8,1% to 8,4) ($p = 0,189$) and mean glucose ($182,6 (\pm 28,8)$ mg/L to $187,5 (\pm 33,9)$ mg/dL) ($p = 0,259$).

Time in hypoglycemia decreased (3,37% to 2,7%) and time in hyperglycemia increased (50,66% to 52,41%) during the lockdown but the differences were not significant.

Conclusions: In our study we found substantial changes in routines in children with T1D during the lockdown but on the other hand we did not find worsening in glycaemic control during those days comparing the two periods of time.

Incidence and severity of new-onset paediatric Type 1 diabetes in the COVID-19 pandemic – a UK multicentre perspective

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Background: Paediatric diabetes has been the focus of attention during the COVID-19 pandemic. There are reports of increased incidence of new-onset type 1 paediatric diabetes and concerns about delayed presentations to the Emergency Department (ED) due to parental fears of SARS-CoV-2, resulting in an increase in the incidence and severity of DKA in children with new-onset diabetes.

Objectives: To characterise the features of children diagnosed with new onset type 1 diabetes in the COVID -19 pandemic exploring the incidence of diabetic ketoacidosis (DKA) and investigating any association with SARS-CoV-2.

Methods: We analysed data of new onset type 1 diabetes in children aged 6 months-17 years presenting from January to July 2020 to 12 paediatric diabetes units (PDUs) in the UK (178 children). Data from the same time period in 2019 (150 children) was compiled for comparison.

Results: There was a significant increase in the number of children with new-onset type 1 diabetes presenting with DKA in 2020 compared to 2019 (79vs49, $p < 0.05$). There was also an increase in the number of children presenting in severe DKA in 2020 when compared to 2019 (36vs16). The incidence of new onset type 1 diabetes from January to July 2020 was similar to the previous 4 years. An apparent increase in 2020 was noted in two units, both from inner city localities with a highly diverse ethnic mix. 11 children were tested for COVID -19 serology and all were negative. Two children tested positive for COVID -19NS-RT-PCR and presented with severe DKA. In 2019 35% of children had symptoms of less than 2 weeks (of which 43% were in DKA), 46% of children in 2020 presented with symptoms less than 2 weeks (of which 47% were in DKA). The short period of type 1 diabetes symptoms before presenting in DKA in 2020 does not suggest a delay in diagnosis. The short period of symptoms of type 1 diabetes at presentation during the study period and the severity of DKA raises the possibility that infection with SARS-CoV-2 may have been a trigger resulting in loss of β -cells contributing to the rise in incidence and severity of DKA also accelerating the development of diabetes.

Conclusions: Our study did not provide evidence that the COVID-19 pandemic is leading to a marked increase in incidence of paediatric type 1 diabetes. However, there was increased incidence and severity of DKA during the study period in 2020.

P1-30

Metabolic Control and Health-Related Quality of Life in Children with Diabetes Mellitus during the COVID-19 Pandemic: Results from a Prospective Swiss Cohort Study

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Introduction: The COVID-19 pandemic led to regional lockdowns and restrictions associated with changes in lifestyle and quality of life (QoL) thus potentially burdening metabolic control in Diabetes Mellitus (DM). We examined whether the stages of restrictions lead to changes in QoL and metabolic control in children with DM.

Methods: Starting in April 2020, this monocentric prospective longitudinal cohort study included children attending the outpatient diabetes clinic at a tertiary children's hospital. In addition to the repeated assessment of SARS-CoV-2 antibodies and symptoms, screen time and physical activity, reported elsewhere, health-related QoL (HrQoL) through Kidscreen-10 (T-scores >50 represent a better, <50 a poorer QoL than the reference population), BMI-SDS, HbA1c, mean glucose (MG), variability (%CV) and Time in Range (TIR) were assessed at 2-3-monthly scheduled visits. Parameters were assigned to the following pandemic phases:

1. 16.03.20 – 10.05.20 Lockdown with closed schools, shops, restaurants and social activities
2. 11.05.20 – 18.10.20 no restrictions
3. 19.10.20 – 21.12.20 slowdown with assembly restrictions and business closing hours
4. 22.12.20 – 28.02.21 lockdown with closed shops, restaurants and social activities, but open schools

For statistical analysis, we applied mixed-model-analysis between different phases and Pearson double-sided correlations.

Results: We assessed 54 children with Type1DM and two with MODY, 53.4% male and 46.6% female and median age of 12 years (range 1 – 19); Median HbA1c during phase 1 was 7.5% (range 6.2 – 11.0%). BMI-SDS, HbA1c, MG, %CV and TIR did not significantly change during all 4 phases. During lockdown phase 1 HbA1c ($p=0.003$) and %CV ($p=0.05$) were significantly correlated with increasing age. The HbA1c decrease from phase 1 to 2 was greater the older the patients were ($p=0.029$). The HrQoL showed significant increase from phase 1 to 2, decreased HrQoL mean scores in phases with high restrictions (1: 46.7 (32.2 – 65.2), 3-4: 46.7 (36.4 – 77.1)), or after back to school in Phase 2 (46.7 (31.3 – 83.5)), but normal T-scores during the rest phase 2 (50.7, 32.4 – 83.6).

Conclusions: The children with DM participating in the study showed a stable metabolic control through different phases of the pandemic, despite impaired HrQoL during phases with higher restrictions. Nevertheless, in older patients, metabolic control was transiently compromised during school closure.

Consistent with prior studies, children with diabetes seem to activate sufficient resources for their diabetes management even during the COVID-19 pandemic if they have a regular (school) routine and medical care; other authors substantiate the importance of parental support.

Fat, Metabolism and Obesity A

P1-31

Efficacy and Safety of Setmelanotide in Individuals With Obesity Due to POMC or LEPR Deficiency: Phase 3 Results From Pivotal and Supplemental Cohorts

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Background: Disruption of the melanocortin-4 receptor pathway by genetic variants in *POMC/PCSK1* or *LEPR* can result in hyperphagia and severe early-onset obesity. In the primary analyses of 2 pivotal Phase 3 trials, the melanocortin-4 receptor agonist setmelanotide was associated with significant reductions in body weight and hunger in patients with obesity due to proopiomelanocortin (POMC) or leptin receptor (LEPR) deficiency. These previously presented primary analyses were conducted in pivotal cohorts with 21 total patients; however, additional patients were subsequently enrolled.

Methods: In 2 single-arm, multicenter, Phase 3 trials of setmelanotide in patients with obesity due to POMC (NCT02896192) or LEPR deficiency (NCT03287960), patients aged ≥ 6 years received setmelanotide for 12 weeks. Those with ≥ 5 kg weight loss (or $\geq 5\%$ if weighing <100 kg at baseline) entered an 8-week placebo-controlled withdrawal sequence followed by an additional 32 weeks of open-label setmelanotide treatment. Primary endpoint was the proportion of patients with $\geq 10\%$ weight loss at ~ 1 year. Secondary endpoints included mean percent change in "most" hunger score at ~ 1 year. Adverse events (AEs) were also assessed. This updated analysis includes patients enrolled in both the pivotal and supplemental cohorts.

Results: A total of 15 patients with POMC deficiency (10 pivotal, 5 supplemental) and 15 with LEPR deficiency (11 pivotal, 4 supplemental) were enrolled. In the POMC trial, mean age was 17.2 (range, 7.0–30.0) years, and mean (SD) body weight and BMI were 111.3 (35.8) kg and 39.2 (8.2) kg/m², respectively. In the LEPR trial, mean age was 21.7 (range, 8.0–37.0) years, and mean (SD) body weight and BMI were 132.5 (39.3) kg and 49.2 (13.0) kg/m², respectively. A total of 85.7% of patients (12/14; $P<0.0001$) in the POMC trial and 53.3% (8/15; $P<0.0001$) in the LEPR trial achieved

≥10% weight loss at 52 weeks. The mean (SD) percent change in body weight from baseline to 52 weeks was −25.8% (9.7%; $P<0.0001$) and −12.3% (7.5%; $P<0.0001$) in the POMC and LEPR trials, respectively. In patients aged ≥12 years, mean (SD) percent change in most hunger score at 52 weeks was −27.1% (−28.1%) and −42.7% (−27.5%) in the POMC and LEPR trials, respectively. There were no treatment-related serious AEs. The most common AEs were injection site reaction and hyperpigmentation.

Conclusions: In patients with early-onset genetic obesity, this expanded POMC/LEPR data set showed clinically meaningful improvements in weight loss and hunger sustained after 1 year on setmelanotide, consistent with earlier pivotal findings.

P1-32

Sex hormones drive changes in lipoprotein profiles in adolescents; early implications for cardiovascular disease risk

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Prior to menopause, it is known that women have a lower risk of cardiovascular disease (CVD) and coronary heart disease compared to age-matched men; it is reported that women have around half the CVD risk and almost a 10-year delay in first myocardial infarction event compared to men. Sex differences in serum lipids could contribute to CVD risk through driving atherosclerosis, the buildup of lipids in the sub-endothelial intimal layer of medium-sized to large arteries. We hypothesised that sex hormones influence changes in lipids and thus atherosclerosis risk after puberty.

The interrelationship between sex hormones and lipids was explored in pre- and adolescent post-pubertal cis-gendered males ($n=10$ and 17) and females ($n=10$ and 23) and in adolescent transgender individuals under cross-sex-hormone treatment (trans-male/trans-female, $n=26/25$) using NMR-based serum metabolomics assessing 149 lipid measures. Data were analysed by multiple t-tests and logistic regression.

Atheroprotective high-density lipoproteins (HDL) and associated apolipoprotein (Apo)A1 were significantly increased and atherogenic very-low- and low-density lipoproteins were significantly decreased in adolescent post-pubertal cis-females compared to cis-males. Strikingly, these differences were not observed pre-puberty and were induced appropriately by cross-sex-hormone treatment in adolescent transgender individuals, supporting that sex hormones regulate lipid metabolism *in vivo*. Notably, only atheroprotective ApoA1 expressing lipoproteins (HDL) were universally differentially expressed between adolescent cis-males versus cis-females, cis-males versus trans-females and cis-females versus trans-males. In adolescent trans-females, ApoA1 levels correlated positively with circulating oestradiol levels and with the number of months on cross-sex-hormone treatment by linear regression. Finally, ApoA1 was not significantly altered in adolescent post-pubertal individuals with Turner syndrome (females with only one

functional X sex chromosome, rather than the usual two) compared to healthy adolescent controls.

Thus, oestradiol drives a dose-dependent atheroprotective lipid profile through upregulation of HDL and ApoA1, supporting a role for sex hormones in lipid metabolism; this was not affected by chromosome dosage and may help us to understand why males and females are differentially susceptible to CVD from a young age. Together, this could inform sex-specific therapeutic strategies for atherosclerosis and CVD management.

P1-33

Metabolomics in early life and the association with body composition at age 2 years

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Background and Objectives: Early life might be a critical window for adiposity programming later in life. Metabolic profile in early life may reflect this programming and correlate with later life adiposity. We investigated if metabolic profile at 3 months of age is predictive for body composition at age 2 years and if there are differences between boys and girls and between infant feeding types.

Methods: In 318 healthy term-born children, we determined body composition with skinfold measurements and subcutaneous and visceral fat by abdominal ultrasound at age 3 months and 2 years. High throughput metabolic profiling was performed on 3 month blood samples. Using random forest machine learning models, we analyzed if the metabolic profile at age 3 months can predict body composition outcomes at 2 years of age.

Results: Plasma metabolite profile at 3 months of age was found to modestly predict body composition at 2 years of age, based on truncal:peripheral-fat-skinfold-ratio (T:P-ratio), with a predictive value of 75.8%, sensitivity of 100% and specificity of 50%. Predictive value was better in boys than in girls. Of the 15 metabolite variables most strongly associated with the T:P-ratio at 2 years, 11 were also associated with abdominal visceral fat at 2 years of age.

Conclusion: Fifteen plasma metabolites (LysoPC(22:2), dimethylarginine and others) at age 3 months associate with body composition outcome at age 2 years. Five of these are known to be involved in inflammation. These results highlight the importance of the first months of life for adiposity programming, which is potentially a result of low grade inflammation.

P1-34

High prevalence of undiagnosed metabolic dysfunction among children and adolescents with obesity in China

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Objective: The aim here was to describe the characteristics of obese children and adolescents and to determine how the prevalence of comorbidities differed over 10 years in China.

Methods: Obese children and adolescents were enrolled from Department of Endocrinology, Children's Hospital of Zhejiang University School of Medicine in Hangzhou (Zhejiang Province, China). Eligibility was defined by a body mass index (BMI) of ≥ 95 th percentile. Medical and physical assessments were obtained.

Results: 2916 participants (1954 boys and 962 girls) aged 10.5 ± 2.6 years undertook assessment during the recruitment period from January 2008 to December 2017. Average BMI standard deviation score was 3.39 (95%CI range 3.33-3.44). The majority of participants were found with obese related comorbidities, including 1453 (49.9%) dyslipidaemia, 968 (33.3%) hypertension, 1733 (60.4%) abnormal liver function, 1678 (57.6%) NAFLD, 1980 (69.3%) acanthosis nigricans, 996 (34.3%) abnormal glycaemia and 85 (2.9%) Type 2 Diabetes Mellitus. The prevalence of comorbidities has increased significantly over the 10 years in two age groups. The incidence of hypertension has almost doubled from year (2008–2012) to year (2013–2017) in both sex groups aged <10 years and girl group aged >10 years.

Conclusions: Our study reveals that a high prevalence of metabolic dysfunctions among children and adolescents with obesity in China over 10 years, especially hypertension, NAFLD and abnormal glucose metabolism, which indicates the undiagnosed metabolic problems encountered by obese children and adolescents in China, and they should be focused on during subsequent follow-up, especially hypertension.

P1-35

The possible association of the apoptotic marker APO1/Fas with predisposition to metabolic syndrome and mean platelet volume in children

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Objective: To investigate the possible relationship between APO1/Fas, components of metabolic syndrome and Mean Platelet Volume (MPV) in a healthy pediatric population.

Study Design: 185 children, aged 5-17 years old, were enrolled to the study. The participants were divided into subgroups according to age and body mass index percentile (BMI%). APO1/Fas was measured by ELISA and MPV by the MEK-6410K.

Results: Eighty-one children (43.8%) had excess weight (overweight: 27.5%, obesity: 16.2%), which was more prevalent in children ≤ 9 years of age. Sixty-five children (35.1%) exhibited a predisposition to metabolic syndrome. A negative correlation was found between APO1/Fas and predisposing factors for metabolic syndrome, such as weight, glucose, cholesterol, uric acid, LDL, triglycerides and CADI. In contrast, a positive correlation was found between APO1/Fas and CRP. ROC analysis showed a predisposition to metabolic syndrome when APO1/Fas was $<78,46$ ng/ml. A negative correlation was also observed between APO1/Fas and MPV. Furthermore, increased BMI was positively correlated with uric acid, triglyceride concentrations, CADI, SGPT and GGT.

Conclusion: APO1/Fas expression may possibly have a protective role against metabolic syndrome in the paediatric population, through its involvement in angiogenesis, atherosclerosis and increased platelet activity, as expressed by elevated MPV. It may also enhance CRP-mediated protection of cells from necrotic lysis. Finally, close monitoring of all the components of metabolic syndrome in children with excess weight is important from a young age in order to prevent metabolic and cardiovascular complications.

Reversal of metabolic derangement in patient with congenital generalized lipodystrophy treated with metreleptin

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Lipodystrophy syndromes are a heterogeneous cluster of complex, life-threatening, rare diseases associated with reduced levels of leptin and include Congenital Generalized Lipodystrophy (CGL). Patients are at significant risk of developing metabolic problems that include elevated triglycerides, severe insulin resistance, and impaired glycemic control, and abnormalities in multiple organs. We report a case of 16-year-old Emirati female with CGL with special focus on reversal of metabolic abnormalities by metreleptin (a synthetic analog of the hormone leptin).

She was diagnosed with CGL in early childhood based on clinical signs (scant subcutaneous fat, prominent muscles, large jaw, hands and feet, acanthosis and hirsutism) and genetic testing revealed pathological homozygous mutation AGPAT2, c.158del p.(Gly53Alafs*8). She had normal growth throughout childhood (weight and BMI ranged between 50th and 75th centile). Laboratory studies before the age of 13 revealed normal glucose profile, HbA1C, insulin levels, liver enzymes, HDL and LDL cholesterol. Triglycerides were mildly elevated (1.65-3.02 mmol/L).

At age 14 years, she developed severe acanthosis, diabetes, further rise in triglycerides, elevated liver enzymes and fatty liver disease. Diabetes was initially controlled with low dose insulin, but she developed severe insulin resistance within few months with worsening glycemic control resulting insulin requirement reaching 180 units daily (3.6U/kg/day). Despite receiving Fenofibrate 145 mg daily, triglycerides remained high.

Within a few days of initiating metreleptin 5 mg subcutaneous injection (q.d.), a significant reduction in glucose levels and insulin requirement was observed. Insulin Lispro was stopped within 3 days and insulin Lantus dose was tapered rapidly to 5 units daily and then stopped 3 months later.

After stopping insulin, her blood glucose remained normal with fasting glucose ranging between 3.9-5.6 mmol/L and post-prandial below 7.5 mmol/L. Eight months after stopping insulin, HbA1C was 5.2% pre-metreleptin.

Triglyceride level ranged 4.09-7.48 mmol/L in the 6 months pre-metreleptin and dropped to 1.41 three-months post-metreleptin. Triglyceride level was 3.02, 1.84 and 1.42 after 1, 4 and 9 months, respectively, after stopping Fenofibrate.

AST ranged 41-59 IU/L and ALT 57-81 IU/L pre-metreleptin treatment. AST and ALT normalized within 3 months after treatment and remained normal 1 year later (AST 12-16 IU/L and ALT 5-14 IU/L).

The patient had complete reversal of hyperglycemia and hypertriglyceridemia and normalization of hypertransaminasemia with metreleptin monotherapy.

The normalization of liver enzymes is promising for possible long-term prevention of liver cirrhosis, a serious and potentially fatal complication of severe fatty liver disease.

The effect of trans-palmitoleic acid on lipid accumulation and the fatty acid synthase gene expression in hepatocytes

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Introduction: Obesity is among the most prevalent health problems and is associated with increased risk of various metabolic disorders, including type 2 diabetes and non-alcoholic fatty liver disease (NAFLD). Fatty acids comprise a major part of the lipids and have remarkable effect on cell biology. Trans fatty acids (tFAs) are generally a by-product of manufacturing of fats. However, naturally-produced tFAs that are found in milk and dairy products, are suggested to be beneficial for health. Trans-palmitoleic acid (t-PA), a naturally occurring tFA has been shown to be related to better lipid profile including higher HDL-C and lower triglyceride (TG), and associated with decreased insulin resistance, lower metabolic risk and incident of type2 diabetes. Thus, the aim of this study was to investigate the effects of tPA on lipid accumulation in liver cells and the gene expression of fatty acid synthase (FAS) enzyme and the activity of peroxisome proliferator-activated receptor alpha (PPARα), an important nuclear receptor in the regulation of lipid metabolism.

Methods: HepG2 liver cells were cultured and treated with different concentrations of tPA and palmitic acid. Intracellular TG levels were evaluated by Oil red O staining of the cultured cells as well as extraction of cellular lipids and TG measurement with an enzymatic method. The expression of FAS gene was assessed by real-time PCR, after total RNA extraction and the synthesis of cDNA. The activity of PPARα was evaluated by luciferase reporter assay, via transfecting HEK293T cells with the vector comprising the PPARα response element.

Results: Both tPA and palmitic acid caused TG deposition in liver cells; however, the TG levels were significantly lower in cells treated with tPA compared with the cells that were treated with palmitic acid ($P < 0.001$). The gene expression of FAS was enhanced by both fatty acids, but in cells treated with tPA, it was significantly lower than palmitic acid ($P < 0.001$). Treatment of cells with tPA resulted in the activation of PPARα, especially at lower concentrations ($P < 0.001$), while palmitic acid did not have any effect on this nuclear receptor.

Conclusion: The results showed that less TG is accumulated in liver cells treated with tPA compared to palmitic acid which may be due to lower induction of FAS enzyme and activation of PPARα by tPA. Thus this fatty acid has better influence on liver cells compared to its saturated counterpart. Further clinical studies are suggested for assessment of the value of tPA as a beneficial supplement.

P1-38**Are Serum Spexin Levels Associated With Metabolic Syndrome Antecedents In Obese Adolescents?**

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Objective: Spexin is a novel peptide implicated in food intake and satiety. Spexin levels are reduced in obese patients.

Aim: To evaluate the associations of metabolic syndrome (metS) antecedents with serum spexin levels in obese adolescents.

Setting: A university- based tertiary care centre.

Patients and Methods: Eighty consecutive obese adolescents aged 10-18 y and 80 healthy peers were enrolled. Anthropometric measurements, pubertal examinations and clinical blood pressure measurements were performed using standard methods. Fasting blood samples were drawn for glucose, insulin, lipids, uric acid, alanine aminotransferase (ALT) and spexin. Homeostasis-model assessment -insulin resistance (HOMA-IR) was calculated. Metabolic syndrome (metS) was diagnosed using International Diabetes Federation criteria. Associations of serum spexin with clinical and laboratory related variables were assessed. Significance was granted for a p level ≤ 0.05 .

Results: Obese adolescents had lower serum spexin levels than healthy peers (50 pg/mL [25%-75% IQR: 25-98 pg/mL] and 67.0 pg/mL [25%-75% IQR:32.5-126.0 pg/mL; respectively], $p=0.035$). Twenty (25 %) obese adolescents were diagnosed as having metS. Obese adolescents with metS had lower spexin than those without metS (24.5 pg/mL [25%-75% IQR: 15.3-49.5 pg/mL] and 69.0 pg/mL [25%-75% IQR: 42.0-142.0 pg/mL]; respectively $p<0.0001$). The frequencies of hyperuricemia, IR and elevated ALT were similar in obese adolescents with metS and those without metS ($p > 0.05$ for all). Serum uric acid levels were correlated significantly with serum spexin after correcting for body mass index and HOMA-IR ($r=-0.41$, $p<0.05$).

Conclusions: Obese adolescents have reduced spexin levels, and this reduction is more pronounced in those with MS. The MS antecedent that had the most significant association with reduced serum spexin was elevated uric acid.

P1-39**Serum endocan as a predictive biomarker of cardiovascular risk in obese pediatric patients**

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Introduction: Endocan is a soluble dermatan sulfate PG (50kDa), composed by 165 amino acid core protein, that is expressed and secreted by endothelial cells of dermal microvasculature, coronary, pulmonary arteries, and capillaries from adipose tissue. It plays an important role in the pathogenesis of vascular disorders, inflammation, and neoangiogenesis.

Endocan biosynthesis is upregulated by inflammatory cytokines like TNF- α , IL-1, TGF- β 1, and by proangiogenic and growth factors like VEGF, EGF, and FGF-2; conversely, it is downregulated by INF- γ and insulin level, but this effect in obese patients is attenuated by insulin resistance.

Recent studies have already reported that endocan is a valid marker of endothelial cell damage in different conditions like cancers, systemic inflammation, obesity, and cardiovascular diseases, and that could be linked to the severity and outcomes of these disorders.

Objectives: The aims of our study are the following: a) to evaluate the use of endocan serum levels as an indicator of endothelial damage in children and adolescents with high BMI; b) to identify its possible correlation with other metabolic indices.

Methods and Results: The study included 19 patients with obesity (10 males, 9 females), aged between 2-18 years (mean age 11.94 ± 0.52), screened at the Pediatric Endocrinology Unit of Messina (Italy) from October 2018 to May 2020. We assessed weight, height, and BMI, and measured levels of endocan, total cholesterol, HDL-C, LDL-C, triglycerides, blood glucose, and insulin. The results, compared to a healthy controlled group, have shown upraised endocan serum levels in children with high BMI (2.03 ± 1.55 vs 0.82 ± 0.34 ng/mL, $p < 0.001$); demonstrating also a positive correlation trend between endocan and BMI ($p = 0.13$). Furthermore, endocan serum levels were significantly correlated to insulin levels ($p = 0.047$) (HOMA-IR: $p = 0.072$). These findings confirm the link between endothelial damage and insulin resistance in obese children. However, we did not find any association between endocan and lipid profile, or with fasting blood glucose value ($p = 0.926$). We also performed abdomen ultrasound in 12 children, revealing a correlation with steatosis, and with its grade ($p = 0.087$, $p = 0.088$, respectively), despite not raising statistically significant results, given the small sample size.

Conclusions: We can assume that endocan could be used, as a biomarker, also in children with obesity and that could be a valid predictor, in order to stratify the future cardiovascular risk in adulthood.

Liraglutide for the Management of Childhood Obesity

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Introduction: The prevalence of childhood obesity is continuing to increase worldwide and has become a major health concern. There are a number of serious complications to childhood obesity with significant long-term health implications if not managed in a timely matter. These complications include type 2 diabetes mellitus (T2DM), obstructive sleep apnoea (OSA), idiopathic intracranial hypertension (IIH) and non-alcoholic fatty liver disease (NAFLD). At present, lifestyle intervention is the recommended treatment option for childhood obesity and unfortunately, this is only successful in a small number of individuals. Glucagon-like peptide 1 (GLP-1) therapy has shown promising results for weight loss in adults, but data remains limited in the paediatric population.

Methods: Patients with significant complications secondary to obesity (including T2DM, insulin resistance, IIH, OSA, dyslipidaemia, hepatic fibrosis, delayed puberty and depression) attended a multidisciplinary team (MDT) weight management clinic. Individuals were started on once-daily subcutaneous Liraglutide injections and were seen every two weeks. Liraglutide was started at 0.6mg daily and increased, if required, to a maximum dose of 3mg.

Results: 7 patients have completed a 3-month treatment course of Liraglutide, with 3 of the patients completing 6 months in total. All patients are female with a mean age of 14.9 years (range:13-16 years). Mean percentage weight loss was 4.2% (1.2-9.7%) and 5.8% (4-8.2%) at 3 and 6 months, respectively. Significant weight loss (5.3kg, 95%CI 1.93-8.78, $p=0.009$) and significant reduction in body mass index [BMI] (2.09kg/m^2 , 95% CI 0.97-3.20, $p=0.004$) was noted at 3 months of treatment. This further continued with weight loss (6.9kg, 95% CI 1.33-12.53, $p=0.033$) and BMI reduction (2kg/m^2 , 95% CI 0.06-3.94, $p=0.047$) being significant at 6 months of treatment. During this period, one patient was able to discontinue acetazolamide as her IIH had resolved and another patient showed resolution of steatohepatitis. No side effects were reported due to Liraglutide.

Conclusion: The results have shown significant weight loss and BMI reduction in a cohort of adolescents following Liraglutide treatment over a 3 and 6-month period, along with an intense lifestyle programme supported by a dedicated MDT. These results show that the use of Liraglutide within an MDT setting could be a potential treatment option for children and young people with significant complications secondary to obesity.

Sex Endocrinology and Gonads A

Phenotypic Characteristics of Patients with 45,X/46,XY Mosaicism: Growth, Gonadal Pathology and Tumour Risk

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Background: The 45,X/46,XY mosaicism represents a wide spectrum of phenotypes, from phenotypically normal females to males and varying degrees of genital ambiguity. Growth seems to be impaired in these patients. It is associated with increased risk of germ cell tumours.

Aim: To evaluate growth, gonadal function and tumour risk in a large group of children with 45,X/46,XY mosaicism in a single tertiary centre.

Methods: We conducted a retrospective review of the records of patients with 45,X/46,XY mosaicism who presented from 1989 to 2020. The growth and histological results of gonadectomy or biopsy of patients were evaluated. Patients were divided into 3 groups as those with female external genitalia, ambiguous genitalia, or male external genitalia with respect to phenotypic characteristics at diagnosis.

Results: 45 patients were included. The age at diagnosis ranged from 0.03 to 17.5 years. Twenty-eight patients exhibited ambiguous genitalia, 14 patients had female external genitalia and 3 patients had normal male external genitalia. Twenty-four patients were raised as females and 21 patients as males. HeightSDS of 14(31.1%) patients were below -2 SDS at diagnosis and median heightSDS of 21 patients diagnosed before 2 years of age was -0.99(-2.22 / 0.12); however median heightSDS in 24 patients diagnosed after 2 years of age was -2.61(0.3 / -6.2). Short stature was more frequent in females than in males (50% vs 9.5%). Twenty-one patients reached adult height (AH). Growth hormone (GH) treatment was initiated in 10 patients. Although AHSDS of GH treated patients was significantly greater than their heightSDS before GH therapy ($p=0.013$), it was not significantly different from AHSDS of the untreated group. Seventeen (37.8%) patients exhibited phenotypical features and congenital anomalies of Turner syndrome other than short stature.

In female external genitalia group, majority of patients (78.6%) had bilateral streak gonads, in ambiguous genitalia group 37.5% of patients had bilateral dysgenetic testes, 50% of patients had unilateral dysgenetic testis and contralateral streak gonads.

In ambiguous group, 2 patients, raised as female, had gonadoblastoma and germ cell neoplasia *in situ* in their bilateral abdominal dysgenetic testis. In female external genitalia group, one patient with bilateral streak gonad had gonadoblastoma.

Conclusions: Patients with 45,X/46,XY should be screened for congenital anomalies like Turner syndrome. GH therapy seems to improve AH of patients. Both ambiguous group and female group have increased risk of germ cell tumors.

P1-42

Disorders of sex development: clinical and genetic heterogeneity

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Background and Aims: Disorders of sex development (DSD) are a group of rare congenital conditions. Clinical management of patients with DSD is often difficult and requires multidisciplinary approach.

Material and Methods: Twenty-eight patients aged 1 to 18 years with different forms of 46, XY DSD were included. The subjects have undergone a clinical examination, karyotype analysis followed by the next generation sequencing (NGS) using MiSeq (Illumina). We designed HaloPlex (Agilent) gene panel that included coding regions of 80 candidate genes associated with DSD. All variants identified by NGS were confirmed by Sanger sequencing. We performed bioinformatics analysis using OMIM, «1000 genomes», ESP6500, Genome Aggregation Database projects. To assess the clinical significance of the identified variants we used ClinVar database and American College of Medical Genetics and Genomics criteria.

Results: Out of 28 patients pathogenic, likely pathogenic, variants with unknown significance were identified in 11 patients (39 %). In combination with clinical phenotype these variants were determined as causative for DSD. Nine patients (82%) had likely causative variants in one gene (of monogenic origin), while 18% had variants in two genes simultaneously (of oligogenic origin). 43% of the identified gene variants have not been previously reported. The variants in *NR5A1* were associated with gonadal dysgenesis in two patients; the variants in *MAP3K1* were also found in another two patients with gonadal dysgenesis, variants in *AR* – in three patients with CAIS, variant in *MAMLD1* was associated with proximal form of hypospadias, variant in *CYP17A1* was associated with testosterone biosynthetic defect. Among the two patients with variants of oligogenic origin, one had variants in *MAP3K1* and *MAMLD1* genes and was clinically characterized by hypospadias; the second had variants in *AR* and *SEMA3A* and was diagnosed with PAIS. There were also two patients with variants in *NR5A1* of familial inheritance.

Conclusion: NGS-based targeted sequencing is a promising technique to improve the differential diagnosis, genetic counseling and management strategies for patients with DSD.

P1-43

Broad range of phenotypes in an international cohort of 75 DSD individuals with SF-1/NR5A1 variants

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Conclusion and Outlook: More than half of individuals with SF-1 variants had multiple organ abnormalities, with a broad spectrum of phenotypes. Systematic phenotyping together with more comprehensive gene profiling will allow to find patterns in patients with SF-1 variants and to identify likely disease-causing variants in additional genes that might impact the phenotype. Genotype-phenotype patterns will help to evaluate the individual risk for adverse health outcomes and to improve long-term care of individuals with SF-1 variants.

P1-44

Adolescents and young adult men with non-syndromic hypospadias: testicular function and in-depth genetic screening

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Background: Hypospadias affects approximately 1/200 newborn males. Based on the testicular dysgenesis syndrome hypothesis, some may be suspected of having persistent testicular dysfunction later in life. Few clinical data currently support this hypothesis.

Methods: Cross-sectional assessment of hypospadias cases (n=193) and controls (n=50), aged 16-21 years, recruited at Ghent University Hospital and Medical University Vienna. Exams included genital examination, morning blood sampling and diagnostic semen analysis (WHO 2010). Genetic study: exome-based testing of genes (n=241) involved in gonadal development and spermatogenesis in those born appropriate for gestational age (AGA) with poor outcome or familial hypospadias (n=73) and all born small for gestational age (SGA) (n=26). In the latter, a gene panel (n=233) for low birth weight/length and poor growth was also analyzed. Oligogenic variant combinations were sought using Oligogenic Resource for Variant AnaLysis (ORVAL).

Results: None of the participants had experienced problems regarding pubertal onset and progression. Higher gonadotropin levels were found in complex hypospadias and SGA compared to controls (LH 6.7 ± 3.87 and 6.2 ± 2.52 versus 5.0 ± 1.51 U/L; $p=0.001$ and 0.034 ; FSH 5.2 (IQR:4.25) and 3.8 (IQR:3.94) versus 2.7 (IQR:2.03) U/L; $p<0.001$ and 0.004 , respectively). There were no differences between groups in total, free testosterone and dihydrotestosterone concentrations. Insulin-like factor 3 concentrations were higher in hypospadias compared to controls (0.66 vs 0.49 ng/mL, $p=0.001$). Oligo- or azoospermia was found in 19/149 AGA (12.7%) and 13/22 (59.1%) SGA cases compared to 2/50 (4%) controls ($p=0.081$ and <0.001 , respectively). Oligo- or azoospermia was more common in AGA cases with complex hypospadias

(31.3%) compared to isolated hypospadias ($p=0.035$). No difference was seen in SGA cases, stratifying for severity of hypospadias. No (likely) pathogenic variants or variant combinations were found in any of the investigated genes, although some potentially interesting variants of unknown significance were identified.

Conclusion: Steroidogenesis and pubertal development were unaffected in patients with non-syndromic hypospadias, although elevated LH levels suggest subclinical Leydig cell dysfunction in SGA and complex cases. Higher INSL3 potentially reflect relative Leydig cell hyperplasia. Fertility is a major concern, especially in SGA and complex hypospadias. In these groups, the appropriateness of diagnostic semen analyses at the end of puberty should be considered as these exams are non-invasive and inexpensive. As no monogenetic causes nor pathogenic oligogenic combinations were found, further genetic studies in familial hypospadias should focus on multifactorial mechanisms with an emphasis on non-coding variants with a small effect.

P1-45

Bilateral testicular regression: genetic etiology and outcome in a large Belgian series

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Background: Bilateral testicular regression (BTR) is characterized by the absence of both testicles in a newborn male or shortly thereafter, and presenting as bilateral cryptorchidism with undetectable AMH levels and the absence of Müllerian structures on pelvic ultrasound. Depending on when the regression occurs during fetal development, the condition can be associated with a micropenis. Few studies have explored the etiology and long-term outcome of BTR.

Methods: Cross-sectional study of boys/men with BTR (n=31) recruited in five Belgian centers at an age of 14.3 ± 5.4 years. During the study visit a clinical and genital exam was performed. Data regarding initial presentation and management were collected retrospectively. Genetic analysis: exome-based testing of genes (n=241) involved in gonadal development and spermatogenesis.

Results: All had bilateral absent testes or non-functional testicular remnants. Seven out of 31 boys had associated micropenis. BTR diagnosis was established by laparoscopy in 11/31 (35.5%), low AMH levels in 7/31 (22.6%), an hCG-stimulation test in 9/31 (29%) or a combination of these in 4/31 (12.9%). Nine (29%) boys received IM Sustanon during childhood (25-50mg/month for 3-6 months) at a median age of 6 months, with limited or no effect in two. Testosterone replacement was initiated in 21/31 (67.7%) at a median age of 12.4 years (IQR: 1.3). At the study visit, fourteen

had reached Tanner 4-5, and six (42.9%) had bilateral testis prostheses placed at a mean age of 16.5 ± 0.9 years. Mean stretched penile length at the end of puberty was 10.0 ± 2.6 cm, representing a mean penile growth of 3.9 ± 1.4 cm over the course of treatment and a persistent micropenis (< 7.5 cm) in one. Only 1/14 had a final height below his midparental height range. Genetic analysis revealed heterozygous (likely) pathogenic variants in *DHX37* (p.Arg334Trp and p.Arg308Gln) in two cases, respectively. Both had a distinct phenotype, with a severe micropenis (10-20 mm) which showed limited to absent response to (dihydro)testosterone treatment during infancy. One of them developed unilateral neurosensory hearing loss at the age of 8 years. No other (likely) pathogenic variants were found in this cohort.

Conclusion: Pubertal height gain and penile growth with testosterone supplementation are generally satisfactory in BTR. The previously reported involvement of *DHX37* in the etiology of BTR was confirmed in two cases, who both had a micropenis and no response to (dihydro)testosterone in infancy. Further studies are needed to determine whether *DHX37* variants characterize a specific subgroup of BTR with severe undervirilization and possible extra-testicular manifestations.

P1-46

Endocrine & Molecular Genetic Findings In XY Boys Investigated For A Disorder Of Sex Development: the Glasgow Experience

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Introduction: Advances in diagnostic capability in the field of DSD hold great promise but need a regular review.

Objectives: To study the range of endocrine and molecular genetic variation in a group of boys undergoing investigation for XY DSD.

Methods: 157 boys with median age of 0.9 yrs (range, 0, 18) evaluated by the DSD Diagnostic Board in Glasgow from 2016 to 2021 were included. Sequence variants were classified according to ACMG guidelines and, in addition to pathogenic and likely pathogenic variants, variants of uncertain significance (VUS) were assigned as causative or coincidental, depending on whether the phenotype was consistent with genotype, or not.

Results: The median external masculinization score (EMS) was 8.5(2,12). Of 157 boys, an endocrine abnormality was present in 34(22%) with a median EMS of 8.3(2,12) including a disorder of gonadal development(DGD) in 20(13%), LH deficiency(LHD) in

9 (6%), disorder of androgen synthesis(DAS) in 2(1%) and disorder of androgen action(DAA) in 1(0.5%). In the remaining 121(78%) with non-specific DSD(NS-DSD), the median EMS was 9(2,12). Of the 107 boys who had molecular genetic analysis by a combination of methods, variants were found in 8/56(14%) by Sanger sequencing of 7 genes, 1/6(17%) by NGS of 21 genes, and 39/80(49%) by NGS of 56 genes. Of 17 boys with DGD who were tested, 4 had VUS with no phenotypic consistency (*FGFR1*, *LHB*, *CYP11A1*, *NROB1*). Molecular genetic diagnosis was reached in 1/1(100%) patient with DAS identifying variant in *HSD3B3* and in 1/1(100%) patient with DAA with variants in *AR* and *MAMLD1*. Among boys with LHD, 3/8(38%) had *ANOS1*, *GNRHR*, *CHD7* and *FGF8* variants. In 23/79(29%) of boys with NS-DSD who had genetic analysis, causative variants were detected in *MAMLD1*, *DHCR7*, *NR5A1*, *WDR11*, *HSD17B3*, *ANOS1*, *CHD7*, *DHCR7*, *POR*, *HSD3B2*, *KISS1R*, *CYP17A1*, *PROK2*, *SPRY4*, *AR* and *FGF8*. Of these 23 boys, 10 coincidental VUS were also detected in 6 (*PROKR2*, *POR*, *SOX10*, *MAP3K1*, *SPRY4*, *DHCR*, *HSD17B3* and *CYP11A1*). One patient who had not had biochemical evaluation also harboured a VUS in *GATA4* and this was consistent with his phenotype. In total, 19 coincidental VUS were identified in 18 boys with median EMS of 8.8(2,11) (NS-DSD, 14; DGD, 4). EMS in boys harbouring causative variants and normal (NS-DSD, 23) or abnormal (DGD, 2; LHD, 3) endocrine tests was 6(2,12) and 8.5(2,12), respectively.

Conclusions: The degree of undermasculinisation in boys with DSD appears unrelated to the presence of genetic or endocrine abnormalities. Coincidental VUS are commonly encountered in patients with XY DGD and NS-DSD who have no evidence of a gonadal dysfunction or disorder of androgen synthesis, and this requires a careful and standardised interpretation.

P1-47

STK11 gene variant (Peutz-Jeghers Syndrome) presenting with unilateral pre-pubertal gynaecomastia and macro-orchidism without muco-cutaneous pigmentation or gastrointestinal symptoms

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Introduction: We report two siblings presenting with pre-pubertal gynaecomastia and macro-orchidism, who were later diagnosed with Peutz-Jeghers Syndrome (PJS) secondary to a *STK11* gene variant. Importantly neither child fulfilled the clinical criteria for diagnosis at presentation, with no muco-cutaneous pigmentation nor gastrointestinal symptoms.

Case report: Sibling 1 was referred to Paediatric Endocrinology aged 4 years with unilateral gynaecomastia. Examination revealed right-sided gynaecomastia and pre-pubertal macro-orchidism (4mls) without evidence of virilisation (P1, G1) or testicular lumps. Investigations indicated a normal prolactin level, an undetectable oestradiol level, normal tumour markers and low or undetectable androgen levels. An LHRH test demonstrated a pre-pubertal response. A urine steroid profile was normal and a bone age was

not advanced. MRI of the pituitary and abdomen/pelvis did not identify any abnormalities. Six-monthly clinical follow-up did not identify acceleration in height velocity, virilisation or progression of gynaecomastia. Testicular volumes slowly increased to 6mls by the age of 9 years without virilisation. During this time, Sibling 2 was referred to Paediatric Endocrinology aged 3 years. Examination revealed bilateral gynaecomastia and pre-pubertal macroorchidism (4mls) also without evidence of virilisation (P1, G1) or testicular lumps. Baseline investigations were similarly normal. A testicular ultrasound identified bilateral testicular microlithiasis. Neither child had muco-cutaneous pigmentation nor gastrointestinal symptoms. Genetics revealed a heterozygous variant c.910C>T p.(Arg304Trp) in exon 7 of the *STK11* gene in both siblings and their father. Their father subsequently underwent a capsule endoscopy, which identified multiple intestinal polyps throughout his small bowel and confirmed the pathogenicity of this variant and a diagnosis of PJS.

Discussion: Making an early diagnosis of PJS is important so that necessary cancer surveillance can be instituted. Pertinent endocrinology learning points from this case are as follows. Firstly, PJS is a recognised cause of pre-pubertal gynaecomastia due to overexpression of aromatase. We are the first to report a diagnosis of PJS following presentation with pre-pubertal unilateral gynaecomastia and without muco-cutaneous pigmentation or gastrointestinal symptoms. Ongoing surveillance for signs of oestrogen excess (increasing height velocity, advancing bone age and progressing gynaecomastia) is essential, as aromatase inhibitors may be a future consideration. Secondly, PJS is associated with Large Cell Calcifying Sertoli Cell Tumours (LCCSCT). Annual screening via testicular examination and ultrasound is important. In the case of sibling 2, bilateral testicular microlithiasis was not thought to be indicative of widespread tumour. Thirdly, genetic testing and investigation of parents may help confirm a diagnosis in children.

P1-48

Gonadal Outcome in 17 β -HSD deficiency and 5 α -reductase deficiency

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Introduction: 5 α -reductase type 2 deficiency (5 α -RD) and 17 β -HSD type 3 deficiency (17 β -HSDD) are rare differences/disorders of sex development (DSD) in which impairment of steroidogenic enzymes causes undervirilisation in patients with a 46,XY genotype. We aim to enlarge the limited knowledge on long-term gonadal function and gonadal pathology in these conditions.

Methods: Data on phenotype, laboratory results and hormone treatment from patients with genetically confirmed 5 α -RD and 17 β -HSDD aged >16 years from 10 centres in nine countries were collected via the International DSD (I-DSD) Registry. When a gonadectomy or gonadal biopsy had been performed, pathology reports were collected as well as gonadal tissue or images. Data are presented as median (IQR) unless stated otherwise.

Results: Patients with 5 α -RD (n=17) were 12.0 years (5.0-16.5) at diagnosis. External genitalia score (EGS) at first presentation was 7.5 (3.9-9.3). Ten patients were assigned female sex. Five patients changed sex (four female to male) at an age ranging from 15 to 23 years. Gonadectomy was performed in six subjects at age 10 years (6.0-18.3). Subjects without gonadectomy entered puberty spontaneously. However, four were treated with dihydrotestosterone during puberty.

Patients with 17 β -HSDD (n=16) were 13.5 (7.5-19.0) years at diagnosis and had an EGS of 2.5 (0.9-5.3) at first presentation. All subjects were raised female; three decided to change to the male gender at an age ranging from 16 to 25 years. Three subjects were treated with GnRH analogues to prevent virilisation, one of whom changed to the male gender. In 12 patients a gonadectomy was

performed at age 8.0 years (2.5-13.8). Male patients did not require androgen supplementation.

No germ cell (pre)malignancy was present based on the 11 available histology reports. Uniform reassessment of gonadal tissue is being performed.

Discussion: A significant percentage (24%) of individuals with 5 α -RD and 17 β -HSDD changed sex as has been reported in previous studies, mostly in late adolescence/early adulthood. Uncertainty about gender identity development led to the introduction of GnRH analogues in this group of patients to prevent virilisation before making a definitive decision about gonadectomy. When left in situ, endocrine function of the gonads is sufficient in most individuals and germ cell (pre)malignancies seem uncommon in these patients, but central reassessment of gonadal material is ongoing to confirm this finding. Together, these data support a conservative approach towards definitive sex assignment, genital surgery and gonadectomy early in life in these conditions.

P1-49

Biallelic *PPP2R3C* mutations are associated with partial and complete gonadal dysgenesis in 46,XY and 46,XX individuals

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Context: *PPP2R3C* encodes the B γ regulatory subunit of the protein phosphatase 2A (PP2A), which is a serine/threonine phosphatase involved in the phospho-regulation processes of

mammalian cells. We have recently reported homozygous and heterozygous mutations in *PPP2R3C* in patients with syndromic 46,XY complete gonadal dysgenesis (MEGD syndrome) and impaired spermatogenesis, respectively. In this study, we have further investigated the role of *PPP2R3C* in the etiology of gonadal dysgenesis.

Method: We sequenced the *PPP2R3C* gene in four new patients from four unrelated families. The clinical, laboratory and molecular characteristics were investigated. We have also determined the requirement for *Ppp2r3c* in mice using CRISPR/Cas9 genome editing.

Results: We have identified a homozygous c.578T>C (p.L193S) *PPP2R3C* variant in one 46,XX girl with primary gonadal insufficiency, 2 girls with 46,XY complete gonadal dysgenesis, and one undervirilized boy with 46,XY partial gonadal dysgenesis. The patients with complete gonadal dysgenesis had low gonadal and adrenal androgens, low AMH and high FSH and LH concentrations. All patients manifested characteristic features of MEGD syndrome (typical facial gestalt, low birth weight, myopathy, rod and cone dystrophy, anal atresia, omphalocele, sensorineural hearing loss, dry and scaly skin, skeletal abnormalities, renal agenesis, and neuromotor delay).

We then generated mice (C57BL6/N) lacking functional *Ppp2r3c* by using CRISPR/Cas9 genome editing to delete an 1100 bp segment encoding a critical early exon. Heterozygotes for the deletion allele appeared overtly normal and fertile. Timed mates between heterozygous animals were used to generate homozygotes at 14.5 days *post coitum* (dpc) in order to allow inspection of the fetal gonads after the sex-determining period. However, genotyping revealed that no homozygous animals were detected at this stage. Inspection of embryos at earlier stages (9.5 dpc and 8.5 dpc) revealed evidence of dead embryos. Genotyping indicated that this material was derived exclusively from homozygous embryos. We conclude that loss of function of *Ppp2r3c* is not compatible with viability in mice and results in embryonic death from 7.5 dpc or earlier.

Conclusion: Our data indicate essential roles for *PPP2R3C* in mouse and human development. Germline homozygous mutations in human *PPP2R3C* are associated with distinctive syndromic gonadal dysgenesis of varying severity in both 46,XY and 46,XX individuals.

P1-50

Pathogenic variants in the human m⁶A reader YTHDC2 are associated with primary ovarian insufficiency

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Background: Primary ovarian insufficiency (POI) is genetically mediated in up to 30% of cases. Many genes associated with POI have roles in early ovary developmental processes, including meiosis.

Objectives: We investigated the genetic mechanism underlying early-onset POI in three young women presenting with absent puberty: two sisters from a consanguineous pedigree and a third unrelated proband.

Methods: Exome sequencing and filtering using an autosomal recessive model was performed in the affected patients and their unaffected family members. RNA sequencing and quantitative reverse transcriptase PCR were used to study the expression of key genes at critical stages of human fetal gonad development (Carnegie Stage (CS) 22/23, 9 weeks post conception (wpc), 11wpc, 15/16wpc, 19/20wpc) and in adult tissue. Expression data were matched to cell populations using publicly available single-cell RNA sequencing data. Immunohistochemistry was used to study protein expression. Patient peripheral leukocytes were used to investigate the effect of variants of interest on transcript stability and splicing. The cellular expression and localisation of variants were studied using *in vitro* HeLa/HEK-293 cell systems and co-immunoprecipitation studies. *In silico* modelling characterised wild-type and mutant proteins.

Results: Exome sequencing revealed pathogenic variants in YTHDC2 co-segregating with the POI phenotype: in the two sisters, a homozygous variant c. 2567C>G, p.P856R in the HA2 domain; in the third patient, a homozygous c.1129G>T, p.E377* variant. YTHDC2, an m⁶A reader RNA helicase, and its partner

protein MEIOC have been associated with meiotic progression in animal studies. We demonstrated higher YTHDC2 and MEIOC expression in the late (15/16wpc) compared to the early (CS22/23) fetal ovary (log₂FC 1.14, p.adj 2.18E-08), coincident with the female meiotic peak. Higher YTHDC2 (log₂FC 0.5, p.adj <0.05) and MEIOC (log₂FC 5.2, p.adj <0.05) expression was seen in the ovary compared to testis at 15/16wpc. YTHDC2 was highly expressed in the adult testis, corresponding with male meiosis. Single-cell sequencing data localised YTHDC2 expression to human fetal ovary meiotic germ cells. Immunohistochemistry of a 20wpc human fetal ovary showed cytoplasmic staining of YTHDC2 in meiotic cells. Neither YTHDC2 variant affected transcript splicing nor stability. The p.P856R variant did not affect YTHDC2 cellular localization nor YTHDC2/MEIOC co-localization. *In silico* modelling demonstrated that the p.P856R variant results in a more stable, less flexible protein that affects downstream conformational kinetics of the HA2 domain.

Conclusion: We show that the m⁶A reader YTHDC2 plays a key role in meiosis regulation and human gonadal development and associate pathogenic variants within YTHDC2 with POI.

Bone B

P1-51

A Global Natural History Study (NHS) of Fibrodysplasia Ossificans Progressiva (FOP): Normal Long Bone Growth and Abnormalities in Younger Patients over 36 Months

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Background: FOP is an ultra-rare, severely disabling genetic disorder characterised by progressive heterotopic ossification. The

median age at diagnosis is 5 years and patients are supported by multiple specialties. We describe normal long bone growth changes and incidence of bone abnormalities in participants with FOP aged <18 years in a 3-year, prospective, global NHS (NCT02322255).

Methods: Individuals with FOP aged ≤65 years with a documented ACVR1^{R206H} mutation were enrolled. Normal long bone growth changes and abnormalities were assessed over 36 months. Linear growth assessments and knee height measurements were completed in triplicate; linear height was measured with a stadiometer and knee height with a knee caliper. Femur/tibia lengths and abnormalities of epiphyseal plates were determined using low-dose whole-body computed tomography (WBCT).

Results: 114 individuals were included in the Full Analysis Set at Baseline; 66 were aged <18 years. Mean (standard deviation [SD]) change from Baseline to Month 36 in femur and tibia length was highest in males aged <10 at Baseline (6.42 [1.78] cm, n=5) and females aged <8 at Baseline (5.46 [0.69] cm, n=2), respectively, and lowest in males aged 14–<18 at Baseline (0.18 [0.63] cm/0.28 [0.45] cm, n=5). Mean (SD) change in knee height from Baseline to Month 36 was highest in females aged <8 at Baseline (6.75 [0.64] cm, n=2), and lowest in males aged 14–<18 at Baseline (1.48 [1.32] cm, n=5). Some participants recorded knee height losses. No female participants aged 14–<18 at Baseline had measurements for femur/tibia length or knee height at Month 36.

Linear height z-scores decreased over 36 months. Mean (SD) z-scores at Baseline were 0.70 (1.04), 0.08 (1.32) and 0.09 (1.41) for participants aged <8, 8–<15 and 15–<18 years, respectively; the smallest decrease occurred in participants aged <8 at Baseline (–0.09 [0.73], n=8), and the greatest decrease occurred in participants aged 15–<18 at Baseline (–0.96, n=1).

At Baseline, 26 (39.4%) participants aged <18 years had a bone abnormality at knee epiphyseal plates; at Month 36, 9/22 (40.9%) had a recorded abnormality. All knee abnormalities were dense metaphyseal lines. No hand/wrist abnormalities were reported.

Conclusions: Knee height losses and decreasing linear height z-scores, particularly in adolescent participants, highlight difficulties associated with obtaining accurate growth and height measurements in patients with FOP who have worsening skeletal deformities over time. Incidence of knee abnormalities appeared to remain stable over 36 months, although WBCT is less sensitive than radiographs in detecting such bone abnormalities.

P1-52

Impact of Vertebral Fracture on Auxological Profile and Insulin-like Growth Factors of Children after Acute Lymphoblastic Leukemia Treatment

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Purpose: To investigate the overall prevalence of vertebral fractures (VF) following childhood acute lymphoblastic leukemia (ALL) treatment and examine the association of VF with growth trajectory and insulin-like growth factors

Methods: Children (n=172; 59.3 % male) diagnosed with ALL at age between 2 and 18 years were assessed for VF by screening the lateral thoracolumbar spine radiographs (Genant's semi-quantitative method) when treatment was completed (baseline). Anthropometric measurements between pre- to post-treatment period were obtained and the association of VF with insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3) were examined.

Results: Thirty-five children (20.3 %) had vertebral fractures at baseline. Among children with vertebral fractures, 97.1 % had either mild or moderate deformity, and the 5th lumbar vertebrae was the most frequently injured site (20.0 %). Median lumbar spine bone mineral density Z-score was –1.0 (IQR of –1.6 and –0.8) in children with VF. Baseline Z-scores for height and weight were lower in children with VF than without VF (–0.5±1.3 and 0.0±0.9, P=0.01; –0.2±1.6 and 0.3±1.1, P=0.04, respectively). Height Z-score in children with VF had greater height decline than without VF (0.5±0.6 and 0.2±0.8; P=0.02). Children with VF had lower IGF-1 and IGFBP-3 Z-score than without VF at baseline (–1.2±1.0 and 0.0±0.8, P<0.01; –2.3±1.1 and –1.3±1.0, P<0.01). Decrease in IGF-1 level was associated with the presence of VF (OR=0.3(95 % CI of 0.2–0.5), P<0.01).

Conclusion: Substantial number of children encounter VF after ALL treatment is completed and the presence of VF might be associated with compromised auxological state, prominent height decline and IGF-1 deficiency.

P1-53

Growth and Puberty in Patients with Osteogenesis Imperfecta

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Aim: Osteogenesis imperfecta (OI) is a genetic disease of extracellular matrix presenting with varying degrees of skeletal fragility. The study aims to evaluate growth and pubertal characteristics of 83 patients with OI.

Materials and Methods: Patients were classified according to Silience clinical classification criteria. Demographic data, clinical findings, growth and pubertal characteristics were recorded from medical charts, retrospectively.

Results: Eighty-three (31 female/52 male) patients were analyzed in the study.

The median follow-up duration was 4.7 (0.6–17.7) years. Fifty-one (61.4%) patients received bisphosphonate therapy. With treatment, improvement in the median of bone mineral density Z-score of patients with OI-I and OI-III was attained. During follow-up, height-SDS significantly increased in both OI-I and OI-III on osteoporosis treatment; however, patients who achieved final adult height SDS did not improve in height. The frequency of overweight and obesity was found to be increased at the last evaluation compared to admission. Precocious puberty (PP) and early puberty (EP) were found to be 20% and 10% in girls, respectively, and they were 15.7% and 47.3% in boys.

Conclusion: Reduced growth, significant weight gain over time due to impaired mobility and high frequency of PP/EP require effective functional modifications as early as possible in children with OI.

Keywords: Osteogenesis imperfecta, Growth, Puberty

P1-54

Decreased bone mineral density in children receiving long-term anticoagulation is associated with pubertal development

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Background: Children and adolescents with chronic conditions are at increased risk of secondary osteoporosis. In adult patients, long-term anticoagulation (LTA) including Vitamin K antagonist (VKA) treatment is associated with lower bone mineral density and hip fractures. In children and adolescent, risk factors for impaired skeletal health and the role of LTA on bone metabolism during the vulnerable phase of linear bone growth remain poorly defined.

Aims: To assess bone mineral density (BMD) and to identify risk factors for decreased BMD in children with chronic diseases receiving LTA.

Methods: Children under LTA were included in a cross-sectional approach to assess age, height and sex-adjusted BMD on a Hologic QDR 4500. Further investigations included anthropometric and biochemical markers for skeletal metabolism, and carboxylation-specific osteocalcin as marker for Vitamin K status.

Results: 39 children (age 4-18 years) were included, 31 (79%) on VKA and 8 (21%) on direct oral anticoagulants. Mean body length below average (-0.56SDS), BMI was Mean BMD was decreased for both lumbar spine (-0.7SDS) and total body less head (TBLH; -1.32SDS). 9 patients (23%) had a history of fractures. Earlier pubertal stages were strongly associated with decreased BMD-TBLH (-1.9SDS; $p=0.01$). Additionally, low body mass index (BMI) correlated significantly with reduced BMD (R^2 0.24; $p=0.003$). Neither LTA type, treatment intensity nor treatment duration were associated with BMD alterations. Interestingly, the undercarboxylated osteocalcin fraction strongly correlated with patients' age (R^2 0.28; $p<0.001$) but neither with BMD, duration or intensity of LTA. Vitamin D deficiency was detected in 26% of patients with significantly lower values after onset of puberty (-34.5%; $p=0.03$).

Conclusion: In children with chronic diseases under LTA we found substantially reduced BMD. While type of anticoagulation was not associated with BMD, low BMI and delayed progression of puberty represent important risk factors for decreased BMD in children. Awareness of potential modifiers of BMD and high rates of Vitamin D deficiency in pubertal patients could contribute to improve bone health in this vulnerable patient group.

P1-55

Premature epiphyseal fusion induced by a retinoic acid agonist in a young girl with fibrodysplasia ossificans progressiva

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Retinoic acid receptor agonists can have dramatic negative effects on growth and even induce premature growth cessation and epiphyseal fusion (1, 2).

An 11 5/12-year-old, prepubertal girl with fibrodysplasia ossificans progressiva presented in our pediatric skeletal disorders clinic with the concern of early growth cessation. She had participated in a clinical trial of Palovarotene ("MOVE", NCT03312634), a retinoic acid receptor-gamma agonist, since the age of 9 10/12 years. At the visit, she had recently discontinued her participation in the study. During the 19 months since starting on Palovarotene, her height had only increased 1.9 cm to 136.4 cm. A skeletal survey detected fusion of several growth plates that normally remain open until the end of puberty including the growth plates of proximal humerus, distal ulna and distal radius. One year after stopping Palovarotene, she was in early puberty and her height had increased another 3.9 cm to 140.3 cm (-2.6 SDS). Measurements of height, sitting height, and arm span confirmed that growth of arms and legs had ceased, whereas growth of the spine continued.

This report supports previous findings indicating that high-dose retinoic acid receptor agonists can induce premature epiphyseal fusion even before puberty and may therefore cause significant, disproportionate short stature if used in young children. The finding that growth of the spine, but not legs and arms, resumed after the treatment was discontinued suggests that long bones are more susceptible than vertebrae to retinoic acid-induced epiphyseal fusion.

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Chondrocyte regulating and other growth plate genes are invaluable growth regulators: a study on children with short stature from 55 consanguineous families

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Introduction: Statural growth is regulated by multiple genetic, epigenetic and environmental mechanisms. The GH-IGF-1 axis was long believed to be the main linear growth regulator in children until more recent studies showed that the complex regulation of growth plate chondrocytes play an equal role. In order to extend our knowledge about the genes involved in short stature, we studied a unique cohort of children with short stature from consanguineous families living in Sulaymani in Kurdistan, Iraq.

Patients and Methods: Fifty-five consanguineous families, with children shorter than -2.3 SDS at the time of examination (median height -3.3SDS), who were examined at the pediatric endocrine outpatient clinic of the Dr. Jamal Pediatric Teaching Hospital in Sulaimani between January 2018 and February 2020, were included in the study. In families with more than one child with short stature, the shorter sibling was selected as the proband (median age 8 years). Four non-related patients were subsequently excluded due to the later diagnosis of Turner, Edwards and Silver-Russell syndromes. With their consent, the remaining 51 probands' DNA was analyzed by Whole Exome Sequencing (WES) methods. The data were processed by a bioinformatic pipeline and detected variants were filtered using variant analysis software. Selected potentially pathogenic variants were confirmed using Sanger sequencing methods and evaluated by the American College of Medical Genetics (ACMG) standards.

Results: A monogenic cause of short stature was elucidated in 17 of 36 (47%) probands who were analyzed thus far. Pathogenic or likely pathogenic variants were found in genes involved in the GH-IGF-1 axis (*GHR*), in the extracellular matrix of the growth plate (*COL1A2*, *MMP13*, *LTBP3*, *ADAMTS17*), in the regulation and function of chondrocytes (*NPR2*, *PTPN11*, *PCNT*, *CCDC8*, *CTSK*, *FLNB*), and other genes (*PTCH1*, *GALNS*, *DNACJ21*, *ZSWIM6*, *GNPTG*, *SLC34A3*). Thereby, 10 variants were in growth plate genes, thirteen variants are homozygous and eleven variants are novel. Unexpectedly, three variants show autosomal dominant inheritance (*NPR2*, *COL1A2*, *PTCH1*) and one is de-novo (*PTPN11*). The remaining 15 probands are still being analyzed.

Conclusion: Using WES methods, we successfully elucidated the genetic cause of short stature in 47% of probands analyzed thus far. More than half of the probands harbored a pathogenic variant in genes involved in regulation and function of chondrocytes, and/or encoding components of cartilaginous matrix. These results further strength the concept, that genes affecting the growth plate (chondrocytes and the extracellular matrix) play a crucial role in growth regulation.

High rate of positive genetic findings in children born small for gestational age with persistent short stature (SGA-SS): Growth plate genes as key regulators of intrauterine growth

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Background: Ten percent of children born small for gestational age fail to catch-up and remain short during childhood (SGA-SS). Several genes causing SGA-SS have been described, however, in most cases, the mechanisms of prenatal and postnatal growth impairment remain unknown.

Aim: To decipher genetic etiologies within a large single-center cohort of SGA-SS children in order to better understand the pathophysiological mechanisms leading to prenatal and postnatal growth failure.

Patients and Methods: Between the years 2008-2018, a total of 822 patients were treated with growth hormone (GH) in our center, 306 of them were classified as SGA-SS (birth length and/or birth weight <-2 SD for their gestational age and sex, height <-2.5 SD after 4 years of life). In 166/306 GH treated SGA-SS children, the DNA of the child and both of his/her parents was available for genetic testing - these were included to the study. In case of a clinical suspicion on a specific genetic disorder, targeted genetic examination (karyotype/FISH/MLPA/Sanger sequencing) was performed. Children with unknown genetic SGA-SS etiology were subsequently examined using next-generation sequencing methods (whole exome sequencing or targeted panel of 399 growth-related genes). All the genetic variants were classified using American College of Genetics and Genomics (ACMG) guidelines. The parents' DNA was examined by Sanger sequencing to evaluate the segregation of the genetic variants in the families.

Results: The genetic etiology was elucidated in 84/166 (51%) children so far. We confirmed (likely) pathogenic gene variants affecting components of cartilaginous matrix in 22/84 (26%) (*ACAN* [in three], *COL11A1* [in five], *COL1A1*, *COL1A2*, *COL2A1* [in five], *COL9A2*, *FLNB* [in five], *MATN3*), impaired paracrine regulation of chondrocytes in 6/84 (7%) (*FGFR3* [in two], *NPR2* [in three], *SOX9*), *SHOX* gene defects in 11/84 (13%), gene variants affecting other components of intracellular regulation and signaling in 11/84 (13%) (*CDC42*, *KMT2A*, *KMT2D*, *LMNA*, *NSD1*, *SRAP*, *PTPN11* [in two], *SON*, *SOS1* [in two]) genes affecting pituitary development and/or the GH-IGF-1 axis in 13/84 (16%) patients (*GHR*, *GHSR*, *HGMA2* [in two], *IGFALS*, *IGF1R* [in three], *IGF1*, *LHX4*, *OTX2*, *STAT3*, *PTCH1*) Silver-Russell syndrome (11p15 [in eight], *UPD7*) in 12/84 (14%), and miscellaneous single-gene or chromosomal aberrations (*TRPS1*, *TRHR*, *RAI1*, chromosomal microdeletions and/or translocations) in 9/84 (11%) children.

Conclusions: The mechanisms leading to SGA-SS can frequently be identified by modern genetic techniques. The

etiological spectrum reflects the complexity of growth regulation. Genes affecting the structure and function of the growth plate play a key role.

P1-58

AAV liver gene therapy-mediated inhibition of FGF23 signaling as a therapeutic strategy for X-linked hypophosphatemia

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Adeno-associated virus (AAV) gene therapy reached the maturity and a liver-targeting approach is currently used as a replacement treatment for rare hepatic and muscular diseases. X-linked hypophosphatemia (XLH) is a rare disease associated with hyperfunction of fibroblast growth factor 23 (FGF23) in bone and characterized by severe skeletal deformities and short stature. The current medical therapies for XLH requires life-long repeated treatment presenting major limitations as an inadequate treatment compliance due to i) multiple doses per day and severe long-term side effects for the conventional treatment (based on phosphate supplementation and active vitamin D analogs) or ii) an extremely expensive cost for the health care system for the monoclonal anti-FGF23 antibody therapeutic. Here we studied the hypothesis whether the liver-targeting approach could be used as a therapeutic modality for rare diseases associated with hyperfunction of growth factors as XLH, treating this bone pathology with a single injection. We elaborated a novel therapeutic approach for XLH based on a single injection of AAV gene therapy aiming to stimulate the production of a FGF23 neutralizing factor (cFGF23) in the liver in a murine model of XLH, the Hyp-Duk mouse. We demonstrated that one single injection of AAV-cFGF23 treatment led to restoration of impaired skeletal phenotype, and to significant reduction of osteomalacia, bone and joint alterations in Hyp-Duk mice. This provides a proof-of-concept that the liver-targeting approach represents an adequate modality to rescue the growth

factor's hyperfunction, thus opening the new perspectives on the treatment of skeletal diseases by gene therapy.

P1-59

Cartilage-specific knockout of SIRT1 significantly reduces bone quality and catch-up growth efficiency

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Background: Spontaneous catch-up (CU) growth occurs when a growth-restricting factor is resolved. However, its efficiency is sometimes inadequate and growth deficits remain permanent. The therapeutic toolbox for short stature is currently very limited. Our previous studies using a nutrition-induced CU growth model showed that the level of sirtuin-1 (SIRT1) was significantly increased in food-restricted animals and decreased during CU growth.

Aim: This study sought to investigate the role of SIRT1 in modulating the response of the epiphyseal growth plate (EGP) to nutritional manipulation.

Method: Heterozygous collagen type II-specific Sirt1 knockout (CKO) mice were tested for response to our CU growth model consisting of a period of food restriction followed by re-feeding.

Results: The transgenic CKO mice weighed more than the control (CTL) mice, their EGP was higher and less organized, specifically at the resting and proliferative zones, leading to shorter bones. Ablation of Sirt1 in the chondrocytes was found to have a dramatic effect on bone mineralization on micro-CT analysis. The CKO mice were less responsive to the nutritional manipulation, and their CU growth was less efficient. They remained shorter than the CTL mice who corrected the food restriction-induced growth deficit during the re-feeding period.

Conclusions: Sirt1 appears to be important for normal regulation of the EGP. In its absence, the EGP is less organized and CU growth is less efficient. These results suggest that SIRT1 may serve as a novel therapeutic target for short stature.

Mosaic *PHEX* variants are important causes of X-linked hypophosphataemic rickets

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Introduction: X-linked hypophosphataemic rickets (XLH), due to mutations in the *PHEX* (Phosphate-regulating Endopeptidase homolog; X-linked) gene, causes reduced bone and dentin mineralisation and decreased renal phosphate reabsorption. Mosaic *PHEX* mutations are reported only in a few case reports.

We report three male cases, with mosaic pathogenic *PHEX* variants, showing importance of considering this in the diagnosis of XLH.

Case 1 presented at 4 years, with marked bowing of the legs, hypophosphataemia and low tubular reabsorption of phosphate (TRP). He commenced conventional treatment (alfacalcidol/phosphate) but did not tolerate phosphate, continuing to have rickets and bone deformities. Initially, no mutations were found in *PHEX/FGF23*, but the UK 100,000-genome project then suggested a *PHEX* variant. Reanalysis with Sanger-sequencing confirmed this, showing a low-level (35%) de novo mosaic pathological splice site variant: c.1173+5G>C in peripheral blood mononuclear cells (PMBCs), predicted to cause skipping of exon 10. This was originally missed by Sanger and next generation sequencing due to failure to recognise its pathogenicity and low-level mosaicism. Five years after diagnosis, he was then eligible for burosumab. Currently, aged 10 years, he is on 0.5mg/kg/dose burosumab, with healing rickets and height of -1.65SDS.

Case 2 presented at 6 years, with mild tibial bowing. He had rickets, hypophosphataemia and reduced TRP. He was initially given conventional treatment; then burosumab. Sanger-sequencing of *PHEX* showed a mosaic splice site variant (30% mosaicism in PMBCs): c.1645+1G>A, causing skipping of exon 15 and likely nonsense mediated mRNA decay. At 13 years, he is on 0.7mg/kg/dose burosumab, with height of 1SDS.

Case 3 presented at 11 months with macrocephaly, scaphocephaly and short stature. Biochemistry and X-rays suggested XLH. He had a truncating mutation in *PHEX*: c.1157G>A;p.(Trp386*), with 59% level mosaicism in PMBCs. He is currently on burosumab 1.3mg/kg/dose with height of -2.65 SDS, at 5 years.

Discussion: The splice site and frameshift variants have been found before in XLH; however, this is the first time they have been found as mosaic variants. The cases suggest that mosaic *PHEX* variants may not be extremely rare, and give similar phenotypes as non-mosaic mutations. Interestingly, only boys with mosaic *PHEX* variants have been described, whereas XLH in girls is not always rescued by X-chromosome inactivation.

Case 1 had difficulty with conventional therapy and delayed diagnosis meant initial ineligibility for burosumab treatment. This shows the importance to consider mosaicism and splice site variants when there is high clinical suspicion of XLH but genetic analysis is negative.

Diabetes B

Timing of Hypoglycaemia in Patients with Hyperinsulinism (HI): Extension of the Digital Phenotype

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Background: Hyperinsulinism (HI) due to excess and dysregulated insulin secretion is the most common cause of severe and recurrent hypoglycaemia in childhood. High cerebral glucose utilisation in the early hours results in high risk of hypoglycaemia for people with diabetes and carries a significant risk of brain injury. Prevention of hypoglycaemia is the cornerstone of management for HI but the risk of hypoglycaemia at night or indeed the timing of hypoglycaemia in children with HI have not been studied, and thus the digital phenotype remains incomplete and management suboptimal.

Objective: We aimed to quantify the timing of hypoglycaemia in patients with HI, to describe glycaemic variability and to extend the digital phenotype.

Methods: Patients underwent Continuous Glucose Monitoring (CGM) with a Dexcom G4 or G6 CGM device as part of their clinical assessment for either HI (n = 23) or Idiopathic Ketotic Hypoglycaemia (IKH) (n = 24). CGM data was analysed for temporal trends. Hypoglycaemia was defined as glucose < 3.5mmol/L.

Results: 449 hypoglycaemia events totalling 15,610 minutes were captured over a total of 237 days from 47 patients (29 male, mean age 70 months). Mean length of hypoglycaemia event was 35 minutes. There was a clear tendency to hypoglycaemia in the early hours (0300H to 0700H), particularly for those HI patients over 10 months of age where 7.6% of time in this period was spent in hypoglycaemia compared to 2.6% outside ($P < .001$). This tendency was less pronounced in HI patients under 10 months and those negative for genetic mutations as well as those patients with IKH. Despite real-time CGM, there were 42 hypoglycaemia events from 13 separate HI patients lasting > 30 minutes.

Conclusions: In this study, we have taken the first step in extending the digital phenotype of HI by describing the glycaemic trends and identifying the timings of hypoglycaemia measured by CGM. We have identified the early hours as a time of high hypoglycaemia risk for patients with HI and demonstrated that simple provision of CGM data to patients is not sufficient to eliminate hypoglycaemia.

Future work in HI should concentrate on the early hours as a period of high risk for hypoglycaemia and must target personalised hypoglycaemia predictions. Focus must move to the human-computer interaction as an aspect of the digital phenotype that is susceptible to change rather than simple mathematical modelling to produce small improvements in hypoglycaemia prediction accuracy.

P1-62

Epidemiology of type 1 diabetes in children and adolescents: a 50-year, single center experience

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Introduction: Global variations in epidemiology of type 1 diabetes (T1D) exist worldwide. This study is designed to determine the demographic and clinical characteristics of T1D in the past three decades, and to analyze changing trends in epidemiology over the past 50 years.

Methods: Epidemiological and clinical characteristics of 925 patients with T1D were analyzed in three decades between 1991 and 2019. In addition, previously published data of 477 patients before 1991 (1969-90) was compared to data of the current study. Study included patients from all over the country. Patients were stratified into two-year periods according to age at diagnosis.

Results: Mean age at diagnosis decreased significantly from 9.5±4.0 to 7.1±3.6 years within the last 50 years ($p<0.001$). Age at diagnosis peaked at 12-14 years between 1969-90, and from then on this peak decreased from 10-12 years in the first decade, to 4-6 years in the last two decades ($p=0.005$). Boy-to-girl ratio was close to one and didn't change. The most common season of initial admission was winter and autumn, and 35% of patients had infection at the time of diagnosis. Geographical distribution, seasonality, and the presence of infection at diagnosis were similar during the last 50 years. The most common symptoms were polyuria, polydipsia, and weight loss. Prevalence of enuresis nocturna and vomiting increased with younger age ($p<0.001$). In the last 30 years, 47.8% of all patients presented with ketoacidosis, 38.1% with ketosis, 14.1% with only hyperglycemia. Prevalence of ketoacidosis and ketosis as well as severe ketoacidosis at presentation did not change within the last 30 years, although the ratio of mild ketoacidosis increased while that of moderate ketoacidosis decreased over time. Prevalence and severity of DKA were higher among children ≤ 6 years, while duration of symptoms was significantly shorter in comparison to 6-12 and ≥ 12 year age-groups ($p=0.005$, $p<0.001$, and $p=0.008$ respectively).

Conclusion: The age at diagnosis shifted to younger ages in children with T1D during the last 50 years. Nearly half of the patients had ketoacidosis at the time of diagnosis with no change within the last 30 years. The shift to younger ages in T1D during the last half century, in addition to an unchanging prevalence of DKA suggest that awareness of diabetes should be increased in our community in terms of early diagnosis and treatment.

P1-63

Comparison of triglyceride and glucose index and homeostatic model assessment for insulin resistance in children and adolescents with type 2 diabetes mellitus

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Background: Triglyceride and glucose (TyG) index is significantly associated with higher risk of developing type 2 diabetes mellitus (T2DM). The mechanism of the role of TyG index in the development of T2DM is not clear. There are few studies on the relationship between the TyG index and homeostatic model assessment of insulin resistance (HOMA-IR).

Aims: To elucidate the role of the TyG index, studies are needed on the association between TyG index and HOMA-IR. We explored the role of the TyG index in comparison with HOMA-IR in children and adolescents with T2DM.

Research Design and Methods: A total of 180 subjects with suspected insulin resistance disease including obese, overweight, or acanthosis nigricans were involved. TyG index was calculated using $\ln(\text{fasting triglyceride [mg/dL]} \times \text{fasting glucose [mg/dL]}/2)$, and HOMA-IR was calculated as $(\text{Fasting insulin [mIU/L]} \times \text{Fasting glucose [mg/dL]}/405)$. T2DM was diagnosed according to the American Diabetes Association criteria.

Results: The mean age of non-T2DM and T2DM was 9.92 ± 2.56 and 14.25 ± 2.29 years, respectively. T2DM was identified in 57(32%) participants. Significant differences were observed in the TyG index between T2DM and non-T2DM ($p<0.001$). TyG index had a positive correlation with fasting serum glucose (FSG) ($r=0.519$, $p<0.001$), HOMA-IR ($r=0.189$, $p<0.017$), HbA1c ($r=0.429$, $p<0.001$), total cholesterol ($r=0.257$, $p=0.001$), triglyceride (TG) ($r=0.759$, $p<0.001$), and low-density lipoprotein cholesterol (LDL-C) ($r=0.152$, $p<0.001$), and a negative correlation with high-density lipoprotein cholesterol (HDL-C) ($r=-0.107$, $p<0.001$) after controlling for sex, age and BMI SDS. In the ROC analysis, the TyG index [area under the curve (AUC) 0.839] showed a better performance compared to HOMA-IR (AUC 0.645) in identifying patients with T2DM ($p<0.001$). The multivariable regression analysis showed that elevated TyG index was significantly associated with age, FSG, HOMA-IR, TG, LDL-C, and HDL-C (adjusted R^2 0.918, $p<0.001$).

Conclusions: The TyG index has significant association with higher risk of developing T2DM and is superior to HOMA-IR in predicting T2DM in children and adolescents.

Initial Neutrophil/Lymphocyte and Lymphocyte/Monocyte Ratios Can Predict Future Insulin Need in Newly Diagnosed Type 1 Diabetes Mellitus

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Background: The exact mechanism of the partial clinical remission in type 1 diabetes mellitus (T1DM) has not been elucidated yet. The severity of the inflammation at the time of diagnosis may have an impact on the occurrence or duration of this phase.

Objective: We aimed to investigate the relationship between hematological inflammatory parameters at the time of diagnosis in children and adolescents with T1DM and the need for insulin during the first year of the follow-up and the presence of partial clinical remission period as determined according to insulin dose-adjusted HbA1c levels.

Subjects and Methods: A single-center retrospective study was conducted, including patients aged 1-18 years who were diagnosed with T1DM in a tertiary center between 2010-2020. Patients with any concomitant acute or chronic diseases and infections at the time of diagnosis were excluded.

Results: Sixty-eight patients (55.9% female, 64.7% prepubertal) were included in the study, whose mean age was 8.4 ± 4.2 years. A total of 38 patients (55.9%) had partial clinical remission. Serum insulin and C-peptide levels at the time of diagnosis were significantly higher in remitters than non-remitters ($p = 0.026$ and $p = 0.004$, respectively). Initial neutrophil/lymphocyte ratio (NLR) and derived-NLR (d-NLR) levels were significantly lower ($p = 0.011$ and $p = 0.033$, respectively) and lymphocyte/monocyte ratio (LMR) levels significantly higher ($p = 0.005$) in patients who showed an insulin requirement of <0.5 IU/kg/day at the 3rd month after diagnosis. The sensitivity of a cut-off NLR value of 1.64 was 69.2% and the specificity was 59.5%, whereas these were found as 69.2% and 54.8% for the best threshold value (1.17) of d-NLR, respectively. An LMR of 4.71 was found to be the best cut-off value for estimating a low daily insulin requirement on the 3rd month after diagnosis (sensitivity; 66.7%, specificity; 61.5%).

Conclusions: We showed that a lower NLR and d-NLR, or a higher LMR at the time of diagnosis can be used as a predictor for a low need of daily insulin at the 3rd month of T1DM, for the first time in literature.

Efficacy of Use of Continuous Glucose Monitoring System in patients with Congenital Hyperinsulinism

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Background: Hypoglycaemic episodes in patients with Congenital Hyperinsulinism (CHI) are not always detected due to the intermittent measurement of blood glucose concentrations, particularly the asymptomatic episodes. Detecting and treating these episodes is important for prevention of hypoglycaemic brain injury. Although the Continuous Glucose Monitoring System (CGMS) is widely used in adults and children with diabetes, the use in patients with CHI remains limited.

Aim: To determine whether children with CHI can have an effective glycaemic control with the use of CGMS.

Method: 10 patients with CHI, with a mean age of 7.2 years (range 2.1 - 16.07) using a Dexcom G6 real time CGMS (rtCGMS) were included in this retrospective study over 12 weeks. Parental consent to access the data on Dexcom clarity website was obtained. The primary efficacy outcome measured was time in range in normoglycaemia (TIRN), defined as blood glucose (BG) 3.9 to 10 mmol/L. In addition, the number of hypoglycaemia episodes (BG <3.9 mmol/L) per week, time very low (<3.0 mmol/L) and time in hyperglycaemia (>10.0 mmol/L) were evaluated. All parameters were assessed at four and twelve weeks from insertion of CGMS.

Results: The TIRN of the patients included in this study varied from 63.1 to 98.8% after the first four weeks on CGMS. After 12 weeks of using CGM, 70% of our cohort (7/10) showed improved TIRN by 0.2 -2.8%. Though in 30% of our participants (3/10) TIRN was worse after 12 weeks, two due to increasing hyperglycaemic episodes and one due to hypoglycaemic episodes. Hence, 90% of our patients (9/10) had a smaller number of weekly hypoglycaemic episodes, with only one case of increase. 50% of the participants (5/10) had reduction of time in very low hypoglycaemia, with three remaining unchanged and two patients showing increase. 50% of the patients (5/10) had reduction of time in hyperglycaemia, in one patient there was no change whereas in four patients an increase was noted.

Conclusion: After 12 weeks of use of Dexcom G6 rtCGMS in patients with CHI at our centre, we noticed an improvement of TIRN and a decrease in number of weekly hypoglycaemic episodes. Therefore, CGMS can assist CHI patients and families with more effective glycaemic control. This way, we may avoid hypoglycaemic brain injury and optimize treatment. Further studies are needed to assess the potential of CGMS as a decision-making tool in hypoglycaemia management in the CHI cohort.

Mortality in children with monogenic diabetes

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Background: In this study we investigated mortality in children with monogenic diabetes.

Methods: Within the Ukrainian Pediatric Diabetes Register (UPDR) the number of children with type 1 diabetes mellitus (DM1) 0-17 y.o. in 2019 was 9860 (1 in 769), with DM2 - 36 (1 in 210,547) with neonatal DM (NDM) - 66 (1 in 115,000), with MODY - 40 cases (1 in 114,844). We used targeted next generation sequencing (tNGS) of all known NDM genes in any child diagnosed in the first 9 months of life and all known MODY genes in those who was diagnosed after 9 months of life.

Results: Among 106 children with monogenic diabetes 8 patients died to date. 7 (87.5%) had NDM.

We found 3 patients with autoimmune monogenic diabetes mellitus (ADM) with mutations in *AIRE*, *FOXP3* and *LRBA*, 2 of whom had NDM (hemizygous *FOXP3* p.R347H and homozygous *LRBA* p.Glu946Ter). 2 children with ADM/NDM died before age 1 year, and the patient with *AIRE* p.Cys311fs/p.Arg257Ter died at 15 years. He was admitted to ECU with hypoparathyroidism and died due to severe dyselethrolythemia, ischemic stroke and myocardial infarction. The patients with *FOXP3* and *LRBA* died due to respiratory insufficiency and intestinal gangrene respectively. In both NDM cases results of genetic testing were obtained after death.

The patient with a homozygous *IPF1* c.1A>G mutation, was diagnosed with NDM at the age of 6 days and died at 6 months due to cytotoxic syndrome, cholestatic hepatitis, sepsis and systemic multiple organ failure.

2 NDM patients with *EIF2AK3* (p.D164fs/p.E421fs and homozygous p.G1010V) died at an early age. The patient with *EIF2AK3* p.D164fs/p.E421fs was diagnosed with diabetes at the age of 13 weeks and died at 3 months due to cerebral edema. The patient with *EIF2AK3* p.G1010V had multiple inpatient admissions due to cytotoxic syndrome and died at age 2y 2 months due to systemic multiple organ failure.

2 siblings with NDM and *ABCC8* p.I49F died at the age 5 and 9 y.o., where 5 y.o. girl died because of pneumonia (had also severe rickets and curvature of the chest) and her 9 y.o. brother died within 1 day after admission to the ECU because of hyperthermia, cytotoxic syndrome and systemic multiple organ failure.

Conclusions: Whilst ADM and *EIF2AK3* are described as a well known cause of death in patients with monogenic diabetes, the cause of death in patients with *IPF1* and *ABCC8* has not yet been widely described.

The Molecular Genetic Etiology by Whole Exome Sequence Analysis in Cases With Familial Type 1 Diabetes Mellitus without HLA Haplotype Predisposition or Incomplete Predisposition

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Introduction: Family history is observed in approximately 10% of the cases with type 1 diabetes mellitus (T1DM). The most important gene that determines susceptibility is the human leukocyte antigen complex (HLA) on chromosome 6. In HLA genes; specific combinations of alleles at DR3, DR4, DRB1, DQA1 and DQB1 locus either predispose or protective for T1DM. In this study, we aimed to investigate the molecular genetic etiology by whole exome sequence (WES) analysis in cases with familial T1DM who had no HLA haplotype predisposition or incomplete predisposition.

Method: Patients who had at least one first degree relatives with T1DM were included in the study. In the first step, HLA DRB1, DQA1 and DQB1 loci were investigated with polymerase chain reaction-sequence specific oligonucleotide (PCR-SSO) method. In the second step, the presence of variants that could explain the clinic in cases where both tissue types were negative in HLA typing (DQ2 (-) / DQ8 (-)) and only one of the HLA types was found positive (DQ2 (+) / DQ8 (-), and DQ2 (-) / DQ8 (+)) was investigated by WES analysis method.

Results: Four cases (16%) had consanguineous marriage between their parents out of 25 patients (female/male:15/10). Mean age and diabetes duration of the cases were 15.77±5.89 and 8.31±5.71 years respectively. There was celiac disease in one case and Hashimoto thyroiditis in 3 cases.

Both HLA-DQ2 and DQ8 were positive in 17(68%) of the cases. WES analysis applied to one case with DQ2 (-) and DQ8 (-), 7 cases with DQ2 (+) and DQ8 (-), and one case with DQ2 (-) and DQ8 (+). They had no possible pathogen/ pathogen variant. In the

Cases	Gene	Classification	Pathology associated	Zygosity	Mutation type	HGVS-Protein (amino acid exchange)	HGVS-Code (DNA code)
Case 1	CIITA	VUS	T1DM	Heterozygous	Missense variant	p.Ala96Thr	c.286G>A
Case 2	KCNJ11	VUS	T2DM	Heterozygous	Synonym variant	p.Glu51Glu	c.153G>A
Case 3	CASP10	VUS	APS	Heterozygous	Intron variant	-	c.922+36delT

VUS: variants of unknown significance

detailed analysis of genes important in DM etiology, high-scored VUS (variant with unknown efficacy) was found in 3 cases (Table 1). Segregation analysis are ongoing for variants detected in other affected individuals in the family.

Conclusion: In this study, non-HLA genes responsible for development of T1DM were detected in familial T1DM cases. It is planned that the presence of specific genes that have not yet been clarified for the pathogenesis and treatment of T1DM will continue to be investigated by increasing the number of cases without HLA tissue type predisposition with WES analysis.

P1-68

Birth weight and diazoxide unresponsiveness strongly predict the likelihood of congenital hyperinsulinism due to a mutation in ABCC8 or KCNJ11

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Background: Hyperinsulinism is characterised by inappropriate insulin secretion during hypoglycaemia. Mutations in the KATP channel genes, *ABCC8* and *KCNJ11*, are the most common cause of persistent congenital hyperinsulinism. The diagnosis of KATP hyperinsulinism is key for the clinical management of the condition.

Aim: We aimed to determine the clinical features that help to identify KATP hyperinsulinism at diagnosis.

Methods: We studied 761 individuals with KATP hyperinsulinism and 862 probands with hyperinsulinism of unknown aetiology diagnosed before 6 months of age. All were referred for genetic testing as part of routine clinical care. We compared the clinical features of KATP hyperinsulinism and unknown hyperinsulinism cases. We performed logistic regression and receiver operating characteristic analysis to identify the features that predict KATP hyperinsulinism.

Results: Higher birth weight, diazoxide unresponsiveness and diagnosis in the first week of life were independently associated with KATP hyperinsulinism (adjusted Odds Ratio 4.5 (95% CI, 3.4-5.9), 0.09 (0.06-0.13) and 3.3 (2.0- 5.0) respectively). Birth weight and diazoxide unresponsiveness were additive and highly discriminatory for identifying KATP hyperinsulinism (ROC area under the curve for birth weight 0.80, diazoxide responsiveness 0.77, and together 0.88, 95% CI 0.85-0.90). 86% born large for gestation and 78% born appropriate for gestation who did not respond to diazoxide treatment had KATP hyperinsulinism. In contrast, of

those individuals born small for gestation, none who were diazoxide responsive and only 4% of those who were diazoxide unresponsive had KATP hyperinsulinism.

Conclusion: Using the largest cohort of CHI cases referred from routine clinical practise, we robustly demonstrate that individuals with hyperinsulinism born appropriate or large for gestation and unresponsive to diazoxide treatment are most likely to have an *ABCC8* or *KCNJ11* mutation. Given the implications for clinical management of KATP hyperinsulinism, these patients should be prioritised for genetic testing for KATP channel genes.

P1-69

Oxidized lipid-associated protein damage in children and adolescents with type 1 diabetes mellitus: new diagnostic/prognostic clinical markers

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Background: Type 1 diabetes mellitus (DM1), a chronic metabolic disorder of autoimmune origin, has been associated with oxidative stress (OS), which plays a central role in the onset, progression and long-term complications of DM1. The markers of OS lipid peroxidation products, lipid hydroperoxides (LOOH), and also malondialdehyde (MDA) and thiobarbituric reactive substances (TBARS) that oxidatively modify proteins (Pr) (i.e., PrMDA and PrTBARS, respectively), have been associated with DM2, DM1, diabetic neuropathy, and microalbuminuria.

Objective/Subjects: Here, we investigated LOOH, PrMDA and PrTBARS in 50 children and adolescents with DM1 and 21 controls.

Results: The novel OS marker PrTBARS was assessed for the first time in children and adolescents with DM1. LOOH and the pair PrMDA/PrTBARS, representing early and late peroxidation stages, respectively, are found to be significantly higher (130%, 50/90%, respectively, at $p < 0.001$) in patients with DM1 compared to controls. The studied OS parameters did not differ with age, age at diagnosis, sex, duration of DM1, presence of recent ketosis/ketoacidosis, or mode of treatment.

Conclusions: We propose that LOOH, PrMDA and the new marker PrTBARS could serve as potential diagnostic clinical markers for identifying OS in children and adolescents with DM1, and may, perhaps, hold promise as a prognostic tool for future complications associated with the disease.

P1-70

Change in HbA1C predicts future abnormal Oral Glucose Tolerance Tests in children and adolescents with Cystic Fibrosis

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Background: Oral glucose tolerance test (OGTT) is the screening test of choice for Cystic Fibrosis Related Diabetes (CFRD). HbA1C is considered unreliable in diagnosing CFRD because of increased cell turn over in children and adolescents with Cystic Fibrosis (CF).

Objective: To determine the validity of HbA1C as a predictive tool for future abnormal OGTT in CF.

Material and Methods: Data were collected on OGTTs and HbA1C (within 3 months of OGTT) in children and adolescents with CF, over the previous 15 years in a tertiary care centre. Sensitivity and specificity were calculated for HbA1C in predicting abnormal OGTT and for both HbA1C and OGTT in predicting insulin therapy.

Results: 150 OGTT (81 females) were included in this study. 77/150 (51%) had an abnormal OGTT with indeterminate (31/77) being the most common followed by impaired (26/77), CFRD (19/77) and CFRD with fasting hyperglycaemia (1/77).

Sensitivity and specificity of HbA1C (>42 mmol/mol) to predict CFRD on OGTT were 68.4% and 84.3% respectively. HbA1C (>42 mmol/mol) was more sensitive (64.5%) than OGTT (43.4%) in predicting need for insulin therapy. Reducing HbA1C cut-off to > 40mmol/mol, increased sensitivity of HbA1C to detect CFRD on OGTT (78.9%) and need for insulin therapy (74.2%).

Mean HbA1C increased with progressive phases of insulin dysregulation (mean HbA1C 38 (25-48) mmol/mol in normal OGTT, 40 (31-49) mmol/mol in indeterminate, 40 (30-49) mmol/mol in impaired and 48 (34-88) mmol/mol in CFRD).

HbA1C rose from one year before an abnormal OGTT (mean rate of rise 1.7mmol/mol every 6 months). HbA1C was already in diabetic range 42 (37-49) mmol/mol 18 months before having CFRD on OGTT. HbA1C rose by 3 mmol/mol (from 37 to 40) a year before indeterminate and impaired OGTT.

Conclusion: HbA1C (>42mmol/mol) is more sensitive than OGTT in detecting CFRD patients who need insulin therapy. Increase in HbA1C by 3 mmol/mol in a year correlated with indeterminate and impaired OGTT.

Fetal Endocrinology and Multisystem Disorders A

P1-71

Morning salivary cortisol and stress response in term and preterm infants hospitalized in the intensive care unit

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Background: Newborns admitted to the intensive care unit (ICU) are exposed to multiple painful and stressful procedures. It is postulated that high pain exposure in the first weeks of life can have a long-lasting impact on the hypothalamic-pituitary-adrenal (HPA) axis. Assessment of the salivary cortisol (SC) is a useful method for non-invasive monitoring of baseline activity and stress response of HPA axis.

Objective: Analysis of differences in morning concentrations of SC and its stress response between term and preterm children. Evaluation of HPA hyperreactivity to neutral stimulus in newborns hospitalized in ICU.

Methods: Infants hospitalized in ICU were assessed for the study. Preterm neonates were enrolled after completion of 35 weeks of postmenstrual age (PMA). Saliva samples for assessment of morning cortisol concentrations were obtained between 6 and 9 a.m. before routine nursing procedures and at least 60 minutes after feeding. To investigate infants stress response additional saliva samples were collected 20 minutes after 2 types of procedures: nappy change (neutral) and blood sampling (painful). Each procedure was analyzed on the different day.

Results: The study group consisted of 25 (38.46%) term and 40 (61.54%) preterm neonates. Term and preterm infants did not differ in the morning SC (2.27 (1.5-5.25) ng/ml v.s. 2.72 (1.87-5.14) ng/ml, $p=0.4$). The significant increase of SC after vein puncture was observed both in term (1.75 (1.25-3.72) ng/ml v.s. 6.06 (3.45-8.02) ng/ml, $p=0.002$) and premature newborns (2.57 (1.55-3.61) ng/ml v.s. 5.35 (2.59-7.13) ng/ml, $p<0.001$). There was no difference in SC increase after vein puncture between the analyzed subgroups ($p=0.22$). In premature children SC has increased also after nappy change (1.9 (1.45-3.68) ng/ml v.s. 2.84 (1.86-5.6) ng/ml, $p=0.002$).

Conclusion: Median concentrations of morning SC did not differ between term and preterm infants > 35 weeks of PMA. Prematurity did not affect the response of HPA axis to painful procedure, however, significant increase of SC after neutral stimulus may suggest inadequate hyperreactivity of HPA axis in preterm infants.

Clinical characteristics of children with Congenital Hyperinsulinism: Results from the European Registries for Rare Endocrine Conditions (EuRRECa) Project

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Introduction: Congenital hyperinsulinism (CHI) is a group of rare endocrine disorders characterized by repeated episodes of hypoglycemia caused by an excessive insulin secretion from the pancreas beta cells. The etiopathogenesis, phenotype, treatment, and prognosis of individual CHI cases are variable and not completely described.

Aims: To gather and describe clinical and genetic data about CHI cases diagnosed within the large EuRRECa network.

Materials and Methods: From July 2018 to March 2020, a total of 17 investigators from 14 European reference centers embedded in EuRRECa programme (<https://eurrecanet/>) reported 77 cases of CHI using a simple e-Reporting (e-REC) tool. These investigators were subsequently asked to complete a web-based questionnaire that obtained information on the phenotype, diagnostic procedures, genotype, treatment, and long-term sequelae of reported cases. Cases with confirmed CHI genetic etiology and those with no genetic findings were compared.

Results: The questionnaire was completed in 55/77 (71%) of reported cases from 9/14 (64%) centers. Out of 55 cases, 44 (80%) had a clinical diagnosis of CHI. Of these, all presented with clinical symptoms of CHI, in 41/44 (93%) laboratory results confirmed the diagnosis. Twenty out of 44 (45%) cases had proven genetic CHI etiology – variants in genes *ABCC8* in 13, *GLUD1* in 3, *GCK* in 2, and single cases of *KCNJ11* and genetically confirmed Beckwith-Wiedemann syndrome. Thirty-two patients (73%) presented first

symptoms within the first 7 days of life. In 41/55 cases, treatment modalities were reported. CHI cases were most frequently treated with intravenous glucose (28 cases), dietary recommendations (35 cases), diazoxide (33 cases), octreotide (4 cases), long-acting octreotide (1 case), and glucagon (1 case) application. Six children underwent surgery, 5 partial and 1 total pancreatectomy. Currently, 28/44 (64%) children have age-appropriate neurological status and 5/44 (11%) have delayed psychomotor development. Current neurological status was not reported in 11/44 (25%) cases. Compared to the children without known genetic etiology, those with genetically confirmed CHI were treated less frequently with diazoxide (60% vs. 88%), and more frequently with octreotide (20% vs. 0%) and with surgery (30% vs. 0%). The long-term outcomes did not differ between groups (psychomotor retardation was reported in 10% vs. 13%).

Conclusion: This first report on CHI from the EuRRECa network showed significant heterogeneity in etiology, phenotype, outcome, and treatment modalities. Children with genetically confirmed etiology presented with more severe symptoms requiring complex treatment. Octreotide treatment and surgery were used only in children with genetic diagnosis of CHI.

Minipuberty in born small for gestational age infants: a case control prospective pilot study

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Objective: Minipuberty (MP) is still not well defined in small for gestational age (SGA) infants, due to controversial literature data. The present study aims to evaluate MP in SGA infants, both preterm and full-term, compared with those born adequate for gestational age (AGA), during the first year of life.

Design: Case-control, prospective study.

Methods: The study population included 33 SGA newborns (group A), 21 of which full-term (subgroup A1) and 12 preterm (subgroup A2). The control group (B) consisted of 27 AGA newborns, 17 of which full-term (subgroup B1) and 10 preterm (subgroup B2). All the participants were born in the same hospital and period. Sick newborns were excluded from the study. Periodic follow-up included growth parameters, FSH, LH, and Estradiol (E2) or Testosterone (T) serum levels at 3, 6 and 12 months.

Results: In the overall study population, the gonadotropin surge reached greater increase of LH in males at 3 months of age ($p<0.001$) and FSH in females at 3, 6 and 12 months ($p<0.001$), irrespectively of gestational age (GA). LH/FSH ratio remained higher in boys during the entire follow-up ($p<0.001$).

Among the Males: 1)T at 3 months was higher in subgroup A2 vs A1($p=0.001$), and correlated negatively with GA, length and weight at birth ($p<0.05$); 2)LH was higher in subgroup B2 vs B1 at 6 months ($p=0.003$), and in group A vs B at 12 months ($p=0.03$); 3)LH/FSH ratio was increased in subgroup B2 vs B1 ($p=0.004$) at 6 months.

Among the Females: 1)E2 levels at 6 months were higher in subgroup B2 vs B1 ($p<0.05$), and negatively correlated with GA ($p=0.015$) and weight gain ($p<0.05$); 2)LH at 6 months and LH/FSH ratio at 3 months were increased in subgroup A2 vs A1 ($p=0.03$).

Overall preterm boys, either SGA or AGA, displayed higher levels of T at 3 months ($p=0.001$) and LH at 3,6 and 12 months ($p<0.05$), together with increased LH/FSH ratio at 6 months ($p=0.001$). Preterm girls, either SGA or AGA, exhibited higher LH/FSH ratio at 3 and 6 months than full-term girls ($p<0.05$).

Conclusions: Irrespectively of GA, MP occurred with a typical sexual dimorphism and exhibited sex-specific correlations between hormones and perinatal parameters. The condition of SGA and prematurity seemed to enhance and protract MP over time in both sexes, suggesting that prenatal growth failure might influence hypothalamic-pituitary-gonadal axis activation.

P1-74

Pancreatic glucagon-like-peptide-1 receptor expression in congenital hyperinsulinism

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Background: Congenital hyperinsulinism (CHI) is the most common cause of neonatal persistent hypoglycaemia. Current treatment lacks efficiency, and so are methods for differential diagnosis of diffuse and focal histological forms. Novel diagnostic and treatment approaches with the use of another hormone – glucagon-like-peptide-1 (GLP-1) – have been developed.

GLP-1 is one of the key factors for maintaining euglycaemia. It stimulates insulin secretion and inhibits glucagon production. PET scan with GLP-1 agonist (exendine-4) has been proposed for differential diagnosis of diffuse and focal CHI. Infusion with GLP-1 antagonist is promising for patients who are unresponsive to standard treatment (diazoxide, octreotide). However, there is insufficient information regarding GLP-1 receptor expression in pancreatic tissue in patients with CHI. Thus, we conducted a study to evaluate GLP-1 receptor expression in patients with diffuse and focal CHI.

Methods: Informed consent and tissue samples were obtained from 5 paediatric patients with diffuse CHI and 9 children with focal CHI. All patients required surgical treatment due to persistent hypoglycaemia and poor or absent response to diazoxide and octreotide treatment. Histological form in each case was established using immunohistochemistry with insulin and p57 antibodies.

The tissue samples were fixed in 10% formaldehyde solution and embedded in paraffin wax. Immunohistochemistry with GLP-1 receptor antigen (3F52, Developmental Studies Hybridoma Bank, USA) was performed on 3- μ m-thick sections.

Results: All patients carry pathogenic variants in *ABCC8/KCNJ11* genes. The median age at surgery was 4 months in patients with diffuse CHI, 6 months – in focal CHI cases.

Based upon immunohistochemistry with GLP-1 receptor antigen, a focal lesion and diffuse CHI tissue differ significantly. A focus has a form of endocrine islets confluence with apparent staining.

There are no evident discrepancies in diffuse CHI and non-focal region of focal CHI. Pancreatic islets and single endocrine cells express GLP-1 receptor in both groups. Surprisingly, acinar cells show mild but positive staining with GLP-1 receptor antigen.

Conclusion: To the best of our knowledge, it is the first study on GLP-1 receptor expression in CHI. Immunohistochemistry with GLP-1 receptor antigen is able to reveal a focal lesion. While our data are promising for using PET with GLP-1 agonist (exendin-4) for differentiating CHI forms, expression of GLP-1 receptors in acinar cells could interfere with PET scan results. However, not all of the previous studies on pancreatic tissue show presence of GLP-1 receptor in acinar cells. Our results also indicate GLP-1 antagonist treatment might be helpful in both histological forms.

P1-75

Congenital hyperinsulinism diagnosed after 12 months can have a monogenic aetiology

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Background: Congenital hyperinsulinism (HI) is characterised by inappropriate insulin secretion despite low blood glucose which is commonly diagnosed in infancy (before the age of 12 months). Screening of the >20 known genes identifies a mutation in over 45% of cases. The likelihood of identifying a mutation in a known gene in individuals diagnosed after 12 months is not currently known.

Aim: We aimed to identify the prevalence of monogenic hyperinsulinism due to a mutation in a known gene, in patients diagnosed with HI in childhood (aged 1 to 16 years).

Methods: We searched for patients diagnosed with HI between 1 and 16 years of age who had been referred to the Exeter Laboratory for genetic testing. In all patients, we screened for mutations in the known HI genes using Sanger sequencing for first-line testing, followed by targeted next generation sequencing of all known causes if a mutation was not identified. We compared the clinical features of monogenic HI diagnosed in childhood to those diagnosed in infancy.

Results/ Discussion: We identified 173 individuals within the Exeter cohort who had been diagnosed with hyperinsulinism between the ages of 1 and 16 (median 1.8 [IQR 1.2 to 4.0]) years. Pathogenic variants were identified in 24% (41/173) of cases (*ABCC8* (n=11), *GCK* (n=7), *GLUD1* (n=15), *HADH* (n=1), *KMT2D* (n=1), *PMM2* (n=4), *TRMT10A* (n=1) and an X-chromosome deletion (n=1)). The median (IQR) age at diagnosis of hyperinsulinism in individuals with a mutation was 1.7 (1.0 to 2.8) years. For individuals with mutations in *ABCC8*, the median birthweight corrected for gestational age was significantly lower than in those diagnosed before 12 months (3356g vs 4245g, *P*=0.0019, Wilcoxon rank-sum). Given that insulin is a growth factor during gestation, this finding is in keeping with these individuals not having increased insulin secretion *in utero* and suggests their later diagnosis of HI is a result of later disease onset rather than a missed earlier diagnosis.

Conclusion: Screening of the known genes identified mutations in 24% of individuals within our cohort who were diagnosed with hyperinsulinism outside of infancy. These results highlight the need to consider genetic testing for all individuals diagnosed with persistent hyperinsulinism regardless of their age at presentation.

P1-76

Hyperinsulinemic Hypoglycemia in a child with Peroxisomal Biogenesis Disorder due to a Novel PEX1 mutation

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Introduction: Peroxisomal biogenesis disorders - Zellweger Syndrome Spectrum (PBD-ZWS) are rare disorders involving multiple systems including the central nervous system, adrenals, liver and skeleton but hyperinsulinism is not a recognized association. We present a child with PBD-ZWS due to a novel mutation in *PEX1* who developed hyperinsulinaemic hypoglycaemia (HH).

Case Report: A 7 month old boy presented with recurrent hypoglycemia. He was born at 41 weeks of gestation with a birth weight of 3.7 kg (0.48 SDS). He had bilateral sensorineural hearing loss, global developmental delay, hypotonia, visual delay, gastro-esophageal reflux and liver dysfunction. Investigations showed inappropriately high insulin and low 3-hydroxybutyrate and fatty acid levels during hypoglycaemia suggestive of HH. Cortisol was low and a synacthen test confirmed adrenal insufficiency. The patient was treated with hydrocortisone (10mg/m²/day) and diazoxide (maximum dose 15 mg/kg/day) and the blood glucose stabilized. He was initially on parenteral nutrition, which was gradually transitioned on to oral feeds. Subsequently, diazoxide was gradually tapered and stopped and the blood glucose remained stable. At 10 months of age, he was able to fast for 10 hours without hypoglycaemia, with appropriately suppressed insulin at the end of the fast suggesting that HH was transient. His plasma very long

chain fatty acids were elevated suggesting PBD-ZWS. Genetic analysis showed two heterozygous mutations in *PEX1* [c.2097dupT p.(Ile700TyrfsTer42) and c.1838G>A p.(Cys613Tyr)].

Conclusion: Transient diazoxide responsive HH can be associated with PBD-ZWS and occurred at an unusual age (7 months) in our patient.

P1-77

Real-Time Continuous Glucose Monitoring in the Management of Neonates with Persistent Hypoglycemia

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Background: Persistent hypoglycaemia is common in the newborn, due to prematurity or congenital hyperinsulinism (CHI) and is associated with the risk of poor neurodevelopmental outcome. Adequate monitoring is critical in prevention but is dependent on frequent blood sampling. Continuous glucose monitoring (CGM) is increasingly being used in children with type 1 diabetes mellitus who also are at risk from hypoglycemia, but use in neonatology remains limited. Previous studies have highlighted the potential of masked CGM to identify clinically silent episodes of transient hypoglycaemia in the newborn. We aimed to introduce real-time CGM to provide insights into patterns of dysglycaemia and to support the management of infants with persistent hypoglycemia.

Methods: This is a single centre retrospective study of real-time CGM use over a 4-year period in babies with persistent hypoglycaemia. We had used the mean absolute relative difference (MARD), Bland -Altman analysis and Clarke Error grid plots to explore the impact of CGM.

Results: CGMs were inserted in 14 babies: 8 term and 6 pre-term infants, 9 with evidence of hyperinsulinism. The median age at first CGM insertion was 14 days (2-98 days), with a total of 224 days of data collected. A total of 1254 paired glucose values (CGM and blood) were available, and comparison gave a MARD of 11%. The CGM revealed marked fluctuations in glucose levels. There were 22 clinical episodes of hypoglycaemia (blood glucose <2.6mmol/l) and sensitivity for detecting hypoglycaemia was 0.73, specificity 0.94, positive predictive value 0.17 and negative predictive value of 0.99. The CGM data showed that neonates with CHI tended to have greater SD (1.52±0.79 mmol/l vs 0.77±0.22mmol/l, *p*= 0.07) compared to preterm infants.

Conclusion: The CGM data highlighted marked fluctuations in glucose levels in babies with CHI, in contrast to preterm babies, and therefore the challenges of preventing hypoglycaemia in these babies when using intermittent blood glucose levels alone. The low sensitivity despite high specificity of CGM for hypoglycaemia means CGM results in high numbers of false positives but could help to reduce the frequency of blood sampling during normoglycaemia.

Hyperinsulinemic hypoglycemia due to biallelic mutations in the DNAJC3 gene

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Background: DNAJC3 is an endoplasmic reticulum (ER) co-chaperone involved in folding/processing of secretory and transmembrane proteins. The defect in the ER co-chaperone proteins impairs adaptive ER responses and leads to apoptosis, impairment of organ function with multisystemic involvement. Biallelic mutations in the DNAJC3, described in a limited number of cases cause multiple endocrine dysfunction and neurodegeneration of nervous system.

Herein, we report a new patient with severe growth retardation, microcephaly, early-onset hypothyroidism, hyperinsulinemic hypoglycemia and neuromotor retardation due to a novel homozygous mutation in the DNAJC3 gene.

Case Report: A 6.5 month-old boy was presented with growth retardation and hypothyroidism. The parents were first degree cousins. He was born at 27⁺3 gestational weeks because of pre-eclampsia with a birth weight of 610 g (-1.8 SDS) and had been hospitalized for 5 months in a neonatal care unit. At presentation, his height, weight and head circumference was 51 cm (-4.4 SDS), 3120 g (-4.3 SDS) and 33.5 cm (-6 SDS), respectively. He had a triangular face, antevert prominent ears, prognathism, clinodactyly, pectus carinatum and upturned eyebrows. Biochemistry, echocardiography and abdominal ultrasonography were normal. Anterior pituitary hormones were normal. Neurodevelopmental milestones were significantly delayed for age. Brain magnetic resonance imaging scan at 4.5 years of age showed cerebellar and brainstem atrophy and there were T2 hyperintensities in the frontoparietal area, as well as subcortical U fibers. Whole exome sequencing revealed a novel homozygous frameshift variant (c.1314dupG;p.F439Vfs*3) in DNAJC3 gene. An OGTT was performed after the molecular diagnosis revealed previously undiagnosed and clinically asymptomatic hyperinsulinemic hypoglycemia by a glucose level of 34 mg/dl and insulin 2.5 mIU/L at 180 minutes of the test. Blood glucose remained stable on frequent feeding and corn starch at night time without any other intervention.

Conclusion: We report a novel mutation in the DNAJC3 gene causing more severe growth and developmental delay compared to previously described cases. Hyperinsulinemic hypoglycemia is associated with increased morbidity and poor neurodevelopmental outcomes in patients with DNAJC3 gene mutations. Impaired glucose metabolism should be considered and investigated in patients with molecular defects affecting endoplasmic reticulum.

Concurrent hyperinsulinism and hypopituitarism in a 22 month old child due to a novel FOXA2 mutation

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Introduction: Co-existence of congenital hypopituitarism and congenital hyperinsulinemia is extremely rare. We present a case of congenital hypopituitarism and hyperinsulinemic hypoglycemia with a novel FOXA2 mutation.

Case: A 22-month-old girl was referred to pediatric endocrinology due to short stature. She was the first child of healthy, non-consanguineous parents with no relevant family history. Delivery was by cesarean section at 40 weeks gestation. Birth weight and length were 3600 grams (76th percentile) and 48 cm (26th percentile), respectively. At the age of two days, she had an episode of hypoglycemia requiring hospitalisation for 10 days. Her family reported stalled development from the age of nine months and she had a further three episodes of hypoglycemia, but no endocrinological evaluation was performed. Her father had growth hormone deficiency at 10-years-old requiring growth hormone treatment until 16-years-old.

On initial examination, height was 75 cm (-2.76SD) and weight was 8.6 kg (-2.15SD), while mid parental height was 158 cm (-0.87SD). She had no dysmorphic features.

Complete blood count, liver and kidney function tests were normal. She had a low free-thyroxine (0.57ng/dL) but thyroid stimulating hormone was normal (2.09 µl/mL).

Plasma glucose was 36 mg/dL. Hypoketotic hypoglycemia was confirmed by repeated measurements. Plasma insulin was 2.96 u/mL, C-peptide was 1.15 ng/mL during hypoglycemia. Glucagon stimulation test resulted in a rise in plasma glucose to 102 mg/dL. Both cortisol (6.99 mcg/dL) and growth hormone (0.16 ng/mL) response to hypoglycemia was blunted. Ammonia, lactate, b-hydroxybutyrate and non-esterified free fatty acid levels were normal or suppressed. After hospitalization, glucose infusion and diazoxide was started. She had cortisol response (21 mcg/dL) to low dose adrenocorticotropin stimulation test. Levothyroxine (25mcg-day) was started. When euthyroid, growth hormone stimulation test was performed with L-dopa, but there was no appreciable response (0.28 ng/mL). Magnetic resonance imaging of the pituitary gland demonstrated an ectopic posterior pituitary. Growth hormone replacement was started. Normoglycemia was achieved with diazoxide (15 mg/kg-day) and growth hormone replacement (25 mcg/kg-day).

Genetic screening for ABCC8, GCK, GLUD1, HADH, INS, KCNJ11, SLC16A1 and FOXA2 was performed. Sequencing revealed a novel, heterozygous FOXA2 variant (NM_021784.5 c.304delG [p.A102Rfs*11] [p.Ala102ArgfsTer11]) of likely pathogenicity (ACMG guideline). Functional analysis and parents' genetic studies are still ongoing.

Conclusion: *FOXA2* has an important role for both pituitary and pancreatic development. Although the functional analysis is not yet complete, we hypothesize that the detected *FOXA2* mutation is related to the phenotype of this patient.

P1-80

Sphingosine 1-phosphate lyase insufficiency syndrome (SPLIS) as a cause of primary adrenal insufficiency and primary hypogonadism

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Sphingosine 1-phosphate lyase insufficiency syndrome (SPLIS) was described in 2017 as a novel condition affecting sphingolipid metabolism, with bi-allelic loss of function mutations in *SGPL1*. There is a multisystemic phenotype including steroid resistant nephrotic syndrome and primary adrenal insufficiency (PAI) and to a lesser extent ichthyosis, neurological disease and lymphopenia. Hypogonadism is described amongst some affected patients.

To interrogate the steroid hormone related-presentation we reviewed clinical data within our patient cohort with SPLIS and the wider literature. 46 patients have been diagnosed with SPLIS with significant associated mortality (n=23/46, 51%; 4 of these *in utero*). A significant proportion (n=28/46, 60%) presented with glucocorticoid deficiency, some of whom had additional mineralocorticoid deficiency (n=7/28, 25%). The vast majority of those with PAI also had nephrotic syndrome (n= 24/28, 86%). However, amongst 3 kindreds, 3 patients presented with PAI alone, and 1 patient with PAI and neurological disease, interestingly with the same *SGPL1* mutation, c.665 G>A; p.Arg222Gln. Nonetheless, 6 other patients with this mutation manifested both PAI and nephrotic syndrome. Five further patients had adrenal calcifications though biochemistry was not undertaken. Most patients presented with PAI in the first 2 years of life (n=21/28), with the oldest presenting at 11 years. Adrenal calcifications were commonly described in those with documented imaging (n=13/15, 87%).

Primary gonadal failure was reported in 8 male cases, all with concomitant PAI. Presenting features included micropallus (n=7/8) and cryptorchidism (n=8/8), indicating reduced *in utero* androgen exposure. Hypospadias was not reported. All who had biochemical evaluation demonstrated raised basal LH and FSH/exaggerated response to LHRH stimulation, a lack of testosterone response to HCG stimulation and low antimüllerian hormone (AMH) levels. To date there are no reports of pubertal delay in female patients, and they have normal ovarian reserve as evidenced by AMH levels (n=2).

SPLIS is unique amongst sphingolipid disorders in presenting with significant endocrinopathy. Early manifestations suggest an impact on *in utero* adrenal and gonadal development with late disease implying an effect on acute steroidogenesis. The pathological mechanism associated with this sphingolipid pathway disruption needs to be further explored. Investigation for *SGPL1* mutations is warranted in PAI with nephrotic syndrome, but it should also be

considered in the differential of PAI and 46XY DSD. Timely diagnosis allows for initiation of appropriate screening and therapeutics in the syndrome, with significant impact on morbidity and mortality.

Pituitary A

P1-81

Sporadic pituitary adenomas in young patients: clinical and molecular description

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Introduction: Pituitary adenomas (PA) in pediatric and young patients comprise a rare pathology of unknown prevalence. The majority are sporadic, but 5% occur in a familial setting, either as isolated (FIPA) or as part of a syndrome. The identification of genetic alterations has broadened the scope of molecular investigations. We describe the clinical characteristics of patients with sporadic PA arising before the age of 35 years and perform thorough genetic screening for germline variants in probands and relatives.

Patients and Methods: We collected clinical characteristics at diagnosis of 265 patients (≤35 years) with a sporadic PA. Genetic screening was performed via next-generation sequencing using a customized gene panel and array comparative genomic hybridization. Clinical variables were compared among positive and negative patients in the pediatric and adolescent (<19 years) and young adults' cohort (≥19-35 years).

Results: Among the total cohort, mean age was 19.5 years and 63.0% were females. Local mass effect symptoms were present in 23% and prolactinomas were the most frequent (45.3%). We identified disease-causing germline variants in 20 patients (Table 1). Genetically positive patients were younger and had larger tumor size at diagnosis. Healthy family carriers were also identified.

Table 1.

	Case (Gender)	Age	Type of PA	Tumor size (mm)	Surgery	Genetic alteration
Pediatric and adolescents (<19 years)	ME0297(F)	17.3	GH	30.0	Yes	<i>AIP</i> ,c.64C>T;p.R22
	ME0173(M)	10.3	GH	40.0	Yes	<i>AIP</i> ,c.811C>T;p.R271W
	ME0393(M)	17.9	PRL	Macroadenoma	No	<i>AIP</i> ,c.811C>T;p.R271W
	ME0217(F)	13.9	ACTH	55.0	No	<i>AIP</i> ,c.911G>A;p.R304Q
	ME0237(M)	12.9	GH	30.0	No	<i>AIP</i> ,c.811C>T;p.R271W <i>PRKAR1A</i> ,c.221G>A;p.R74H
	ME0199(F)	15.9	PRL	13.0	Yes	<i>MEN1</i> ,c.1010G>A;p.R337H
	ME0377(M)	3.1	GH	38.0	No	<i>CDKN1B</i> ,c.160G>C;p.E54Q
	ME0326(F)	15.0	ACTH	2.0	Yes	<i>CDKN1B</i> ,c.356T>C;p.I119T
	ME0175(F)	15.9	PRL	16.0	Yes	<i>SDHB</i> ,c.166_170delCCTCA;p.P56Yfs*5
	ME0185(F)	10.8	NF	12.0	No	<i>PRKAR1A</i> ,c.221G>A;p.R74H
	ME0247(F)	11.1	PRL	26.0	No	<i>PRKAR1A</i> ,c.221G>A;p.R74H
	ME0461(F)	15.1	PRL	7.8	No	<i>PRKAR1A</i> ,c.221G>A;p.R74H
	ME0391(F)	15.7	PRL	13.0	Yes	<i>PRKAR1A</i> ,c.221G>A;p.R74H
	ME0201(F)	3.6	GH	Enlarged sella turca	No	Xq26.3(135.615.258-136.262.002)X3
	ME0191(M)	23.0	PRL	10.0	No	<i>AIP</i> ,c.26G>A;p.R9Q
Young adults (19–35 years)	ME0270(M)	23.3	PRL	36.0	Yes	<i>AIP</i> ,c.197delA;p.K66Rfs*88
	ME0261(M)	28.2	PRL	36.0	No	<i>AIP</i> ,c.807C>T;p.F269=
	ME0438(F)	30.6	ACTH	7.0	Yes	<i>AIP</i> ,c.26G>A;p.R9Q
	ME0198(F)	33.0	NF	2.5	Yes	<i>PRKAR1A</i> ,c.221G>A;p.R74H
	ME0169(F)	19.0	PRL	10.0	No	<i>CDKN1B</i> ,c.272C>T;p.P91L

Conclusions: Variants in genes associated with syndromic forms of PA were detected in a large cohort of sporadic PA. We have identified novel variants in well-known genes, such as *MEN1* and emphasized the lack of penetrance within families.

P1-82

Cardiac remodeling in patients with childhood-onset craniopharyngioma – Results of HIT-Endo and KRANIOPHARYNGEOM 2000/2007

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Background: Hypothalamic obesity caused by childhood-onset craniopharyngioma results in long-term cardiovascular morbidity. Knowledge about clinical markers and risk factors for cardiovascular morbidity is scarce.

Patients and Methods: A cross-sectional study on transthoracic echocardiographic parameters was performed to determine

the associations with clinical and anthropometric parameters in 36 craniopharyngioma patients.

Results: BMI correlated with the thickness of interventricular septum in diastole (IVSd) ($r=0.604$, $p<0.001$) and left ventricular diastolic posterior wall in diastole (LVPWd) ($r=0.460$, $p=0.011$). In multivariate analyses on risk factors for cardiac remodeling, sex hormone replacement therapy, BMI and male gender were positively correlated with increased left ventricular internal diameter in diastole (LVIDd), $R^2=0.596$, $F=10.323$, $p<0.001$. BMI and insulin resistance were selected as significant independent determinants of IVSd, produced $R^2=0.655$, $F=29.441$, $p<0.001$. Due to wide range of disease duration, 17 pediatric and 19 adult patients were analyzed separately. In the adult subgroup (age at study ≥ 18 years), BMI correlated with IVSd ($r=0.707$, $p=0.003$), LVPWd ($r=0.592$, $p=0.020$) and LVIDd ($r=0.571$, $p=0.026$). In the pediatric subgroup (age at study <18 years), no correlation between TTE parameters and BMI was observed. Only LVIDd correlated with disease duration ($r=0.645$, $p<0.001$). All cardiac functions were within the normal range, indicating no association with functional impairments.

Conclusions: Cardiac remodeling in patients with craniopharyngioma correlated with the degree of hypothalamic obesity, disease duration, sex hormone replacement therapy, male gender and insulin resistance. As echocardiography has limited sensitivity in patients with obesity, further research on more sensitive techniques for cardiac diagnostics in craniopharyngioma patients is warranted.

Pregnancies after childhood craniopharyngioma – Results of KRANIOPHARYNGEOM 2000/2007

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Background: Data on female fertility, pregnancy, and outcome of offspring after childhood-onset craniopharyngioma (CP) are rare.

Study Design: Observational study on pregnancy rate and outcome of offspring after CP in postpubertal, female patients recruited in KRANIOPHARYNGEOM 2000/2007 since 2000.

Results: 451 CP patients (223 female) have been recruited. 269 CP patients (133 female) were postpubertal at study. Six of 133 female CP patients (4.5%) with a median age of 14.9 years at CP diagnosis had 9 pregnancies, giving birth to 10 newborns. Three patients achieved complete surgical resections. No patient underwent postoperative irradiation. Five natural pregnancies occurred in 3 CP patients without pituitary deficiencies. Four pregnancies were achieved in 3 CP with hypopituitarism under assisted reproductive techniques (ART) (after median 4.5 cycles, range: 3–6 cycles). Median maternal age at pregnancy was 30 years (range: 22–41 years). Six babies (60%) were delivered by caesarean section. Median gestational age at delivery was 38 weeks (range: 34–43 weeks); median birth weight was 2,920 grams (range: 2,270–3,520 grams), the rate of preterm delivery was 33%. Enlargements of CP cysts occurred in 2 women during pregnancy. Other severe complications during pregnancy, delivery and postnatal period were not observed.

Conclusions: Pregnancies after CP are rare and achieved in 45% after ART. Close monitoring by an experienced reproductive physician is necessary. Due to a potentially increased risk for cystic enlargement, MRI of cystic CP is recommended during pregnancy. Severe perinatal complications, birth defects, and postnatal morbidity of mothers and offspring were not observed.

Pituitary Duplication – A rare and heterogenous spectrum

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Background: Pituitary gland duplication is a very rare developmental abnormality. It is often associated with other midline anomalies including cleft palate, spinal cord and corpus callosum defects, termed duplication of the pituitary gland-plus syndrome. Of the only 40 cases reported in the literature, most are in females and are often associated with precocious puberty. Duplication of the pituitary gland may arise from blastogenesis defects, with splitting of the rostral end of the notochord, though the exact mechanism is still unclear. Thus far no causative genetic mutations have been found. This is the largest case series that has been described.

Case Series: 8 patients, 4 male, from 4 centres in Europe with duplication of the pituitary gland. Half also had duplication of the pituitary stalk and some had duplication of mammillary bodies, basilar artery (n=3) or nasal septum. All had other anomalies including a palate abnormality (cleft n=5, high arched n=1), dermoid cyst (nasal n=3, palate n=1), hamartoma (third ventricle n=1, soft palate n=1) teratoma (nasopharynx n=1, palatine n=1) and persistent craniopharyngeal duct (n=2). One patient had a partial agenesis of the corpus callosum with a midline brain lipoma, and duplicated thyroglossal cyst. Spinal column defects were seen in three patients including cervical cleft, and another with an Arnold Chiari malformation and myelomeningocele. Three female cases and one male had precocious puberty. Another male patient had undescended testes with partial hypogonadotropic hypogonadism and partial growth hormone deficiency. Hearing impairment primarily from chronic ear infections occurred in 38% of patients. Half of the patients had visual impairment, with two patients having optic nerve hypoplasia, and another with possible small optic discs. Four patients were diagnosed with mild learning difficulties, and of these patients, two had seizures and sleep problems. A patent ductus arteriosus and patent foramen ovale were the only cardiac abnormalities reported. There was one death in this cohort in early childhood, and the eldest are now in their third decade. Six of the 8 children underwent whole exome sequencing (with trio analysis in 5 patients), but no relevant genetic variants were identified.

Conclusion: This case series highlights the phenotypic spectrum associated with duplication of the pituitary gland. This will be informative for the patient, their family, and the clinicians to

highlight the possible associated pathology, and to direct their management. Future research should be directed towards ongoing collaboration to further characterise this syndrome, and to discover possible aetiological factors.

P1-85

Auxological and endocrine aspects in pediatric patients with type 1 Narcolepsy. Results of long-term follow-up in a pediatric endocrinology center

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Introduction: Type 1 Narcolepsy is a rare pediatric condition characterized by central hypersomnia secondary to hypocretin deficiency. It can also involve the neuroendocrine axis, in particular determining obesity and central precocious puberty (CPP).

Objectives: The primary aim of this study is the evaluation of endocrine and auxological aspects at diagnosis and during follow-up in children affected with T1N, in treatment with Sodium Oxibate or not.

Methods: We retrospectively evaluated medical records of 98 consecutive patients affected with T1N during the period 2004-2020. We evaluated auxological, biochemical and radiological parameters for investigate endocrine-metabolic complications.

Results: 98 consecutive patients fulfilled inclusion criteria and were recruited for the study: 53 boys e 45 girls. Median follow up was 36 ± 16 months. Median age at diagnosis was 10,4 ± 3,2. At diagnosis we find a median height (SDS) of 0.6 ± 1.1 and BMI (SDS) of 1.1 ± 1.1. Overweight was reported in 25/97 (25.7%) and obesity in 33/97 (34%).

A diagnosis of CPP was confirmed in 21/98 cases (21.4%) without significative gender differences. Treatment with GnRH agonist was necessary in 11/21 cases (52.3%). The other hormonal investigations were all within the limits of normality.

Patients treated with Sodium Oxibate at 12 months of follow up were 46/98 (46.9%). After 36 months of follow up, we find a

significative difference in BMI SDS between Sodium Oxibate treated vs untreated patients ($0,0 \pm 1,3$ vs $1,3 \pm 0,4$) ($p < 0.003$).

62 patients reached their final height, with a median SDS of 0.5 ± 1.1 in boys and 0.3 ± 1.2 in girls. Target parental height was 0.2 ± 0.8 SDS in boys and 0.3 ± 0.7 in girls. There were no statistical differences between treated and untreated groups.

Conclusions: The results of our study confirm an increased frequency of CPP and obesity in T1N patients compared to general population. The treatment with Sodium Oxibate leads to an improvement of the BMI which also persist at 36 months of follow up. To our knowledge, these are the first results regarding the final height in a large series of patients diagnosed with T1N in pediatric age. IGF1 levels were in the normal range and stature SDS during follow-up and final height were in the range of parental target height.

P1-86

Adding a protease inhibitor to sampling tubes increases the acylated ghrelin and decreases the desacylated ghrelin levels in girls

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Introduction: Ghrelin is a growth hormone-releasing acylated peptide stimulating the appetite, mainly produced in the stomach, and with an important role in pubertal development (1). Two ghrelin forms have been described, acylated (AG) and desacylated (DAG), but it is debated whether DAG is an active hormone or a degradation product of AG (2). Our aim was to evaluate the effects of adding the protease inhibitor 4-(2-aminoethyl) benzenesulfonyl fluoride hydrochloride (AEBSF) to sampling tubes and acidification of plasma on levels of AG and DAG in girls with suspected central precocious puberty (CPP).

Methods: 13 girls aged 6.6 to 10.1 years with suspected CPP undergoing a gonadotropin-releasing hormone stimulation test during 2015-2017 at the Departments of Paediatrics, at Örebro or Uppsala University Hospital were included. Blood samples were collected at 0 min in pre-cooled EDTA tubes with or without AEBSF at a final concentration of 2mg/ml. After cold centrifugation, HCl at a final concentration of 50 µmol/l, was added to 50% of the plasma tubes containing AEBSF. The AG and DAG concentrations were measured by ELISA kits. Comparison was performed using one-way ANOVA for repeated measurements.

Results: The mean plasma AG levels were significantly higher after the addition of AEBSF only (650.9 ± 257.1 pg/ml) or AEBSF+HCl (681.2 ± 299 pg/ml) compared to the concentrations without additives (247.6 ± 123.4 pg/ml, $p < 0.01$ for both comparisons). There was no significant difference between the AG levels after AEBSF and AEBSF+HCl addition. The plasma levels of DAG were significantly lower after the addition of AEBSF+HCl (69.3 ± 30.6 pg/ml) and even further lowered after the addition

of AEBSF only (56.3+/- 30.9 pg/ml) compared to the concentrations of DAG in tubes without any additives (149.9 +/- 73.7 pg/ml, $p < 0.01$ for both comparisons).

Discussion: Due to the unstable nature of AG, special procedures are required for accurate measurement of its plasma levels in children, including the use of a protease inhibitor like AEBSF. However, DAG was still measurable indicating that it may not only be a degradation product of AG.

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P1-87

GHSR protects the emergence of limited sex differences in anxiety-related behaviors in adult mice after long term THC administration during peri-adolescence

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As marijuana use during adolescence has been increasing, the need to understand the effects of its long-term use becomes crucial. Previous research suggested that marijuana consumption during adolescence increases the risk of developing mental illnesses, such as schizophrenia, depression, and anxiety. Ghrelin is a peptide produced primarily in the gut and is important for feeding behavior. Ghrelin and its receptor, the growth hormone secretagogue receptor (GHSR) play important roles in mediating stress, as well as anxiety and, depression-like behaviors in animal models.

Here, we investigated the effects of chronic Tetrahydrocannabinol (THC) administration during adolescence (P42-55), in GHSR (GHSR^{-/-}) knockout mice and their wild-type littermates in relation to anxiety-like behaviors.

We found that continuous THC exposure during peri-adolescence did not lead to any significant alterations in anxiety-like behavior of adult mice, regardless of genotype. However, males and females GHSR^{-/-} mice responded differently to THC exposure in limited parameters.

These data indicate that in the presence of intact GHSR signaling protects the emergence of limited sex differences in anxiety-related behaviors in adult mice after continuous THC administration during peri-adolescence.

P1-88

Pituitary microadenomas in childhood – is follow-up with diagnostic imaging necessary?

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Aim: We aimed to investigate the growth potential of pituitary microadenomas and cystic lesions < 10mm in children, and to evaluate how reproducible the measurements were on magnetic resonance imaging (MRI).

Design: Retrospective observational study.

Methods: 74 children were included < 18 years at first pituitary MRI, and diagnosed with a microadenoma (microadenoma producing ACTH, GH or TSH excluded) or cyst < 10 mm. The term probable microadenoma was used when the solid lesion was less distinct. Children with prolactinoma were included for testing of measurement accuracy. Pituitary lesion size at first and last MRI was reviewed by a neuroradiologist. All individual MRI examinations were re-evaluated by two radiologists.

Results: 74 children had a non-hormone producing microadenoma, probable microadenoma or cystic lesion, median age 12 years (range 3 – 17), 55 of those underwent repeated MRI, median number 3 (range 2 – 7), with a median follow-up time of 37 months (range 4 – 189). The most common symptoms were precocious puberty (n= 27, 36%) and growth disturbances (n=22, 30%). Among these 74 children, 32 had hormonal treatment (10 GH and nine GnRH analogue). An additional 12 children with prolactinoma, median age 16 years (range 12 – 17), underwent repeated MRI, median number 5.5 (range 2 – 11), median follow-up time 73.5 months (range 26 – 120). None of the non-hormone producing microadenoma, probable microadenoma or cyst, with no hormonal deficiency increased significantly in size during follow-up (Table 1). One child with a cystic lesion developed hormonal deficits as the cyst grew, and another child had a prolactinoma that increased in size due to bad compliance to medication. Two reviewers agreed that no lesion could be identified in 38/269 MRI exams, in 51/231 (22%) there was disagreement about lesion location. They also disagreed in 34/460 (7%) MRI measurements to an extent that would have been considered progression in lesion size (> 2mm).

Conclusion: Non-hormone producing pituitary microadenoma or cystic lesions in childhood with no hormonal disturbances show small, clinically irrelevant size variations that do not require intervention or extended follow-up with MRI.

Table 1. Median size at initial and last MRI.

Initial diagnosis, repeated MRI	Number	Median size (range) mm at initial MRI	Median size (range) mm at last MRI
Microadenoma	8	4.5 (2 – 6)	4.5 (0 – 6)
Probable microadenoma	35	3.0 (2 – 7)	3.0 (0 – 7)
Cystic lesion	12	3.6 (1 – 7)	4.0 (1 – 7.2)
Prolactinoma	12	6.0 (4.8 – 8.8)	3.9 (0 – 6.4)

P1-89

The Pituitary Tumour Module: Developing a Condition Specific Module within the European Registries for Rare Endocrine Conditions (EuRRECa)

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Introduction: The European Registries for Rare Endocrine Conditions (EuRRECa) project aims to support the needs of the endocrine and bone community by facilitating the collaboration between patients, health care professionals and researchers across Europe and beyond. It is a project funded by the European Union's health programme and is the affiliated registry of the European Reference Network for Rare Endocrine Conditions (Endo-ERN). It consists of two registries: an electronic reporting tool, e-REC (e-Reporting of Rare Conditions), which collects the number of new cases encountered every month, and the core registry, which collects a set of core data elements and allows the registering of new and existing patients. e-REC has been collecting new cases of

endocrine conditions since 2018. To date, pituitary adenoma is the most commonly reported condition with over 1800 cases reported so far.

Aim: To develop a pituitary tumour module within the EuRRECa core registry for the registering of cases of this condition. A secondary aim is to detect cases showing aggressive tumour behaviour, including aggressive pituitary tumours and carcinomas.

Methods: A group of experts from Endo-ERN, ESE and ESPE in the field of hypothalamic and pituitary disorders as well as pituitary tumours met remotely on several occasions between December 2020 and March 2021 to develop a consensus on relevant data fields, including aggressive pituitary tumour.

Results: A total of 40 variables were grouped in 10 domains that collect several aspects of the care of patients with pituitary tumours. These 10 domains included clinical phenotype, visual impairment, secreted hormones, medical therapy, surgical therapy and irradiation therapy, imaging, genetics, therapy outcomes and patient status. Questions aimed at identifying aggressive tumours were included in the imaging section. The module will be incorporated into EuRRECa's core registry platform and will be available to complete if the diagnosis of any form of pituitary tumour is selected. Details of these domains will also be widely disseminated through EuRRECa's data dictionary. The expert group will advise on the frequency for the completion of this module.

Conclusion: Pituitary tumour is the most reported condition in e-REC. The development of a dedicated registry will provide the clinicians with the opportunity of sharing aspects of the disease and care of their patients with health care professionals and the research community. A working group consisting of experts across the patient age span from several centres across Europe proved to be a successful strategy in reaching consensus rapidly.

Craniopharyngiomas presenting as incidentalomas: results of KRANIOPHARYNGEOM 2007

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Purpose: Childhood-onset craniopharyngiomas (CP) are diagnosed due to clinical symptoms (symCP) or incidentally (incCP). We investigated clinical manifestations and outcome in incCPs and symCPs.

Methods: IncCP were discovered in 4 (3m/1f) and symCP in 214 (101m/113f) CP recruited 2007–2014 in KRANIOPHARYNGEOM 2007. Age, sex, height, body mass index (BMI), tumor volume, degree of resection, pre- and postsurgical hypothalamic involvement/lesions, pituitary function and outcome were compared between both subgroups.

Results: Reasons for imaging in incCP were cerebral palsy, head trauma, nasal obstruction, and tethered-cord syndrome, whereas headache (44%), visual impairment (25%), and growth retardation (17%) lead to imaging in symCP. Tumor volume at diagnosis was smaller in incCP (median 2.39 cm³; range: 0.14–4.10 cm³) when compared with symCP (15.86 cm³; 0.002–286.34 cm³). Age, gender, BMI, height, hydrocephalus, tumor location, and hypothalamic involvement at diagnosis of incCP were within the range of these parameters in symCP. Complete resections were achieved more frequently (3/4 patients) in incCP when compared with symCP (20%). Surgical hypothalamic lesions were distributed similar in incCP and symCP. Irradiation was performed only in symCP (33%). No noticeable differences were observed concerning survival rates, endocrine deficiencies, BMI, height, functional capacity and quality of life of the 4 incCP cases when compared with the symCP cohort.

Conclusions: IncCP are rare (1.8%) and characterized by lack of endocrine deficiencies, resulting in normal height and BMI, no hydrocephalus, and smaller tumor volume at diagnosis when compared with symCPs. Outcome of the observed incCP is similar with symCP.

Thyroid A

The effect of preoperative calcitriol prophylaxis on post-thyroidectomy hypocalcaemia in children

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Background: Transient or permanent hypoparathyroidism is one of the most well-known complications of total thyroidectomy and may lead to symptomatic hypocalcaemia. Treatment of post-thyroidectomy hypocalcaemia usually consists of postoperative calcium and/or vitamin D supplementation. In 2013 we implemented prophylactic pre-thyroidectomy calcitriol supplementation for all children undergoing total thyroidectomy at Amsterdam UMC. The objective of this study was to evaluate the efficacy of this prophylactic calcitriol supplementation in preventing post-thyroidectomy hypocalcaemia in children.

Methods: In a retrospective case study we included all children (age < 18 years), who underwent a (sub)total or completion thyroidectomy in Amsterdam UMC, between 2000 and 2020. Patients were divided into two groups, patients with preoperative calcitriol supplementation, and those without (controls). Hypocalcaemia was defined as total serum calcium concentration of < 2.0 mmol/l. Primary outcome measure was the occurrence of hypocalcaemia in the first 72 hours after surgery. Secondary outcome measures were occurrence of symptomatic hypocalcaemia, need for medical intervention for hypocalcaemia and length of hospitalization.

Results: A total of 51 patients were included; 26 with calcitriol prophylaxis and 25 controls. There was no significant difference in occurrence of hypocalcaemia (17/26 prophylaxis group; 18/25 control group). Median post-operative calcium concentrations in the first 72 hours were significantly higher in the group with prophylaxis at 12-17 hours after surgery (2.12 vs 1.96 mmol/l), 30-35 hours (2.26 vs 2.01 mmol/l) and 36-41 hours (2.17 vs 1.92 mmol/l). Occurrence of symptomatic hypocalcaemia, need for medical intervention and length of hospitalization were not significantly different between the groups (Table).

Conclusion: While calcitriol prophylaxis resulted in somewhat higher postoperative calcium concentrations, it did not reduce the occurrence of hypocalcaemia and did not affect clinical outcome measures such as occurrence of symptomatic hypocalcaemia and length of postoperative hospitalization.

Table 1. Hypocalcaemia outcome of 51 pediatric thyroidectomy cases.

	Calcitriol prophylaxis (n = 26)	Controls (n = 25)	p-value
Age at surgery in years (median, range)	14 (3-17)	13 (1-17)	0.828
Indication for surgery			
Prophylactic	2	6	0.276
Benign disease	13	9	
Malignant disease	11	10	
Extent of surgery			
No lymph node dissection	18	18	0.564
Central lymph node dissection	4	3	
Central+lateral lymph node dissection	4	2	
Node picking	0	2	
Hypocalcaemia < 72 hours	17	18	0.764
Symptomatic hypocalcaemia < 72 hours	6/17	5/18	1.000
	1 not reported	2 not reported	
Permanent hypocalcaemia	5	9	0.305
Length of hospitalization in days (median, range)	3 (2-8)	3 (2-10)	0.356

P1-92**Emotional Intelligence scores in children and adolescents with subclinical hypothyroidism - correlation with serum serotonin and thyroid stimulating hormone (TSH) concentrations**

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Introduction: Thyroxine is important for nervous system development. Subclinical hypothyroidism (SCH), a mild thyroid dysfunction, is associated with impaired cognitive function in children and mood disorders in adults. Serotonin is also involved in brain development, mood and behavior modulation. The possible interaction between thyroid function tests, serum serotonin concentrations and emotional intelligence, was studied.

Methods: 224 schoolchildren from Peloponnese in Greece, aged 11-19 years old, were included into the study, of which 26.3% had SCH. Emotional quotients (EQ), such as well-being, self-control, emotionality and sociability were assessed using the TEIQue-ASF questionnaire, and TSH, fT4 and serum serotonin concentrations were also evaluated.

Results: Children and adolescents with SCH had lower EQ total score ($p<0.001$), EQ Well-being score ($p=0.025$), EQ

Self-control score ($p=0.029$), EQ Emotionality score ($p=0.029$) and EQ Sociability score ($p=0.010$) and lower serum serotonin concentrations ($p<0.001$).

Conclusions: A possible association between TSH and serotonin levels is suggested affecting emotional intelligence scores in children and adolescents. Emotional intelligence seems to be negatively affected in children and adolescents with subclinical hypothyroidism. Further clarification of the role of thyroid hormones and serotonin in the developing brain is needed in order to elucidate the effect of a possible crosstalk between the hypothalamus-pituitary-thyroid axis and the serotonin pathway on emotional intelligence, cognitive ability and other potential brain functions in children and adolescents.

P1-93**Lymphocyte population in children and adolescents affected by Graves' disease. Potential predictive tool of disease severity**

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Introduction: Graves-Basedow disease (GD) is the most common cause of thyrotoxicosis in pediatric age. Multi-factorial pathogenesis stand on the basis of the autoimmune disorder activation, leading to lymphocyte imbalance that include increased CD4+ and CD8+ subtypes, increased CD4+/CD8+ ratio and B cells dysregulation. The aim of this study is to determine the

potential prognostic value of lymphocyte population parameters in pediatric GD.

Methods: Thyroid hormone profile, TRAb titre, lymphocyte population and clinical data of all pediatric subjects (aged <18 y) with new diagnosis of GD were collected. All of them were referred to the Department of Pediatric Endocrinology of Regina Margherita Children's Hospital in Turin in the period November 2017-April 2021.

Results: The data of 10 subjects (2 males, 8 females; age 11.7 ± 3.47 years old) with newly diagnosed GD in a follow-up period of 2.4 ± 0.8 years are represented in table 1.

Pearson correlation coefficient among CD4+/CD8+ ratio and fT3 levels and thyroid volume at diagnosis was 0.72 ($p=0.04$) and 0.81 ($p=0.004$) respectively. Positive correlation coefficient was observed also among CD4+/CD8+ ratio and TRAb titre at diagnosis and after 6, 12 and 24 months (0.89, 0.89, 0.73 and 0.77; $p=0.02$, $p=0.01$, $p=0.03$ and 0.04 respectively). The ATD dose correlation coefficient after 6 and 12 months with CD4+/CD8 ratio showed also a similar course (0.88 and 0.78, $p=0.001$ and $p=0.02$ respectively). After 2 years of follow-up, 2/10 patients underwent thyroidectomy, 2/10 had disease remission and 6/10 are still under ATD treatment.

Conclusion: Among lymphocyte population parameters, the CD4+/CD8+ ratio seems to be positively related to higher fT3 levels and goiter size at diagnosis, higher TRAb titre in the first two years and higher ATD dose in the first year after the diagnosis. These are preliminary data which need to be confirmed in longer follow-up period and larger cohorts.

P1-94

Evaluation of children with intrathyroidal ectopic thymus

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Background: Intrathyroidal ectopic thymus (IET), a benign lesion due to aberrant thymic migration during embryogenesis, is often discovered incidentally. Most of the reports in the literature describe individual cases or small series. We aimed to present the ultrasound (US) features, diagnostic methods, and follow-up of IET in children and adolescents.

Methods: We searched our database of patients under 18 years old with a nodular thyroid lesion detected by US, between January 2007 and December 2019. In 30/255 (11.7%), IET was diagnosed.

Results: The study included these 30 patients (20 males/10 females), mean age 5 years (0.1-12.2, median 5.6) with 34 lesions diagnosed by US as 'incidentalomas'. None of the patients had palpable nodules. On US, IET appeared as a hypoechoic lesion, with multiple punctuate internal echoes. 29/34 of lesions had well-defined margins. The most common location of IET was in the middle part (27/34) of the left lobe (19/34). The mean longest diameter at diagnosis was 6.4 (2.5-21, median 4.5) mm. Sonographic follow-up was available in 25 patients with 27 lesions. The mean time of observation was 2.7 (0.3-7.5, median 2.1) years. While 13/27 cases showed decreased size or regression during follow-up, the other 13 increased in size, and there was no change in size in one. Fine needle aspiration (FNA) was performed in 5 patients and surgery in one.

Discussion: IET should be considered in the differential diagnosis of pediatric thyroid nodules as a cause of FNA and/or surgery. Regular US monitoring can be used safely in the follow-up of this lesion.

	Diagnosis	At 6 months	At 12 months	At 24 months
TSH mcUI/ml	<0.005	2.46 ± 0.51	2.8 ± 0.9	2.64 ± 0.66
FT4 pg/ml	42.8 ± 4.7	12.4 ± 5.06	16.32 ± 1.69	12.57 ± 4.29
FT3 pg/ml	14.7 ± 8.12	4.38 ± 2.27	7.46 ± 1.04	4.96 ± 2.36
TRAb UI/L	19.3 ± 24.1	7.1 ± 6.7	13.7 ± 17.3	10.9 ± 14.4
Thyroid volume SDS	2.98 ± 0.47			
Total lymphocyte count/mcL	2657 ± 706.1	-	-	-
CD4+/CD8+ ratio	2.19 ± 0.9	-	-	-
ATD dose (μ g/kg/day)	0.33 ± 0.1	0.12 ± 0.1	0.14 ± 0.1	0.09 ± 0.01

P1-95

Prevalence and Characteristics of thyroid nodules in a pediatric population with congenital hypothyroidism

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Objective: To assess the characteristics of thyroid nodules among infants diagnosed with congenital hypothyroidism and to discuss the interest of a systematic screening.

Material and Method: A retrospective study of children with congenital hypothyroidism due to dysmorphogenesis was carried out at the pediatric endocrine center in Kremlin Bicêtre hospital, Paris, between 1999 to 2020. A screening ultrasound for thyroid nodules was then performed from July 2019 to July 2020 if no if no recent analysis was found (>3 years).

Results: 78 patients were included with median age of 14 years [8-21]. The cause of hypothyroidism was disorder of iodine organification in 50/78 patients, disorder of iodine uptake in 3/78, disorder of thyroglobulin synthesis in 7/78, and unclassifiable in 18/78 patients. 42/78 patients were supplemented with L-thyroxine. 10 Nodules and 1 multinodular goiter were detected In 8 and 1 patient respectively during follow-up (median average of 2.5 [1-3] and median size of 17 mm [5-37]). 1/10 nodule was classified TI-RADS2, 5/10 TI-RADS 3 and 4/10 TI-RADS 4. Fine needle aspiration biopsy were realised in 3 patients, and 5 had thyroidectomy. Diagnosis was thyroid cyst in 6/10 patients, Follicular lesion in 1/10, papillar carcinoma in 2/10 (1/2 patient with TPO gene mutation) and 1 multinodular thyroid.

Conclusion: The prevalence of thyroid cancer in our pediatric population is 2.5%, the prevalence of nodules is 7.6% including 20% of malignant nodules. Thyroid cancer occur in younger patients in the context of dysmorphogenesis. Given the importance of this pathology in patients with dysmorphogenesis, we recommend a regular ultrasound follow-up at least every 3 years, as well as a systematic genetic analysis at diagnosis to identify possible pathogenic variants.

P1-96

Thyroid storm and transient bulbar myopathy in a 22-month-old girl with Graves' Disease

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22-month girl presented with 3 days of cough and fevers, 2 weeks of rhinorrhoea and frequent "clearing of throat" and 6 months of diaphoresis and growth spurt. On examination, she was

flushed and diaphoretic with a large goitre. She had a low grade fever (T=37.9) with signs of cardiac compromise (bounding pulse sinus tachycardia [HR=200bpm]). She was hypertensive [BP=145/90mmHg] and tachypnoeic [RR=36/min] with respiratory distress and right-sided crepitations. She had a raised JVP but no peripheral oedema or hepatomegaly. Length (98th percentile) was well above expected (mid-parental height 10-25th percentile). She had a family history of hyperthyroidism and diabetes.

Initial investigations:

Test (reference range)	Value
TSH (0.70-5.97mU/L)	<0.005
fT4 (12.3-22.8pmol/L)	>100
fT3 (3.69-8.46pmol/L)	45.5
TSH receptor antibodies (<1.8U/L)	>20
TPO antibodies (0-34IU/mL)	343
Thyroid ultrasound	Diffuse enlargement, heterogeneous. No nodules.
Chest X-ray	Mild Cardiomegaly
ECG	Left ventricular hypertrophy, sinus tachycardia
Echocardiogram	Mild left ventricular hypertrophy

Rapid clinical deterioration (pyrexia, agitation, vomiting, and worsening cardiorespiratory status) occurred, despite commencing carbimazole 0.9mg/kg/day, propranolol 0.6mg/kg/day, and Lugol's iodine, and resulted in an overnight ICU admission. It was then noticed she was unable to manage oral secretions and had profound proximal myopathy (positive Gowers' sign). Bulbar myopathic dysphagia was confirmed on modified barium swallow, and was thought to be secondary to thyrotoxic myopathy after exclusion of a neurological event, Myasthenia Gravis or other myopathy and with subsequent resolution. Free T4 normalised after 2 weeks, free T3 by 3 weeks and she was treated with "block-and-replace" therapy from 7 weeks.

This is the youngest reported case of thyroid storm and first of bulbar myopathy complicating paediatric thyrotoxicosis. Less than 35 cases of thyroid storm have been reported in children (youngest 2 years). Consequently, evidence guiding diagnosis and management is limited, and published diagnostic criteria for thyroid storm (Burch Wartofsky Point Scale and Japanese Thyroid Association) are for adults with limited utility in the paediatric population. Thyrotoxic myopathy presenting as dysphagia has been described in case reports and series in adults, but not in children. Management includes considering the differential Myasthenia Gravis, which can be associated with Grave's disease, and treatment of thyrotoxicosis. Consistent with adult literature, where resolution of bulbar myopathy occurred with normalisation of thyroid function from 3 days to 14 weeks, in our case resolution of proximal myopathy took 6 weeks and dysphagia 3.5 months.

The association between serum Thyrotropin within the reference range and cardiometabolic risk in obese children

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Background: The adaptive increase of serum thyrotropin (TSH) levels in obese subjects may affect the metabolic regulation of body tissues and thus promote an unfavorable cardiometabolic profile.

Aim: To investigate the association between serum TSH, free thyroxine (FT4) and cardiometabolic risk factors in euthyroid obese children and adolescents.

Material and Methods: Four hundred ninety-one Caucasian euthyroid obese children and adolescents (age 9.93 ± 2.90) were recruited. Subjects with genetic and/or endocrine causes of obesity, diabetes, chronic diseases, chronic pharmacological therapies and overt or subclinical hypo-/hyperthyroidism, arterial hypertension were excluded. Each patient underwent clinical and auxological examination and laboratory workup including an OGTT and the measurement of serum TSH, FT4 and lipid profile. Homeostasis model assessment of insulin resistance (HOMA-IR) and for β -cell function (HOMA-B), triglyceride to high density lipoprotein cholesterol (TG/HDL-c) ratio, total cholesterol to HDL-c (Tc/HDL-c) ratio, atherogenic index of plasma (AIP), insulinogenic index, area under the glucose curve (AUCglu) and area under the insulin curve (AUCins) were calculated.

Results: The mean TSH level in our cohort was 2.31 (range 0.48-5) mU/L with a mean FT4 level of 16.62 (range 12-22) pmol/L. Two hundred twenty-five subjects (45.8%) had a high-normal TSH level (TSH 2.3-5.0 mU/L), among whom 151 subjects (67.1%) were severe obese (BMI standard deviation (SD) ≥ 2.5 according to the WHO reference). Increasing concentrations of TSH were associated with increasing values of BMI SD ($B = 0.067$, $p = 0.012$), Tc level ($B = 2.860$, $p = 0.040$), LDL-C level ($B = 3.017$, $p = 0.022$), Tc/HDL-c ratio ($B = 0.080$, $p = 0.046$), HOMA-IR ($B = 0.376$, $p = 0.009$), AUCglu ($B = 4.636$, $p = 0.021$) and AUCins ($B = 19.501$, $p = 0.022$) after adjustment for some confounding variables (age, sex, pubertal stage, HOMA-IR, BMI-SD). In addition TSH level was positively correlated with BMI-SD ($r_s = 0.113$; $p = 0.012$), Tc ($r_s = 0.121$; $p = 0.008$), LDL-c ($r_s = 0.104$; $p = 0.031$), TG/HDL-c ($r_s = 0.104$; $p = 0.033$), Tc/HDL-c ($r_s = 0.134$; $p = 0.005$) fasting plasma insulin ($r_s = 0.114$; $p = 0.012$), HOMA-IR ($r_s = 0.123$; $p = 0.007$), HOMA-B ($r_s = 0.133$; $p = 0.004$), AUCglu ($r_s = 0.178$; $p = 0.005$), AUCins ($r_s = 0.122$; $p = 0.045$), AIP ($r_s = 0.100$; $p = 0.040$). However, no association was found between serum TSH and dyslipidemia, impaired glucose metabolism and severe obesity. None of the analyzed cardiometabolic risk factors were predictive of a high-normal TSH level. Serum FT4 was negatively associated with BMI-DS ($B = -0.044$, $p = 0.000$) and negative correlated with fasting plasma glucose ($r_s = -0.110$; $p = 0.016$).

Conclusions: Even in euthyroid obese children and adolescents increasing TSH is associated with an increasing cardiometabolic risk.

Hypothyroid Screening in Children with Down Syndrome - A Service Evaluation

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Background: Individuals with Down Syndrome are at an increased risk of developing thyroid disease. Given that thyroid disorders represent a preventable cause of neurodevelopmental impairment, early detection and treatment are essential to maximise cognitive abilities in this already impaired population. This service evaluation sought to assess the efficacy of the Down Syndrome Hypothyroid Screening programme in its uptake and subsequent diagnosis of hypothyroidism.

Methods: A report of all children with known Down Syndrome was obtained from the Greater Glasgow and Clyde Down Syndrome database. Children were excluded if they were under the age of 2 years or had been a resident for less than 2 years within the region. Electronic Patient Records were used to access baseline characteristics and results of venous Thyroid Function Tests (TFTs) for all children born with Down Syndrome. Data on TSH capillary screening were obtained via the Scottish Newborn Bloodspot Screening lab. Data were collected on each child's previous 3 screening samples and the time between screening was calculated in decimal years. From this, the children referred to Endocrinology following abnormal screening and those subsequently commenced on levothyroxine therapy following referral were identified.

Results: We identified 248 children with Down Syndrome (122 male). 20 children were excluded as they were <2 years old or residents for <1 year. This left 228 children (114 male). The mean age of our cohort was 9.9 years, range (2.1-22.7). 3 children received no screening in their lifetime. Of those screened, 92% of patients received screening within the last 1.0 decimal years (207/225) and a further 3.1% (7/225) of patients received screening within the last 1.5 years. 7 of the 225 children had only been screened once ($n = 218$). 74 children (33.9%) had 1.0 years or less between their previous screenings. A further 118 children (54.1%) had 1.5 years or less between each screen. 21 children (9.3%) had abnormal screening, which resulted in referral to Endocrinology for 20 children. One child had normal TFTs and so was not referred. Of the 21 children with abnormal screening, 16 (76.2%) were commenced on Levothyroxine therapy.

Conclusion: Within Greater Glasgow & Clyde, the hypothyroid screening programme is effective in monitoring and detecting thyroid disease. The majority of children with Down Syndrome

receive hypothyroid screening annually. Of those screened, 9.3% of children had abnormal screening results, with 76.2% of these children commenced on Levothyroxine therapy.

P1-99

Early adiposity rebound in children with congenital hypothyroidism diagnosed by newborn screening

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Background: It is reported that children with congenital hypothyroidism (CH) are at increased risk of developing childhood obesity. Moreover, it is known that the timing of adiposity rebound (AR) in childhood is strongly linked with future obesity. Aims of our study were to explore the timing of AR and to identify factors affecting AR in a cohort of children with CH diagnosed by newborn screening and treated with levothyroxine.

Design: one-center, retrospective study.

Methods: We included in this study the patients with permanent CH diagnosed from 1994 to 2012, treated with levothyroxine from the first month of life and followed at least until 8 years of age. We determined subgroups of normal body mass index (BMI) and obesity/overweight (BMI $\geq$ 85th percentile) by the latest BMI at 8 years of age and subgroups for different CH etiology (i.e. dysgenesis and dyshormonogenesis). BMI at each age and the age of AR were compared with World Health Organization (WHO) references. Correlation of age and BMI at AR with BMI at 8 years, initial severity of hypothyroidism and initial levothyroxine dosage were examined.

Results: Sixty-nine patients (44 females) with permanent CH were recruited in this study. The age at AR was 3.44 ± 1.36 and 3.36 ± 1.21 years in boys and girls, respectively, and occurred significantly earlier than in WHO references (5.0 years in boys and 5.6 years in girls, $p < 0.001$ for both sex). Age at AR showed significant negative correlation with BMI at 8 years ($r = -0.274$, $p < 0.05$). There were no significant relationships between timing of AR and initial thyroid function or initial levothyroxine dosage. BMI at AR and at 8 years of age correlated positively ($r = 0.460$, $p < 0.001$). The prevalence of obesity/overweight at 8 years of age was 29%. BMI at AR was 16.69 ± 1.34 kg/m² in obesity/overweight subgroup and 15.63 ± 1.28 kg/m² in normal BMI subgroup ($p < 0.01$). BMI at 8 years of age was 22.38 ± 1.84 kg/m² in obesity/overweight subgroup and 17.04 ± 1.68 kg/m² ($p < 0.001$). Age at AR, BMI at AR, and BMI at 8 years of age were not different between the 47 patients with dysgenesis and the 22 with dyshormonogenesis.

Conclusion: Children with permanent CH showed significantly earlier AR compared to normal WHO references, which could predispose to obesity. Earlier AR was not related to the initial severity of hypothyroidism nor to the etiology of CH.

P1-100

Serum fibroblast growth factor 21 (FGF-21) levels of children and adolescents with Hashimoto's thyroiditis, before and after L-thyroxin medication

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Background: Fibroblast growth factor 21 (FGF-21) is a complex molecule involved in lipid and glucose metabolism. FGF-21 shares biochemical pathways and sites of action with thyroid hormones. Current data correlate FGF-21 levels to thyroid function. The aim of the present study was to investigate possible associations among FGF-21 levels, resting metabolic rate (RMR), lipidemic profile and L-thyroxin replacement therapy treatment in children and adolescents with Hashimoto's thyroiditis and hypothyroidism.

Methods: Sixty children and adolescents (age range 5-18 year old), with newly diagnosed Hashimoto's thyroiditis (30 in hypothyroidism, 30 in euthyroidism) and 30 age and gender matched healthy participants (control group) were enrolled. Anthropometric data were recorded; biochemical parameters RMR and serum FGF-21 levels were assessed in all participants. Participants with Hashimoto's thyroiditis and hypothyroidism were thereafter administered L-thyroxin replacement therapy. Six months after initiation of L-thyroxin medication, serum FGF-21 levels were re-evaluated.

Results: At baseline, serum FGF-21 levels were measured lower in the hypothyroidism group compared to the control group, but this difference was not statistically significant ($p > 0.05$). Despite the increase in serum FGF-21 levels after 6 months of L-thyroxin treatment, this augmentation did not reach significance ($p > 0.05$). Free thyroxin levels correlated positively to FGF-21 levels in both the total study population ($r = 0.399$, $p < 0.01$) and in the group with hypothyroidism at baseline ($r = 0.385$, $p < 0.05$). Participants with hypothyroidism and euthyroidism presented elevated triglyceride levels ($p < 0.05$). L-thyroxin treatment had no impact on RMR, lipid concentrations or glycemic parameters. An increase in fat mass and free fat mass was reported in the hypothyroidism group after L-thyroxin administration, independently of serum FGF-21 levels.

Conclusions: In the present novel study of FGF21 levels in youngsters with hypothyroidism due to Hashimoto's thyroiditis, serum FGF21 levels are measured lower than in healthy individuals and increased after treatment with L-thyroxin, although without statistical significance. Further studies with a large number of young patients with severe hypothyroidism due to Hashimoto's thyroiditis are needed to confirm the association between FGF-21 levels and thyroid function.

Adrenal B

P1-101

The management of adrenal cell carcinoma in a single tertiary centre: 25 year experience

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Background: Adrenal cortical carcinoma (ACC) in children is rare and aggressive, with the mainstay of treatment being surgical resection, although there have been recent improvements in outcomes with chemotherapy. Further characterisation of the presenting features and biochemical markers are needed to support earlier diagnosis. Refractory hypertension related to high cortisol concentrations prior to surgery, and post-operative decrease in cortisol can be challenging to manage. Focus on endocrine management has not been previously described.

Case Series: 34 patients (age 2 weeks–10 years (y), median 2.35y, 17 female) presenting between 1996 and 2021 with an ACC. Patients were either low (n=15), borderline (n=2), or high (n=17) malignancy risk based on histology and tumour size. The most frequent presentations included virilisation (n=29), hypertension (n=20), cushingoid appearance (n=15), and rarely gynaecomastia. 38% patients had an identified genetic mutation, either *TP53* (n=10), with most being high risk (n=8), or a mutation associated with Beckwith Wiedemann syndrome (n=3), which were either borderline (n=1) or high (n=2) risk. Elevated cortisol concentrations were seen in most patients, with loss of circadian rhythm in one third. Androgen concentrations were also frequently elevated (Androstenedione 88%, DHEA-S 61%, Testosterone 93%). Urine steroid profile pre-surgery revealed elevated androgen and cortisol metabolites. Refractory hypertension necessitated the use of metyrapone (n=3) and ketoconazole (n=3). All patients underwent surgical resection, a laparoscopic approach evolving over time, and 32% received adjuvant chemotherapy. Elevated biochemical markers resolved post-surgery, and most patients received intravenous hydrocortisone infusions post-operatively. All were discharged on hydrocortisone replacement (10mg/m²/day; duration 0.1-8y, median 1y). Those treated with mitotane (n=8) required a higher dose (15-17mg/m²/day), with added fludrocortisone (n=3), and thyroxine (n=2). The mortality rate was 32% in this cohort, although comorbidities were contributing factors in at least two patients.

Conclusion: This series describes the most frequent presentations in this rare and aggressive disease, and highlights the essential role of genetic diagnosis in influencing disease progression and treatment. Our practice has evolved to include post-operative

intravenous hydrocortisone infusion in all patients to mitigate the effect of the rapid fall in cortisol. The duration of hydrocortisone requirement in this cohort was highly variable. Future research is required into the use of newer agents such as pasireotide or mifepristone to decrease cortisol concentrations in those with refractory hypertension, as they may have fewer side-effects and reduce morbidity.

P1-102

Correlation of 11-oxygenated C19 androgens with the clinical and biochemical characteristics in premature adrenarche

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Background: Premature adrenarche (PA) is defined as the appearance of pubic and/or axillary hair in girls younger than 8 years old and caused by the rise in adrenal androgen production including dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), and androstenedione (A4). DHEAS ≥ 40 µg/dL is accepted as the biochemical marker of adrenarche. However, adrenals also produce 11-oxygenated C19 androgens such as 11β-hydroxyandrostenedione (11OHA4) and 11β-hydroxytestosterone (11OHT). The aim of our study was to investigate the relation of 11-oxygenated C19 androgens with the clinical and biochemical characteristics of PA.

Subjects and Methods: A cross-sectional study was conducted to quantitate plasma DHEA, DHEAS, A4, androsterone, 17OH-pregnenolone, 11OHA4 and 11OHT using tandem mass spectrometry (LC-MS/MS) in 53 girls with idiopathic PA aged between 3.6-8.5 years. Age-matched 35 girls without PA were defined as the control group. Anthropometric data were collected. Advanced bone age was defined as chronological age/bone age (CA/BA) ratio < 1.1. DHEAS > 1300 µg/L was defined as exaggerated PA.

Results: Forty-nine patients had Tanner 2, four had Tanner 3 pubic hair, and all had Tanner 1 breast development. The height and BMI-SDS were higher in the patients compared to controls (p<0.001). Mean CA and BA of the patients were 6.8±1.1 and 7.6±1.4 years, respectively. Median concentrations of DHEA, DHEAS, A4, androsterone, 17OH-pregnenolone, 11OHA4 and 11OHT were 1.099, 559.3, 0.275, 0.677, 0.4685, 6.64 and 0.0465 µg/L, respectively. While DHEA, DHEAS, A4, androsterone and 17OH-pregnenolone concentrations were higher (p<0.0001), no difference in 11OHA4 and 11OHT concentrations were noted in patients compared to controls. In patient group, a positive correlation between 11OHA4 and DHEA, DHEAS, A4 and 17OH-pregnenolone (p<0.0001, 0.03, 0.004 and <0.0001, respectively) were observed, while no correlation existed between 11OHT and others. Patients with advanced BA had higher 11OHA4 (p=0.01) and DHEA (p=0.04) than the ones without advanced BA. CA/BA ratio was negatively correlated with 11OHA4, DHEA and 17OH-pregnenolone (p=0.003, 0.008, 0.001). There was no difference in 11OHA4 levels between patients with exaggerated PA and the others (p=0.410). In the patient group, 11OHA4

concentrations were similar in overweight/obese patients and patients with normal BMI. Plasma DHEAS, DHEA and A4 showed higher sensitivity to segregate PA patients than 11OHA4 (area under curve: 0.87, 0.80, 0.79 and 0.62 for DHEAS, DHEA, A4 and 11OHA4, respectively).

Conclusion: Although 11OHA4 correlated with adrenal androgens and associated with advanced bone age, our findings do not ascribe a significant role of 11-oxygenated androgens in the pathophysiology of premature adrenarche in girls.

P1-103

Leukocyte telomere length in children with Congenital Adrenal Hyperplasia

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Introduction: Exposure to chronic stress and hypercortisolism is associated with decreased leukocyte telomere length (LTL), a marker for accelerated biological aging and cardiovascular disease. Children with congenital adrenal hyperplasia (CAH) are treated with glucocorticoids. The aim of our study was to investigate LTL in children with CAH and its relation with CAH subtype, daily glucocorticoid dose and treatment quality.

Methods: This prospective observational cohort study included children and adolescents, aged 1-18 years, with genetically confirmed CAH due to 21-hydroxylase deficiency. LTL was determined at two consecutive outpatient clinic visits (mean 4.1 ± 0.7 months apart) by monochrome multiplex quantitative real-time polymerase chain reaction. At each visit, all subjects underwent detailed clinical (height, weight) and endocrinologic evaluation, including determination of 17-hydroxyprogesterone and androstenedione concentrations, and were classified as undertreated, optimally treated or overtreated accordingly. BMI z-score (BMI-z) was calculated according to *International Obesity Task Force* definitions. The influence of clinical factors on LTL was investigated using linear mixed models.

Results: We studied 78 children and adolescents prospectively. Of those, 33 (42%) were girls, 63 (81%) had classic CAH, 70 (90%) received hydrocortisone and 8 (10%) prednisolone. Median age at first visit was 12.0 years (IQR 6.2–15.1), and median BMI-z 0.51 (IQR -0.16–1.43). Optimal treatment was achieved in 48 (62%)/42 (55%) patients at first and second visit, respectively, versus

undertreatment in 22 (29%)/32 (42%), and overtreatment in 7 (9%)/2 (3%). Median LTL at first visit was 1.18 (IQR 1.04–1.40); mean Δ LTL was 0.02 ± 0.09. After adjustment for age, sex, and BMI-z, children with classic CAH had shorter LTL than children with non-classic CAH (coefficient -0.29, 95% CI -0.52; -0.06, p=0.012). In addition, treatment success influenced LTL (global p=0.007): overtreated children had shorter LTL (coefficient -0.07, 95% CI -0.12; -0.03), while undertreated children had similar LTL (coefficient 0.01, 95% CI -0.05; 0.03) compared with children on optimal treatment. Children using prednisolone had shorter LTL than children using hydrocortisone (coefficient -0.34, 95% CI -0.51; -0.16, p<0.001). LTL was not associated with hydrocortisone-equivalent dose.

Conclusions: In children and adolescents with CAH due to 21-hydroxylase deficiency, LTL is shorter in the classic than in the non-classic form of the disease, as well as in overtreated patients or patients treated with long-acting glucocorticoids. These findings may be attributed to chronic exposure to supraphysiologic glucocorticoid concentrations, and indicate that LTL may be used as a biomarker for monitoring optimal treatment with glucocorticoids.

P1-104

"Cortison-loop" is an educational tool, which helps ensure the quality of care for children with adrenal insufficiency

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Background: Adrenal insufficiency is a severe condition, which occurs for numerous different reasons. Diseases often require a period or even a lifelong treatment of cortisone and/or mineralocorticoid. Ensuring that families of patients who suffer from adrenal insufficiency have a high level of understanding and knowledge of the disease from the outset is key to them comprehending the severity of the disease, which in turn increases the chances of good compliance to treatments throughout the life of the patient. Incomplete knowledge and education of the disease could lead to the patient's life being at risk in certain situations such as Infections, trauma, etc.

Patient care in Sweden de-centralised and divided between University and county hospitals. The county hospitals have a limited amount of patient, as well as a limited amount of experienced staff. The quality of patient care and the level of patient's education could vary between hospitals. Longitudinal data on the impact of standardized education in adrenal insufficiency is lacking.

Aim: An attempt to standardize the national quality of education for children and their families in understanding the disease of adrenal insufficiency and managing cortisone treatments in different conditions.

Result: The work was initiated by the national nursery group in paediatric endocrinology. They worked out a "worksheet" to be

used for the education of patients in all paediatric clinics throughout the country. The worksheet contains questions on two sides of a loop. The upper part has evidence-based knowledge given to patients and families during their first visit to the children's clinic. The other part contains the questions that were asked face to face with patients during their follow up. The backside of the "worksheet" contains facts to support the caregiver in the conversation with the patient/family. The "worksheet" should be used continuously during any follow-up meetings at the clinic.

Conclusion: Standardizing the education using the "worksheet" in all clinics across the entire country, will lead to an increase in the quality of patient care and mean that every patient will receive the same education regardless of the level of experience and training of the staff at the clinic they are visiting.

P1-105

The genetic etiology of ACTH-dependent aldosterone hypersecretion in hypertensive patients without Primary Aldosteronism

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Introduction: Compelling evidence suggests that Primary Aldosteronism (PA) is much more prevalent than previously thought, accounting for more than 20% of patients with resistant hypertension. Although, major advances have been made in the field of genetics underpinning sporadic and familial forms of PA, the etiology of mild forms of PA is poorly understood. In previous studies, we identified a distinct cohort of patients without PA who exhibited ACTH-dependent aldosterone hypersecretion. Following sequencing of *KCNJ5* gene, we detected two novel variants in two patients of this cohort, which were shown via electrophysiological studies to impact *KCNJ5* function.

Objective: To examine if genetic variation in genes implicated in aldosterone synthesis/secretion play a role in ACTH-mediated aldosterone hypersecretion.

Methods: Whole Exome Sequencing (WES) on NovaSeq 6000 platform (Illumina), was performed in 21 hypertensive patients without PA, who exhibited ACTH-dependent aldosterone

hypersecretion. Variant calling was performed following the GATK guidelines and we extracted the genetic variation of 25 genes associated with PA. Considering the pivotal role of ion channel genes in the pathogenesis of PA, we also filtered for variants residing in ion channel genes. Qualifying variants had a gnomAD frequency < 1% and were deemed as pathogenic by in-silico tools.

Results: Nine patients of our cohort (9/21, 42.9%) carried potentially damaging variants in genes implicated in the pathway of aldosterone biosynthesis. In particular, in seven patients we detected seven rare and potentially damaging variants in six genes previously associated with PA (*KCNK9*, *KCNK5*, *ATP13A3*, *SLC26A2*, *CACNA1H*, *CACNA1D*). The variant detected in *KCNK9* (p.V221M) gene was novel. We also report two variants in two novel candidate susceptibility genes for mild forms of PA, *KCNK16* (p.P255H) and *CACNA2D3* (p.V557I)

Conclusion: Genetic variations in aldosterone synthesis/secretion-regulating genes may contribute to aldosterone hypersecretion under conditions of stress by priming the adrenal cortex to respond to ACTH. We also identified two novel candidate susceptibility genes for a mild form of PA, *KCNK16* and *CACNA2D3*, and one novel variant in *KCNK9*.

P1-106

Plasma Proteomics in Healthy Subjects with Differences in Tissue Glucocorticoid Sensitivity Identifies a Novel Proteomic Signature

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Background: Tissue sensitivity to glucocorticoids is characterized by significant inter-individual variation in terms of therapeutic response and susceptibility to several stress-related disorders. Proteomics approaches, combined with appropriate bioinformatics analysis, offer a comprehensive description of molecular phenotypes with clear links to human disease pathophysiology.

Objective and Hypotheses: To investigate the usefulness of plasma proteomics in identifying a proteomic signature that could distinguish glucocorticoid resistant from glucocorticoid sensitive subjects and provide clues of the underlying physiological differences.

Methods and Results: One hundred one (n=101) healthy volunteers were given a very low dose (0.25mg) of dexamethasone at midnight, and were polarized into the 10% most sensitive (S) and 10% most resistant (R) according to the 08:00h serum cortisol concentrations the following morning. One month later, DNA was isolated from peripheral blood mononuclear cells, and plasma samples were collected. Sequencing analysis did not reveal any

mutations or polymorphisms in the human glucocorticoid receptor (*NR3C1*) gene. Subsequently, we determined the proteomic profile of plasma samples using Liquid Chromatography - Mass Spectrometry (LC-MS/MS). One hundred ten up-regulated and sixty-six down-regulated proteins were identified in the S compared to the R group. Interestingly, most of the up-regulated proteins in the S group were involved in erythrocyte gas exchange and platelet activation, suggesting a state of the organism that is more capable to respond to stressful stimuli. To predict response to cortisol prior to administration, a random forest classifier was developed by using the proteomics data, in order to distinguish sensitive from resistant individuals. Among the proteins identified, apolipoprotein A4 (APOA4) and gelsolin (GSN) were the most important variables in the classification, necessitating further investigation to determine their prognostic capacity.

Conclusions: A proteomic profile indicating erythrocyte gas exchange and platelet activation was observed in the S compared to the R group. These findings indicate that a proteomics signature may differentiate the most glucocorticoid resistant from the most glucocorticoid sensitive subjects, and may be useful in clinical practice. In addition, it may provide clues of the underlying molecular mechanisms of the chronic stress-related diseases, including myocardial infarction and Alzheimer's disease.

P1-107

Corticoic Acids: Renaissance of a Forgotten Class of Steroids

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Initially discovered in the 1970s, the C₂₁ steroidal acids α -cortolic acid, β -cortolic acid, α -cortolonic acid and β -cortolonic acid present the terminal oxidative products of cortisol metabolism. Undergoing renal elimination, these corticoic acids have been assumed to represent up to 25% of total urinary cortisol metabolites. However, their analysis has been difficult, only few data has been published in adults, and this class of steroids has become practically forgotten. Since data in children are lacking and nothing is known about their metabolism during human development, we aimed at establishing a more practical analytical method and determined their urinary concentrations in a high number of healthy subjects.

5 ml aliquots of 24-hour urine samples were used for sample work up consisting of solid phase extraction (C18 cartridges), strong anion exchange and derivatization to

2-propylester-trimethylsilylether derivatives. Subsequently, the corticoic acids were quantified by targeted GC-MS using a nonpolar GC column and selected ion monitoring.

Baseline separation of all corticoic acids was achieved. Calibration graphs were linear in the chosen calibration range ($R^2 > 0.98$). Regarding precision and accuracy, coefficients of variation were smaller than 10%, the difference between measured and expected concentrations was less than 15%. The detection limit was 100 pg (injected) with a signal-to-noise ratio of 3.

The method was used to analyze 24-hour urine collections from 240 healthy children (120 boys, 120 girls, aged 3-18 years, all participants in the DONALD study). The profile of corticoic acids was dominated by α -cortolonic acid with excretion rates up to 70 $\mu\text{g/d}$. When excretion rates of the four corticoic acids were summed, all subjects excreted less than 130 $\mu\text{g/d}$ (range: 11.0 $\mu\text{g/d}$ - 127.3 $\mu\text{g/d}$). In relation to neutral urinary cortisol metabolites, total corticoic acids only represented about 1% (range: 0.69% -1.51%) of overall daily glucocorticoid secretion. While higher age led to increased excretion rates, the children's sex did not significantly affect the amount of daily excreted corticoic acids.

Conclusion: A new and less complicated method for quantification of urinary corticoic acids using GC-MS was developed, evaluated and successfully applied to 240 specimens from healthy children, adolescents and young adults and first reference values were established. Baseline separation of all four corticoic acids was achieved on a nonpolar GC column. Excretion of corticoic acids increased with age. However, corticoic acids' proportion of total urinary cortisol metabolites only added up to about 1%, a percentage much lower as hitherto estimated.

P1-108

Circadian rhythm of cortisol in saliva in obese children with clinical signs of hypercortisolism

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Due to the increase in prevalence of childhood obesity, more obese children are referred to the endocrinologist for the hypothalamus-hypophysis-adrenal axis assessment. The circadian rhythm (CR) of cortisol in saliva (SAF) may constitute a non-invasive, first line test to exclude hypercortisolism on obese children.

Aim: To evaluate possible disturbances of CR of SAF in obese children with clinical signs of hypercortisolism.

Design: Cross-sectional, age-matched, observational, prospective study. Subjects: Inclusion criteria for obese (OB) were BMI-centile $\geq 95^{\text{th}}$ and clinical signs of hypercortisolism. Exclusion criteria: non-Cushing syndromic obesity. NW inclusion criteria: $10^{\text{th}} \leq \text{BMI-centile} \leq 85^{\text{th}}$, absence of acute or known chronic

disorders. Elimination criteria for both groups: incomplete or insufficient sampling, erroneous time collection, corticosteroid therapy. Cushing Syndrome (CS) diagnosis was based on clinical signs, biochemical tests and MRI images.

Methods: Saliva was collected at 8 a.m. (SAF8) and 23 p.m. (SAF23). SAF was measured by current ECLIA (Roche). Relative change at night (RCh%) was calculated as: $[(SAF8 - SAF23) / SAF8] \times 100$. Subrogates of insulin resistance, HOMA-IR and TG/HDLcholesterol, were calculated in OB.

Results: 142 children: 69 obese (median age: 11.6years; 62 non-CS and 7 confirmed CS); weight gain and growth retardation (12.9%), moon face (28.5%), red striae (14.3%), headache (6.9%), hypertension (19%), hypertrichosis/hirsutism (39.7%), HOMA-IR>2.0 (60.3%), acanthosis nigricans (65.1%), gonadal dysfunction in girls (17.4%), acne (19%), dyslipidemia (80%), severe obesity (BMI-SDS $\geq$ 3, 50.8%). 73 NW children (10.5years). SAF23 significantly decreased in NW and non-CS groups ($p < 0.0001$). Higher BMI-SDS was associated to lower SAF8 ($r = -0.79$, $p < 0.001$) and RCh% ($r = -0.38$; $p < 0.001$), therefore, data were adjusted by BMI-SDS (table, $***p < 0.0001$ or $**p < 0.001$ versus NW). A higher proportion of TG/HDL $\geq$ 3 index was observed in non-CS children with RCh%<50%.

	Median(3 rd -97 th)		
	NW	Obese non-CS	CS
SAF8(nmol/L)	12(5-25)	7(3-15)***	36(14-44)
SAF23(nmol/L)	2(2-4)	2(2-5)	21(9-82)
RCh%	78(54-90)	66(31-86)**	41(26-49)

Conclusions: In NW children, SAF by ECLIA decreased at least 50% at night being the RCh% a useful tool to interpret cortisol CR. In a small group of children with confirmed CS, SAF23 did not overlap to those obtained in NW or non-CS. Obese non-CS children had lower cortisol secretion in the morning and a lesser amplitude in the difference between morning and night SAF concentrations. Of concern, this result was associated to a more deleterious lipid profile in the obese. Non-CS obese may have a RCh%<50% (suggesting a blunted diurnal cortisol profile), therefore, this index should be interpreted with caution.

In the electrochemiluminescence immunoassay (ECLIA) method, the presence of various endogenous compounds and the use of certain pharmaceutical agents may cause interference in results, on the other hand liquid chromatography-mass spectrometry (LC-MS/MS) method allows measurement of 17 adrenal steroids at the same time without these interferences.

We aimed to evaluate the effectiveness of LC-MS/MS method in diagnosis of patients with hyperandrogenism and to compare the results with ECLIA/ELISA methods.

Method: Ninetysix girls who admitted with premature adrenarche (PA), hirsutismus aged between 6-18 years were included. Serum total testosterone and DHEA-S levels were measured by ECLIA; serum 17-OH progesterone (17-OHPG) levels were measured by ELISA method, plasma steroid hormones including total testosterone, DHEA, DHEA-S, DHT, androstenedione, 17-OHPG were measured by LC-MS/MS. Normal values were evaluated according to Tanner stages.

Results: Thirty seven of the patients were PA (38.5%), 24 PCOS (25%), 5 non-classical CAH (5.2%) and 30 (31.2%) idiopathic hirsutismus. While menstrual cycles were regular in 10 (41.6%) of PCOS cases, secondary amenorrhea or oligomenorrhea was described in 14 (58.4%). Eighteen (18.8%) of the cases were obese and 32 (33.3%) were overweight.

According to LC-MS/MS method 36 (37.1%) of DHEA, 18(18.6%) of androstenedione, 20 (20.8%) of DHT, 15 (15.8%) of DHEA-S, and 6 (6.4%) of total testosterone measurements were elevated. At least one of the androgens were increased in 58 (60%) of the patients. The highest androgen was DHEA; in PA 24.3% , in PCOS 64.0% and in idiopathic hirsutismus 27.6% of patients had increased DHEA levels. By ECLIA method median DHEA-S level was 124.7mg/dL (8.3-625), while by LC-MS/MS it was 61.2mg/dL (0.1-618.4) ($p < 0.001$). In all cases, median 17-OHPG level was 147.5ng/dL (0.3-1338) by ELISA, 44.85 ng/dL (0.3-2248) by LC-MS/MS method. In 21 (21.8%) of the cases, 17-OHPG level was above 200ng/dL by ELISA, while normal values were found in 16 (76.1%) of them by LC-MS/MS. In 5 (5.2%) of these cases, genetically proven non-classical CAH was diagnosed.

Conclusion: In evaluating children and adolescent girls with hyperandrogenism; LC-MS/MS method is more valuable than other methods. By LC-MS/MS, false positive 17-OHPG and DHEA-S measurements will be minimized and unnecessary investigations can be prevented. DHEA was the highest androgen/ androgen precursor in patients with PA, PCOS and idiopathic hirsutismus.

P1-109

Plasma steroid panel with liquid chromatography-mass spectrometry (LC/MS-MS) method: utilization in differential diagnosis of hyperandrogenism

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Introduction: The etiology of hyperandrogenism is diverse and diagnosis is based on history, clinical findings, reliable measurement of steroid hormones and genetic analyzes.

P1-110

Current Management Of Acute Adrenal Insufficiency Related Adverse Events In Children- Results Of An International Survey Of Specialist Centres

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Background: There is a wide variation in the reported rate of acute adrenal insufficiency (AI) related adverse events (sick day episodes and adrenal crises) between centres.

Objective: Evaluate the level of consensus on the criteria that should be considered 'essential' for defining and managing adverse events associated with acute AI in children.

Methods: Three groups of clinicians including active users of the International Congenital Adrenal Hyperplasia & International Disorders of Sex Development (I-CAH/I-DSD) Registries (n=66), non-active users of I-CAH/I-DSD (n=35) and the EuRRECa e-Reporting Registry (n=10) were approached to complete an online survey.

Results: 56 clinicians from 27 countries responded to the survey; the response rates for the three Registry groups were 42 (65%), 11 (31%) and 3 (30%), respectively. Written corticosteroid management plans and one to one patient/parent education were provided by 54 (96%) and 51 (91%) clinicians, respectively; 33 (59%) provided steroid-aware emergency cards. 56 (100%) clinicians advised an increase in glucocorticoid dosing (sick day dosing) in the event of fever; 55 (98%) and 53 (95%) advised sick day dosing in the event of severe infection (eg. pneumonia) and major surgery, respectively. Less common indications for sick day dosing included vaccination and mild afebrile intercurrent illness, recommended by 17 (30%) and 9 (16%) clinicians, respectively. The most frequently reported sick day dosing regimen was tripling the total daily dose of hydrocortisone and administering 3 times daily, reported by 24 (43%) clinicians. 40 (71%) specified the duration of sick day dosing as ≥ 48 hours for severe infections. Vomiting and diarrhoea were the most common indications for IM hydrocortisone, reported by 34 (61%) and 25 (45%) clinicians, respectively. Over 50% of respondents indicated that essential clinical criteria for an adrenal crisis should include fatigue and nausea or vomiting and over 60% indicated that the criteria should include hypotension, hyponatraemia, hyperkalaemia and clinical improvement following parenteral glucocorticoids. In the event of adrenal crisis, 47 (84%) reported that the majority of patients were admitted to hospital. A bolus parenteral injection of hydrocortisone and glucose infusions were the most frequently administered medications, reported by 50 (89%) and 32 (57%) of clinicians, respectively.

Conclusions: Although there is considerable variation in the definition and management of AI related adverse events in children amongst specialist centres, there is also good evidence of consensus that can be used to develop standardised criteria for developing benchmarks and facilitating care improvement.

Fat, Metabolism and Obesity B

P1-111

Insulin resistance following childhood craniopharyngioma may influence neural response to food cues in food reward-related brain regions: a preliminary investigation

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Background: Craniopharyngioma is a rare, suprasellar tumour, which, together with associated surgery or radiotherapy, results in damage to the hypothalamus and severe obesity in approximately 50% of cases. The multi-factorial mechanisms underlying the development of obesity in craniopharyngioma are not well understood. Hypothalamic damage in craniopharyngioma has been associated with dysfunctional parasympathetic nervous system activity leading to altered glucose metabolism and hyperinsulinemia (van Iersel et al., *Endocrine Reviews*, 2019). Furthermore, additional evidence in lean and obese volunteers suggests a link between insulin resistance, neural responses to food and obesity (Cheke et al., *Neuropsychologia*, 2017). We therefore hypothesised that insulin resistance in craniopharyngioma may alter neural response to food cues and thereby contribute to obesity.

Method: A feasibility study of 11 young craniopharyngioma patients (median [range] age = 14 [10-23]y; BMISDS = 1.3 [-1.5-3.9]; 5F/6M) with full clinical characterisation was conducted, including measurement of body composition using bioelectrical impedance and an oral glucose tolerance test (n = 10); during which preliminary functional neuroimaging data on the neural response to food cues, in *a priori* regions of interest, during fasting and post-glucose ingestion were collected (n = 9). HOMA-IR was calculated to assess insulin resistance. As this feasibility study was not powered for null hypothesis significance testing, we focussed on measure of effect size (Kendall's Tau correlation coefficient).

Results: Normal glucose tolerance (based on WHO criteria) was found (median fasting glucose = 4.45mmol/L) in all but one patient, who had Type 2 diabetes (removed from HOMA-IR correlational analyses below as an outlier). Four patients were classed as insulin resistant, with a HOMA-IR of > 2.5 (median HOMA-IR = 3.11). No evidence for a correlation was found between HOMA-IR and body fat % ($\tau=-.25$), fat mass (kg) ($\tau=-.22$), or BMISDS ($\tau=.00$). Preliminary evidence was found for a positive correlation between HOMA-IR and (i) fasting response to food cues in the insula ($\tau=.43$) and the putamen ($\tau=.52$), and (ii) post-glucose response to food cues in the amygdala ($\tau=.62$) and nucleus accumbens ($\tau=.43$). By contrast, BMISDS was negatively correlated with the neural response in the hypothalamus during fasting ($\tau=.56$) and post-glucose ($\tau=-.56$).

Conclusion: These preliminary findings in this small group of craniopharyngioma patients suggest that insulin resistance may influence the neural response to food cues before and after glucose consumption in reward regions of the brain, different to those regions influenced by body mass.

Trial registered with ISRCTN (isrctn.com/ISRCTN86005167).

P1-112

Evaluation of the BigO behavioral indicators in overweight and obese children and adolescents

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Background: Obesity represents one of the most challenging public health problems of our century. According to the World Health Organization, there is a need to create reliable monitoring and behavioral systems, and to investigate their effectiveness in preventing childhood obesity.

Objective: To evaluate the BigO behavioral indicators in a pediatric population in Greece.

Methodology: The study was carried out as part of the four-year European BigO project (<http://bigoprogram.eu>, Horizon2020, No. 727688). Overweight and obese children and adolescents aged 9-18 years participated in the study following approval by the local Committee on the Ethics of Human Research. Written informed consent was obtained by parents/guardians in all cases. The data collection system included the BigO technology platform, which interfaces with a Smartphone and Smartwatch, and records data objectively (using inertial sensors and GPS) for each patient. Participants used the BigO system for at least 4 weeks. Data were then transmitted to BigO servers to extract behavioral indicators, including: (a) physical activity/exercise and (b) dietary habits. Behavioral indicators included: average steps per hour daily, average activity counts per hour daily, average food visits daily, average public park visits daily, average fast food (take away) visits daily, average supermarket (grocery stores) visits daily, average athletic sports visits daily, average food outlets visits daily, average cafe visits daily, average bars visits daily and average food cafe bar visits daily. For the correlation analysis, data with zero values have been omitted.

Results: The study population consisted of 867 children and adolescents (448 males, 419 females; mean age $\pm$ SD: 12.645 $\pm$ 2.445). Subjects were classified as having obesity (n=644, 74.3%), overweight (n=203, 23.4%) or normal BMI (n=20, 2.3%) according to WHO cut-off points. In subjects with obesity, BMI correlated positively with average steps per hour daily ($\rho=0.102$, $p=0.010$), average activity counts per hour daily ($\rho=0.117$, $p=0.003$), average food visits daily ($\rho=0.221$, $p=0.001$), as well as average daily visits to fast food (take away) places ($\rho=0.262$, $p=0.001$), food outlets ($\rho=0.274$, $p<0.001$), café shops ($\rho=0.288$, $p<0.001$), and food cafe bars ($\rho=0.154$, $p=0.007$). In overweight subjects, BMI correlated positively with average athletic sports visits daily ($\rho=0.287$, $p=0.041$).

Conclusions: These novel methodologies will enable scientists and public health authorities to collect and analyze objective daily behavioral data in children and adolescents with overweight and obesity, and implement appropriate public health policies and/or strategies at a local level.

P1-113

Are you considering Idiopathic Intracranial Hypertension when evaluating a patient with obesity?

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Introduction: Obesity is a recognised risk factor for raised intracranial pressure in the adult population but is still under-recognised in children and young people. The pathophysiology of raised intracranial pressure in relation to obesity remains unclear. The aim of our study is to investigate the association between idiopathic intracranial hypertension (IIH) and obesity in children and young people.

Method: Patients diagnosed with IIH by the neurology team at a tertiary children's hospital were identified over a two-year period. Data including the patients' growth parameters, presentation, investigation and treatment was collected and analysed.

Results: Eighteen patients (M:F 7:11) were identified with a mean age at diagnosis of 11 years (± 3.3 SD; range: 6 to 15 years). The mean BMI was 30.3kg/m² (range: 13.9 to 58.2kg/m²) and the mean BMI SDS was +2.5 (range: -1.24 to +4.46). 72.2% of the patients had a BMI SDS greater than 2.

12 (66.6%) patients presented with both headaches and eye signs (visual disturbances or ophthalmology findings). 3 patients were asymptomatic, with papilloedema identified on routine optician review. All patients required a lumbar puncture. Only 7 patients were able to have a successful lumbar puncture on the ward with no or little sedation. The others had the procedure performed in theatre or the radiology department. 9 patients required general anaesthetic. 15 patients were treated medically (acetazolamide and/or topiramate), 2 had long-term neurosurgical interventions (ventriculoperitoneal and ventriculoatrial shunts) and 1 patient did not require either.

Conclusion: The results of this study show that females are more likely to develop IIH compared to males and that there is a clear link between IIH and obesity. Hence, awareness about the potential diagnosis of IIH in patients with obesity needs to be raised to ensure early identification and management to avoid permanent visual loss.

P1-114

EuRECa Registry Genetic Obesity Survey Results

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Introduction: The diagnosis and treatment of patients with rare diseases is often difficult as most clinicians do not encounter them. Therefore, centralization and collaboration between centers of expertise is necessary. European Reference Networks (ERN's) such as RareEndoERN provide a platform for this, with one of its main thematic groups having a specific focus on rare growth and obesity disorders. Genetic obesity encompasses a heterogeneous group of conditions, classically divided into non-syndromic and syndromic obesity. These disorders are rare and can be challenging to diagnose. More knowledge on clinical presentation and core features is needed. Using the EuRECa's e-reporting platform (e-REC) which was established in July 2018, we aimed to assess routine clinical data in order to understand the diagnostic processes and clinical outcome of cases with Genetic Obesity.

Methods: A survey was sent out to centers that registered patients with genetic obesity in the EuRECa Registry. The questionnaire used a secure on-line tool (Webropol). All information

provided was kept in compliance with the UK Data Protection Act (2018) and General Data Protection Regulation (GDPR 2016/679). No personally identifiable data were collected. Data on reporting center, diagnosis, patient characteristics, comorbidities and treatment were collected.

Results: Seven European centers registered 37 cases (35 children/2 Adults) of which 32 surveys were completed. Of these 37 cases, there were 3 Prader-Willi syndrome (PWS) and 1 pseudo-hypoparathyroidism (PHP) cases registered as part of the rare genetic obesity survey. 57 PWS and 44 PHP cases were also reported separately in the growth & obesity and calcium/phosphate thematic groups respectively. For our analysis, PWS and PHP cases were excluded. Diagnosis was confirmed in 78% (25/32) of which 48% was syndromic. Median age of onset was 2 years (14/29); median age at last review 12yrs; median BMI SDS +3.21. Reported clinical features included hyperphagia 67%, developmental delay 37%, endocrine dysfunction 33%; short stature 20% and tall stature 10%. Reported comorbidities were: acanthosis nigricans 26%; dyslipidemia 13%; hypertension 13%; diabetes mellitus 10%; sleep apnoea 10%; non-alcoholic liver disease 3%. Reported treatments included: diet 77%; lifestyle intervention 55%; parental coaching 26%; pharmacotherapy 26%; metformin 3%; orlistat 3%; none of the patients had bariatric surgery.

Conclusion: Using surveys through registries such as EuRECa can enable clinicians to collaborate and collect data on genotype/phenotype and clinical outcomes in rare conditions, aiding in the development of management strategies, including clinical trials. This form of collaboration will ultimately improve patient care.

P1-115

Circulating C1q Complement/TNF-Related Protein (CTRP)-13 Levels in Obese Children and Its Relationship with Metabolic Disorders

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Background: C1q/tumor necrosis factor-related proteins (CTRPs) are the recently recognized members of the adipokine family, secreted from adipose tissue. Some types of CTRPs, including CTRP-13, play an important role in energy metabolism in humans. Also, CTRP-13 was found as an anorexigenic factor in experimental studies.

Objective: We aimed to investigate serum CTRP-13 levels in obese and healthy children, as well as the relationship between CTRP-13 and other adipokines, metabolic parameters, or binge eating disorder (BED).

Subjects and Methods: Clinical (metabolic syndrome, BED) and biochemical (glucose, insulin, lipids, leptin, adiponectin, CTRP-13 levels) parameters were assessed in pubertal subjects. There was no organic etiological cause in obese patients.

Results: The obese group consisted of 60 children [24 males (40%); median age: 14.7 (13.0 - 16.4) years] and the control group included 45 healthy children [15 males (33.3%); median age: 15.2 (14.1 - 16.5) years]. Body mass index SD scores were 2.7 (2.3 - 3.1) and -0.5 [(-1.2) - 0.6] in obese and control groups, respectively ($p < 0.001$). Serum adiponectin and CTRP-13 median levels were significantly lower in obese children than those in healthy children (7.1 vs 20.1 $\mu\text{g/mL}$, $p < 0.001$; 64.7 vs 103.8 ng/mL, $p < 0.001$, respectively). Serum leptin levels were significantly higher in the obese group than the control group (median; 46.4 vs 7.2 ng/mL, $p < 0.001$). CTRP-13 levels correlated negatively with BMI SD scores (Spearman rho = -0.237, $p = 0.015$) and positively with high-density lipoprotein-cholesterol levels (HDL-C) (Spearman rho = 0.218, $p = 0.026$). There was no significant difference in serum CTRP-13 concentrations in terms of the presence of metabolic syndrome or BED.

Conclusions: We demonstrated significantly lower CTRP-13 levels in obese children than the healthy ones, for the first time in literature. Childhood obesity seems to be causing dysregulation in adipokine production and function, including the down-regulation of CTRP-13. The positive correlation between CTRP-13 and HDL-C levels suggested a possible effect of this adipokine on lipid metabolism and it can be used as a marker for dyslipidemia in childhood obesity.

P1-116

An Evidence-based Framework to Evaluate Melanocortin-4 Receptor (MC4R) Pathway Relevance for Obesity-associated Genes

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Background: The MC4R pathway is the principal regulator of mammalian energy balance through its modulation of energy intake and energy expenditure. Variants in genes associated with the MC4R pathway can result in rare genetic diseases of obesity. Clinical data in patients with genetic defects in the MC4R pathway indicate that setmelanotide, an MC4R agonist, can effectively reduce weight and hunger in scientifically rationalized obese subpopulations in which MC4R-pathway deficit is a contributing factor to obesity. Here we introduce an evidence-based framework designed to evaluate various genes' relevance to the MC4R pathway to identify those genetic patient populations most likely to benefit from long-term setmelanotide therapy.

Methods and Results: This framework utilizes a set of clinical (human genetics) and non-clinical experimental evidence to evaluate MC4R pathway relevance and is based on the core principles of the NIH ClinGen *Gene-disease Clinical Validation* approach which is the industry standard for assessing gene-disease relationships. Human genetic evidence helps define the contribution of the gene to human obesity, while experimental evidence assesses involvement of the gene in the function of MC4R pathway. The cumulative burden of this evidence is used to classify MC4R pathway genes into four strength-based tiers: very strong, strong, moderate, weak. The nature, quantity, and quality of evidence required for each tier builds upon that of the previous tier, with higher

ranked genes being most likely to define patient populations potentially responsive to long-term setmelanotide treatment. Based on a comprehensive literature review, 118 MC4R pathway genes were identified and rank ordered: 8 “very strong”, 29 “strong”, 22 “moderate”, 59 “weak”. Importantly, clinically meaningful weight and hunger score reductions following treatment with setmelanotide have been previously demonstrated in patients with obesity due to variants in 6 genes, all initially classified as “very strong” or “strong”, lending credence to this framework for the selection of patient populations most likely to benefit from long-term setmelanotide therapy.

Conclusion: This framework provides robust means of selecting MC4R pathway relevant genes and supports clinical investigation of setmelanotide responsiveness in an additional 31 “very strong/strong” genes including *LEP*, *SIM1*, *MRAP2*, and *KSR2*. A clinical trial in patients with these 31 gene variants will commence before the end of 2021.

P1-117

Serum Fibroblast Growth Factor 23 and Klotho concentrations in children and adolescents with obesity

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Background: Obesity in childhood and adolescence represents one of the main health problems of the 21st century. Fibroblast Growth Factor 23 (FGF-23) and its co-receptor, Klotho, play an important role in mineral metabolism, however, little is known about their role in obesity.

Objective and Hypothesis: To determine the concentrations of FGF-23 and Klotho in children and adolescents with overweight and obesity.

Methods: Three hundred and twenty subjects [163 males (50.9%), 157 females (49.1%), 158 prepubertal (49.4%), 162 pubertal (50.6%)], aged [mean $\pm$ standard deviation (SD)] 10.5 $\pm$ 2.8 years, were studied prospectively for one year. Subjects were classified as obese (n=211, 66%), overweight (n=99, 30.9%) and of normal BMI (n=10, 3.1%) and were enrolled in a one-year lifestyle intervention program of diet and physical exercise. Body composition and biochemical and endocrinologic parameters were determined at the beginning and at the end of the study. The study was approved by the Committee on the Ethics of Human Research, and written informed consent was obtained by all parents.

Results: Following one year of implementation of the lifestyle intervention program, there was a significant decrease in BMI (p=0.001), total cholesterol (p=0.001), low-density-lipoprotein

(LDL) (p=0.001), HbA1C (p=0.021) and FGF-23 (p=0.004) concentrations, and percentage of body fat (p=0.001). In addition, there was a significant increase in high-density-lipoprotein (HDL) (p=0.001), parathormone (PTH) (p=0.001), 25-OH-Vitamin D (VitD) (p=0.003), adiponectin (p=0.001) and Klotho (p=0.001) concentrations, and percentage of muscle mass (PMM) (p=0.001). Klotho concentrations correlated negatively with the waist-to-hip ratio (p=0.001) and VitD (p=0.022), and positively with PTH (p=0.050). The change in FGF-23 concentrations correlated positively with the change of Apolipoprotein1 (Apo1) (r=0.200, p=0.001), while the change in Klotho concentrations correlated positively with the change in BMI (r=0.169, p=0.009), diastolic blood pressure (r=0.267, p=0.022), waist circumference (r=0.319, p=0.001), Apo1 (r=0.171, p=0.011), HOMA-IR (r=0.259, p=0.001), PMM (r=0.226, p=0.004) and adiponectin (r=0.215, p=0.002). Finally, the change in BMI correlated positively with the change in FGF-23 (r=0.364, p=0.023) and Klotho (r=0.462, p=0.001) concentrations in subjects that entered puberty, while the change in BMI correlated positively with Klotho change in males (r=0.438, p=0.001). Participants had normal kidney function [(mean value $\pm$ SD), Urea: 29.1 $\pm$ 6.3 mg/dL; Creatinine: 0.5 $\pm$ 0.1mg/dL].

Conclusion: These findings indicate an association between bone-derived FGF-23, its co-receptor Klotho, obesity and cardiovascular risk factors. More studies are needed in order to determine the role of FGF-23 and Klotho as biomarkers of childhood obesity, especially in adolescence.

P1-118

Rare heterozygous variants in genes of the leptin-melanocortin satiety pathway contribute to childhood obesity

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Background: The central melanocortin system is highly involved in the control of energy metabolism, receiving and integrating numerous metabolic signals, such as leptin, and biallelic mutations in several genes of the pathway have been reported in severe obesity. However, whether and how heterozygous rare sequence variants (hetRSVs) in genes of this satiety pathway contribute to the development of obesity is poorly explored.

Objective: Our aim was to define whether hetRSVs in 13 genes involved in the leptin-melanocortin pathway contribute to early obesity by comparing their prevalence in 1066 children and adolescents with obesity and a country-matched control population.

Patients and Methods: A transversal study of 1066 patients below 18 years with obesity (BMI $>+2$ SDS, **OB**: 48.6% females; 54.4% prepubertal; 71.7% Caucasians; age: 10.37 $\pm$ 3.44 years, BMI:

+4.38±1.77 SDS) was carried-out with next generation sequencing (NGS) analysis of *ADCY3*, *CPE*, *LEP*, *LEPR*, *MC3R*, *MC4R*, *MRAP2*, *NCOA1*, *PCSK1*, *POMC*, *SH2B1*, *SIM1* and *TBX3* performed. Rare (population frequency <0.01) heterozygous variants with a combined Annotation Dependent Depletion (CADD) score of “deleteriousness” >20 and >25 in each gene were considered and their relative frequency compared with that in a control population (C, n=1012).

Results: A total of 199 patients of the OB group (18.8%) and 81 controls (8.0%) carried heterozygous RSVs in the 13 selected genes (OR=2.64, 95%CI=2.00-3.47, $p<0.0001$), 101 patients vs. 45 controls when considering RSVs with CADD>25 (9.47% vs. 4.44%, OR=2.25, 95%CI=1.56-3.23, $p<0.0001$). No significant differences in the prevalence of hetRSVs in *ADCY3*, *LEP*, *LEPR*, or *TBX3* were observed between OB and C. In contrast, OB showed a significantly higher prevalence of hetRSVs with CADD>20 in *CPE*, *MC3R*, *MC4R*, *MRAP2*, *NCOA1*, *PCSK1*, *POMC*, *SH2B1* and *SIM1*. These intergroup differences were particularly relevant for *POMC*, *PCSK1*, *MC4R* and *NCOA1*.

Conclusions: The burden of heterozygous rare variants in leptin-melanocortin pathway genes, particularly in *POMC*, *PCSK1*, *MC4R* and *NCOA1*, in childhood obesity is higher than in general population, so they likely contribute to the early development of obesity in these patients.

P1-119

Diagnostic precision of the Tri-Ponderal Mass Index (kg/m³) to identify the metabolic risk phenotype in obese children and adolescents

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Introduction: The metabolically healthy obese phenotype (MHOF) defines obese patients who have preserved insulin sensitivity and who do not have metabolic complications: lower risk of cardiovascular disease and type 2 diabetes in adulthood.

Recent studies indicate that TMI (kg/m³) estimates the percentage of body fat more accurately than the BMI and it has been proposed to substitute the use of the BMI z-score values by those of the TMI.

TMI values remain very uniform in both boys and girls from the age of 8 to 18 years (*), so a single cut-off point can be used to identify overweight (TMI ≥ 13.8 and ≤ 15.2) and obesity (TMI ≥ 15.3).

Objectives: To determine the prevalence of MHOF and the obese phenotype with metabolic risk (MUOF) in a cohort of obese children and adolescents and to establish the predictive capacity of the Tri-Ponderal Mass Index (TMI) and other anthropometric parameters to identify these patients.

Patients and Methods: Cross-sectional study of 239 obese patients (125 males) between 8 and 18 years of age, 45.9% of which have class 3 obesity. The ROC curves are used to find the best cut-off point for TMI, BMI, BMI z-score value (zsBMI) and waist-to-height ratio (WHtR).

Results: The prevalence of MUOF in our cohort is 64.4% without observing differences between sexes, increasing with age and with the degree of obesity. MUOF component frequency: 1. Blood glucose ≥ 100 mg/dl: 0.8%. 2. plasma triglycerides ≥ 150 mg/dl: 17.6%. 3. HDL-c ≥ 40 mg/dl: 27.6%. 4. TAS ≥ p90 and TAD ≥ p90: 38.1% and 14.6% respectively. The TMI has a sensitivity of 75.8 and a specificity of 42.2 for identifying MUOF patients. The best cut-off point for TMI is 18.7 kg/m³, for zsBMI +3.5 SDS, for BMI 30.4 kg/m², and for WHtR 0.62.

Conclusions: The diagnostic accuracy of TMI to identify children and adolescents with metabolic risk is similar to that of BMI and WHtR. However, it greatly facilitates and simplifies the categorization of the degree of obesity in both sexes in the age range of 8 to 18 years.

(*) Carrascosa A, Yeste D, Moreno-Galdó A, Gussinyé M, Ferrández A, Clemente M “et al Body mass index and tri-ponderal mass index of 1,453 healthy non-obese, non-undernourished millennial children. The Barcelona longitudinal growth study *An Pediatr (Bar)*. 2018;89:137-143.

P1-120

Monogenic obesity in children: focusing on SH2B1 deletion

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Introduction: Monogenic obesity refers to a group of rare, early-onset forms of obesity and accounts for about 7% of patients with severe pediatric obesity. Recent reports demonstrate the emerging role of Src-homology-2 (SH2) B adaptor protein 1 (Sh2b1), an important component in the leptin-melanocortin pathway, as a key regulator of leptin and insulin signaling, with possible roles in the pathogenesis of obesity and diabetes. SH2B1 deletions are found to be associated with obesity, insulin resistance, hyperphagia and developmental delay in humans; however, only a few children with SH2B1 deletions have been described so far.

Methods: We describe the phenotype of n=7 children (3 male; age range: 2.8 – 18.0 years) with heterozygous SH2B1 deletions and present their BMI trajectories from birth onwards. Screening for obesity-associated co-morbidities was performed for all children at time of genetic diagnosis.

Results: All children with SH2B1 deletions had a normal BMI at birth but presented an extreme weight gain during the first

5 years of life. Hyperphagia was not a constant feature of the patients. A broad spectrum of neurodevelopmental abnormalities, including speech delay, learning difficulties, autistic traits, behavioural problems (aggressiveness) and attention deficit hyperactivity disorder was observed. In most cases developmental delay was the reason for genetic testing. Five patients presented with elevated fasting insulin levels, one patient developed diabetes mellitus type 2 at the age of 9 years, four patients had dyslipidemia and four developed non-alcoholic fatty liver disease at an early age.

Discussion/Conclusion: SH2B1 deletions in children were found to be associated with severe, early-onset obesity and developmental delay. Obesity-associated co-morbidities appeared early in life. Early genetic diagnostic testing in suspicious patients and early screening for co-morbidities is recommended. New therapeutic approaches, including setmelanotide, a MC4R agonist, are currently available for children with SH2B1 deletions in the context of clinical trials.

Growth A

P1-121

Higher rates of non-skeletal complications in achondroplasia compared to the general population: a UK matched cohort study using the CPRD database

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Objectives: Achondroplasia (ACH) is a rare, genetic skeletal dysplasia, resulting in impaired endochondral bone growth and leading to multisystem complications. We aimed to estimate rates

of non-skeletal complications in ACH patients compared with general population controls.

Methods: Retrospective cohort study using UK Clinical-Practice-Research-Datalink (CPRD-GOLD), identifying an ACH cohort. Study index date was defined as ACH first record between 01/01/1987-31/12/2018. ACH cases were index date matched (1:4) by age, sex, general practitioner (practice-level) and linkage ability to Hospital Episode Statistics database with control patients, defined as those without evidence of skeletal/growth disorders. Read codes defined complications of interest based on ACH literature; we calculated event rates per 100 person-year and rate ratios [RR] (95% confidence intervals, CI) to compare cohorts.

Results: We identified 541 ACH cases and 2,052 matched controls: 51% female, mean age 29 years (y), range 0-94y at index date. Mean follow-up time was 14.5y for ACH cases and 19.1y for controls. The rate of complications across a range of body systems was significantly higher among ACH patients than matched controls (range RR=1.18 for cardiovascular conditions to RR=8.81 for developmental conditions) [see Table]. Complications differed by ages when compared to controls; e.g. rates of developmental issues, ENT (otitis media/tonsils) and apnoea were higher in children, cardiovascular conditions, depression and seizures in adults, and musculoskeletal pain and hearing loss significantly affected both.

Conclusion: This study illustrates that ACH patients have significant non-skeletal multisystemic complications when compared to an appropriate matched general population cohort which are seen throughout the lifespan.

Specific complication*			
Body system	RR (95% CIs)	Statistically significantly higher RR in ACH compared to controls	No difference in RR between ACH cases and controls
Cardiovascular	1.18 (1.08-1.30)	- Chest pain/angina - Hypertension	- Coronary disease - Myocardial infarction - Stroke
Developmental	8.81 (5.29-14.68)	- Developmental delay - Speech delay	
ENT	3.03 (2.71-3.38)	- Enlarged tonsils - Hearing loss/deafness - Otitis media - Voice abnormality	Sinusitis
Mental Health	1.58 (1.40-1.77)	- ADD/ADHD/adjustment disorder - Depression/anxiety - Self-harm/suicidal ideation	Substance abuse
Metabolic	1.29 (1.10-1.50)	Obesity	- Diabetes - Hyperlipidaemia - Dementia
Neurological	7.72 (5.38-11.10)	- Seizures - Hydrocephalus/ ventriculomegaly	
Other	1.76 (1.65-1.87)	- Gastrointestinal issues - Headache - Pain-musculoskeletal	Sexual health/ gynaecological issues
Respiratory	4.16 (2.99-5.81)	Apnoea/sleep disordered breathing	Sleep disorder

*Specific conditions with <5 events are not shown in Table but contributed to body system total: motor delay (Developmental); middle ear dysfunction and tracheomalacia/bronchomalacia (ENT); 'other' mental health (Mental Health); craniocervical stenosis, failure to thrive, subdural haematoma (Neurological)

P1-122

Short stature in Protein Arginine Methyltransferase 7 (PRMT7) mutations: first evidences of growth response to rGH treatment

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Protein arginine methyltransferase 7 (PRMT7), a member of a family of enzymes that catalyse the transfer of methyl groups from S-adenosyl-L-methionine to nitrogen atoms on arginine residues, is involved in multiple biological processes, such as signal

transduction, mRNA splicing, transcriptional control, DNA repair, and protein translocation.

Currently, 12 patients with homozygous/compound heterozygous mutations in PRMT7 gene have been described defining the human disorder known as Short Stature, Brachydactyly, Intellectual Developmental Disability and Seizures syndrome (SBIDDS) (OMIM #617157). Short stature is probably a pathognomonic feature of SBIDDS, although growth hormone deficiency (GHD) has never been described before.

We report the endocrine manifestations and rGH (recombinant growth hormone) response of two female dizygotic twin sisters (Twin A and Twin B), born small for gestational ages, with novel biallelic variants in PRMT7. Whole exome sequencing analyses showed the same compound heterozygous mutation in PRMT7 gene (p.Cys407Tyr of maternal origin; c.1323+2T>G of paternal origin) in both twins.

Due to severe short stature and growth impairment (Height Twin A -2.75 SDS; Height Twin B -2.95 SDS), at six years of age, endocrine investigations to rule out GHD were performed, showing GHD in Twin A (peak GH at arginine test: 4.61 µg/L; peak GH at glucagon test: 5.14 µg/L; IGF-I 47 ng/mL, -2.19SDS) and an appropriate GH response in Twin B (peak GH at arginine test: 11.8 µg/L; IGF-I 52 ng/mL, -2.05SDS). No other pituitary deficiency was found.

They were started on rGH at different dosages according to the underlying diagnosis: replacement dosage of 0.025 mg/kg/day in

Twin A and 0.035 mg/kg/day in Twin B, as expected in SGA with birth weight <-2SDS.

After one year therapy, Twin A, diagnosed having GHD, gained 7.5 cm, with a growth velocity (GV) of 2.06SDS for her age and a height gain (Δ HT) of 0.52SDS (from HT -2.75SDS to HT -2.23SDS according to Cacciari Growth Charts). On the other hand, Twin B, treated as short stature in SGA, gained even 9.4 cm, showing a GV of 4.1SDS for sex and age and Δ HT of 0.88SDS (from HT -2.95SDS to HT -2.07SDS).

In conclusion, our findings provide further data of endocrine manifestations associated with *PRMT7* mutations including GHD. Considering the short-term good response to rGH, further studies are needed in these patients to confirm outcomes in the long-term and Δ HT at adult height.

P1-123

Growth and nutrition improvement with recombinant growth hormone in prepubertal patients with Silver-Russell syndrome

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Objective: Silver-Russell syndrome (SRS) is an imprinting disorder characterized by severe intrauterine and postnatal growth retardation and feeding difficulties. Patients can benefit from recombinant growth hormone (rGH) therapy which has shown its positive effect on adult height. Our objective was to assess the short-term effects of rGH therapy on growth and nutritional status in prepubertal patients with SRS.

Design: Retrospective analysis of growth and nutritional features in molecularly proven SRS patients during the first two years of rGH therapy.

Methods: Data from 64 prepubertal SRS patients with either loss of methylation in the 11p15 *IGF2/H19* region (LOM 11p15, n=51, 80%) or maternal uniparental disomy of chromosome 7 (upd(7)mat, n=13, 20%) were analyzed.

Results: The mean age of patients at rGH therapy onset was 3.6 (1.3;7.5) years. The mean height gain was 0.9 (0.0;3.4) standard deviation score (SDS) after one year of treatment ($p < 0.0001$) and 1.3 (0.4;4.8) SDS after two years ($p < 0.0001$). The ideal weight for length/height (WfH), reflecting the nutritional status, increased from 81% (62;100) at rGH onset, to 84% (67;103) after one year of treatment ($p = 0.044$) and to 87% (69;108) after two years ($p = 0.044$). The proportion of SRS patients above the targeted WfH of 85% increased from 25.4% at rGH therapy onset to 61.7% after two years of treatment ($p < 0.0001$). When comparing the WfH evolution between patient with rGH therapy onset before and after the age of 4 years, we identified a better gain between after one ($p = 0.009$) and two years ($p=0.011$) in patients with an earlier rGH start.

Conclusion: In prepubertal patients with SRS, the first two years of rGH therapy at standard doses improve both height and nutritional status. Gain weight must be closely monitored and

controlled in these first years of rGH treatment. Further studies to precisely assess body composition in these patients and the rGH impact are needed. Our data suggested a better impact on nutritional status if rGH therapy is started before 4 years of age.

P1-124

Management of endocrine aspects of Noonan syndrome across Europe: A subanalysis of a European clinical practice survey

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Aim: There is a current lack of international guidelines for managing the endocrine aspects of Noonan syndrome (NS). A clinical practice survey was developed to identify knowledge gaps and differences in the management of patients with NS across Europe.

Materials and Methods: A 60-question clinical practice survey was developed for clinical geneticists, paediatric endocrinologists and paediatric cardiologists directly involved in treating and managing patients with NS. The survey was implemented via the SurveyMonkey online platform and circulated by several European and national specialist societies. Contingency tables and the Chi-Squared test for independence were used to examine differences between specialties and countries.

Results: Responses from 364 physicians from 20 European countries were included in this analysis: endocrinologists (40%), geneticists (30%), and cardiologists (30%). To monitor growth, endocrinologists tend to refer to national growth charts for the general population, and geneticists generally use NS-specific

growth charts. Many endocrinologists (52%) perform growth hormone (GH) stimulation tests in patients with NS and short stature with low IGF1 levels (10% never perform these tests, and 36% always perform these tests regardless of IGF1 levels). Sixty six percent of endocrinologists begin GH treatment for short patients in early childhood (4–6.9 years). Half of them (55%) considered a threshold for GH treatment of -2 standard deviation score (SDS) according to national growth charts. Respondents from all specialities had the following concerns about GH treatment: hypertrophic cardiomyopathy (HCM) (59%), increased risk of malignancy (46%), and limited efficacy (31%). There were significant discrepancies between respondents regarding the meaning of HCM as a contraindication for GH. When asked if they consider HCM a contraindication to the use of GH therapy, many skipped this question, and of those who replied, many selected the option ‘cannot answer’, suggesting a high level of uncertainty. There were 21 reported adverse cardiac responses to GH treatment from <10% of respondents. While the majority had not encountered malignancies during GH treatment, 6 were reported (4 brain tumours, including 3 dysembryoplastic neuroepithelial tumours, and 2 leukaemias). Around half of the surveyed endocrinologists expected GH treatment to produce a typical final height gain of 1–1.5 SDS.

Conclusion: For the first time, results from this survey describe current clinical practice for managing the endocrine aspects of NS within Europe. These data will allow us to identify gaps in the knowledge of this rare genetic disorder, highlighting important topics for education and further research.

P1-125

PROPEL2: a phase 2, open-label, dose-escalation and dose-expansion study of infigratinib in children with achondroplasia (ACH)

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Background: ACH, the most common short-limbed skeletal dysplasia, is characterized by defective endochondral ossification resulting from gain-of-function mutations in the fibroblast growth factor receptor 3 (*FGFR3*) gene, a negative regulator of endochondral bone formation. Current treatment options are non-targeted, ineffective, or painful interventions aimed at preventing or treating complications. Infigratinib is an orally bioavailable and selective FGFR1–3 tyrosine kinase inhibitor in development for FGFR-related conditions. In vitro data with infigratinib showed inhibition of FGFR1–3 activity with reversal of established growth arrest in chondrocytes. *In vivo* studies revealed dose-dependent improvements in foramen magnum and long bone length in *Fgfr3*^{Y367C/+} mice following treatment with infigratinib.

Methods: PROPEL2 is a prospective, phase 2, open-label dose-finding study of infigratinib that aims to provide preliminary evidence of safety and efficacy in children with ACH. Eligible subjects 3–11 years of age who completed at least 6 months of observation in PROPEL (a prospective clinical assessment study in children with ACH) will participate in PROPEL2. It consists of dose escalation with an extended treatment phase (ESC-ET), followed by a dose-expansion phase (EXP) to confirm the selected dose. A pharmacokinetic (PK) sub-study will evaluate the PK profile of infigratinib and major metabolites. The primary endpoints of ESC-ET are treatment-emergent adverse events and change from baseline in annualized growth velocity (AGV). Subjects (n=40) are enrolled in

ascending dose cohorts of approximately 10 subjects/cohort (4 cohorts planned) and treated for 6 months at their assigned dose, continuing for an additional 12 months with dose modifications as required. The primary endpoint of EXP is change from baseline in AGV at the dose identified from ESC. Up to 20 new subjects will be enrolled in this phase and receive infigratinib (mini-tablets, administered orally once daily) for 12 months. Main secondary objectives include safety/tolerability of infigratinib and changes from baseline in anthropometric parameters, including body proportions. Exploratory objectives are evaluation of changes in ACH disease burden and quality of life.

Current Status: PROPEL2 is currently enrolling; the planned total enrollment is 78 children with ACH (40 ESC-ET, 20 EXP, 18 PK sub-study). Following completion of PROPEL2, subjects have the opportunity to enroll in an open-label long-term extension study to assess the safety and efficacy of long-term administration of infigratinib in children with ACH.

P1-126

Identification and tissue-specific characterization of novel SHOX-regulated genes in zebrafish highlights SOX family members among other genes

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SHOX deficiency causes a spectrum of clinical phenotypes related to skeletal dysplasia and short stature, including Léri-Weill dyschondrosteosis, Langer mesomelic dysplasia, Turner syndrome, and idiopathic short stature. *SHOX* controls chondrocyte proliferation and differentiation, bone maturation, cellular growth arrest and apoptosis via transcriptional regulation of its direct target genes *NPPB*, *FGFR3*, and *CTGF*. However, our understanding of *SHOX*-related pathways is still incomplete. To elucidate the underlying molecular mechanisms and to better understand the broad phenotypic spectrum of *SHOX* deficiency, we aimed to identify novel *SHOX* targets. We analyzed differentially expressed genes in *SHOX*-overexpressing human fibroblasts (NHDF), and confirmed the known *SHOX* target genes *NPPB* and *FGFR* among the most strongly regulated genes, together with 143 novel candidates. Altogether, 23 genes were selected for further validation, first by whole-body characterization in developing *shox*-deficient zebrafish embryos, followed by tissue-specific expression analysis in three *shox*-expressing zebrafish tissues: head (including brain, pharyngeal arches, eye, olfactory epithelium), heart, and pectoral fins. Most genes were physiologically relevant in the pectoral fins, while only few genes were also significantly regulated in head and

heart tissue. Interestingly, multiple *sox* family members (*sox5*, *sox6*, *sox8*, *sox18*) were significantly dysregulated in *shox*-deficient pectoral fins together with other genes (*nppa*, *nppc*, *cdkn1a*, *cdkn1ca*, *cyp26b1*, *cy26c1*), highlighting an important role for these genes in *shox*-related growth disorders. Network-based analysis integrating data from the Ingenuity pathways revealed that most of these genes act in a common network. Our results provide novel insights into the genetic pathways and molecular events leading to the clinical manifestation of *SHOX* deficiency.

P1-127

Evaluation of early puberty in boys and girls with Silver-Russell Syndrome: Discordance between testicular growth and pituitary-gonadal hormones in male cases

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Background: In Silver-Russell Syndrome (SRS), it is known that puberty starts early, frequency of premature adrenarche increases and adrenarche progresses aggressively. However, data regarding gonadal functions and testicular development in males during pubertal period is still insufficient.

Methods: Twenty-four cases (9F, 15M) who were followed-up with diagnosis of SRS between 1990-2020 were included in the study. The diagnosis of SRS was based on the Netchine-Harbisson clinical scoring system. Age at onset of puberty, physical and gonadal characteristics at different pubertal stages were recorded.

Results: At the time of study, 6 cases were pubertal, while 8 completed puberty. The median age at onset of puberty in female and male cases were 9 (7.8-10.9) and 10.6 (9-14.9) years and relatively early, respectively. Girls reached adrenarche at a median age of 8.8 (8.2-9.9) years while boys reached at 11 (9.3-14.1) years. Congenital genital anomalies were present in 47% of boys. Prepubertal median testicular volume (with orchidometer) was 1ml (0.5-2) and testicular volume SDS was -1.8 (-3.4 and 0.2). The mean height and body mass index (BMI) SDS in prepubertal period (age; 7.2±1.7 years) was -3.1±0.9 and -2.1±1.7, respectively. At the onset of puberty (age; 10.6 ± 2 years), mean height and BMI SDS increased up to -2.2±0.9 and -1.1±1.4, respectively. Age at onset of puberty and BMI SDS were negatively correlated ($r=-0.584$, $p=0.028$). Median testicular volume of 5 male cases who completed puberty was 11ml (9-15) and testicular volume SDS was -3.3 (-3.4 and -2.0). FSH, LH and testosterone levels were at normal pubertal levels in these patients. While bone age (median SDS -2.8; -7.2 and 1.3) was delayed in the prepubertal period, significant advancement was observed at the onset of puberty (median SDS -0.5; -4.3 and 3.1) ($p=0.003$). Prepubertal gynecomastia and high estradiol/estrone levels were observed in 2 patients with early puberty. For girls, median age at menarche was

13.6 years and all periods were regular. The median final height was 155.6cm in boys and 148.5cm in girls.

Conclusion: In SRS, onset of puberty is earlier. During puberty, there is an increase in BMI and acceleration in bone maturation. In boys, testicular volume does not correlate with pituitary-gonadal hormone levels. Therefore, findings such as somatic growth, acceleration in bone maturation, gynecomastia should be evaluated rather than testicular volume to evaluate pubertal onset. Thus, it will be possible to improve the height prognosis and to plan appropriate treatment.

P1-128

Evaluation of Persistent Short Stature in Children Born Small for Gestational Age without Catch-up Growth

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Aim: The majority of children born small for gestational age (SGA) demonstrate spontaneous catch-up growth in height by the age of two years; however, approximately 10-15% of SGA newborns are at risk of having subnormal growth and persistent short stature (PSS).

Method: We evaluated clinical, anthropometric, and laboratory characteristics of the 86 children with PSS who were born SGA.

Results: 29.8% of the patients were SGA just for weight, 8.8% were just for length, and 61.4% were for both. The rate of consanguineous marriage was 39.3%. 32.5% of patients had at least one parent with height-SDS ≤ -2 , and 10.4% had both parents with short stature. The frequency of premature births was 20.2%. All patients presented with either a height-SDS of ≤ -2 or had a height of more than 2.0 SDS below the midparental-height. Median height-SDS was -3.2. Besides marked short stature, a vast amount of the patients had significant clinical features. The most recurrent features associated with short stature were facial dysmorphism (55.1%) and microcephaly (55.1%). Other additional features included some degree of developmental delay or intellectual disability, skeletal abnormalities/disproportionate stature, heart or renal abnormality, cryptorchidism, and hearing loss. Among 41 patients (17F/41M) who reached pubertal onset, the median age at pubertal onset was 10.1 years in girls and 11.5 years in boys. The median height at pubertal onset was 125 cm in girls and 129 cm in boys. Precocious puberty and early puberty were found to be 6.7% and 14.6%, respectively. Four (5.6%) patients had delayed puberty. Two fraternal twin girls had primary gonadal insufficiency (PGI), two boys developed PGI secondary to bilateral cryptorchidism. All four patients had a normal karyotype. Sixty-four children were started on recombinant growth hormone (GH) treatment, and the majority (76.5%) of them were diagnosed with GH-deficiency. The median GH dose was 35 $\mu\text{g/kg/day}$, and duration of therapy was 3.6 years. Height-SDS increased significantly over the first and second years of treatment in the GH-deficient group. GH response in

GH-deficient group was significantly greater than the non-GH deficient group in the first two years of treatment. Median adult-height gain SDS was 0.4 in GH-deficient patients, and it was -0.6 in the non-GH deficient group.

Conclusion: Short-statured patients born SGA should be examined in terms of accompanying features. Although the response to GH treatment is a better GH-deficient group, final adult-height may remain below the general population. Further studies are needed to elucidate the etiology in SGA with PSS.

P1-129

Computer-aided facial analysis as a tool to identify patients with Silver-Russell syndrome and Prader-Willi syndrome

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Introduction: Genetic syndromes often show suggestive facial features that provide clues for the diagnosis. Considering the high number of genetic syndromes and the possible overlap of some features, memorizing facial gestalt is a challenging task for clinicians. DeepGestalt technology, and its app Face2Gene, has a growing impact on the diagnosis and management of genetic diseases by analyzing the features detected in one or more facial images of affected individuals.

Methods: 23 pediatric patients with clinically or genetically diagnosed Silver-Russell syndrome (SRS) and 29 pediatric patients with genetically confirmed Prader-Willi syndrome (PWS) were enrolled between December 2020 and April 2021. One frontal picture of each patient was acquired. Top-1, top-5 and top-10 sensitivity was analyzed. Correlation with the specific genetic diagnosis was investigated. When available, pictures of the same patient at different ages were compared.

Results: In the SRS cohort Face2Gene showed a top-1, top-5 and top-10 sensitivity of 39%, 65% and 91% respectively. Two patients (8.7%) were not correctly diagnosed by the app; this did not change after adding clinical features. Thirteen SRS patients had SRS suggested with high level of probability. In 44% of genetically confirmed patients SRS was the first syndrome suggested while in clinically diagnosed patients, SRS was suggested as top-1 in 28% of cases ($p=0.49$). In 22% of SRS patients a picture at the age of the diagnosis or at a younger age than the age of enrollment in the study was available. For pictures obtained at a younger age (mean age at diagnosis 2.61 years, range 0.17-9 years; mean age at enrollment 7.3 years, range 1-17 years), Face2Gene performed better in younger patients and for all patients SRS was suggested as top-1, albeit with variable degree of probability. In the PWS cohort the top-1, top-5 and top-10 sensitivity were 76%, 97% and 100% respectively. Twenty-one percent of PWS patients had PWS

suggested with high level of probability. PWS was suggested as top-1 in 60% of patients genetically diagnosed with mUPD and in 83% of patients presenting with paternal deletion of chromosome 15q11-13.

Conclusions: Face2Gene app can be a useful tool to support clinicians in the diagnosis of SRS and PWS. The sensitivity is higher in PWS patients and was comparable throughout all age ranges. In SRS patients, the app performed better in the younger age group, probably due to more pronounced facial features at a younger age.

P1-130

Study design and baseline characteristics of children enrolled in PROPEL: A prospective clinical assessment study in children with achondroplasia (ACH)

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Background: ACH is the most common short-limbed skeletal dysplasia, affecting between 1 in 15,000 to 1 in 30,000 live births. Children and adults with ACH have disproportionate short stature, with a final height of approx. 131 cm for males and 124 cm for females. People with ACH are prone to significant co-morbidities, including obstructive sleep apnea, chronic otitis media with conductive hearing loss, spinal stenosis, and a propensity towards obesity. In some infants, narrowing of the foramen magnum may result in compression of the spinal cord with neurologic sequelae, requiring timely neurosurgical intervention. There are currently no approved therapies for the treatment of ACH in either the US or the EU, and current treatment options are non-targeted,

ineffective, or painful interventions aimed at preventing or treating complications of ACH. Infigratinib is an oral FGFR1-3 inhibitor in development as a therapeutic option for ACH. The PROPEL study is a prospective, non-interventional study examining baseline growth parameters and health status in children being assessed for potential enrollment into interventional studies with infigratinib.

Methods: Children with ACH between the ages of 2.5 and 10 years are eligible for enrollment in PROPEL, and are evaluated at baseline, month 3, month 6, and every 6 months thereafter. The primary endpoint is annualized height velocity. Secondary endpoints include: change from baseline in other growth parameters (including body proportionality); analysis of bone biomarkers (e.g. bone alkaline phosphatase, collagen X fragment); and the occurrence of medical events and surgical procedures. Participants will be enrolled in the study for a minimum of 6 months up to a maximum of 2 years.

Results: A total of 75 children (64% female, mean±SD age 6.3±2.4 years) have been enrolled to date at 19 sites in Europe, Australia and North America. Their heights at study entry were within the ±2 SDs for ACH growth charts, with a mean±SD and median height percentile of 43±27 and 50 respectively, indicating that the participating children are a good representation of the population of interest. Additional demographics, baseline characteristics and medical history will be presented at the meeting.

Conclusions: The PROPEL study is underway with a planned total enrollment of 200 children with ACH. This sample size is considered enough to characterize the natural history of the condition and lead to sufficient enrollment in Phase 2 (PROPEL2) and/or Phase 3 interventional trials of infigratinib in children with ACH.

Growth Hormone and IGFs A

P1-131

The impact of lockdown regulations caused by the COVID-19 pandemic on adherence to recombinant human growth hormone therapy: Evidence from real-world data

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Background: We hypothesised that, due to the COVID-19 lockdown regulations, patients are at home more often and may, therefore, more diligently administer their growth hormone (GH) injections on a regular basis.

Aim: To investigate the impact of COVID-19 lockdown regulations on adherence to recombinant human GH (r-hGH) therapy in patients with growth disorders, using real-world data.

Patients and Methods: Adherence data were extracted between March 2019–February 2020 (before COVID-19) and between March 2020–February 2021 (during COVID-19) from the easypod™ connect ecosystem, which accurately records and transmits the date, time and r-hGH dose injected by the easypod™ electromechanical injection device. We selected countries that provided adherence data for ≥50 patients both before and during the COVID-19 pandemic. The stringency index (SI; composite measure of nine indicators including school/workplace closures and travel bans, rescaled to a value of 0–100) was extracted from <https://ourworldindata.org>. The mean SI during the COVID-19 period was calculated, and categorised as high (≥70 [75th percentile of SI within the included countries]) versus low (<70). Adherence was categorised as optimal (≥85% of prescribed doses administered) versus suboptimal (<85%) in the period before and during COVID-19. Multilevel logistic regression analyses (patient and country level) were performed, with adherence as the dependent variable and the interaction between period (before and during COVID-19) and SI (fixed value per country) as independent variables.

Results: Adherence data were available for 10,360 patients before and 8,213 patients during the COVID-19 period from 10 European countries (Czech Republic, Finland, France, Germany, Ireland, Italy, Spain, Sweden, Switzerland, UK), six South/Latin American countries (Argentina, Brazil, Chile, Colombia, Guatemala, Peru), two Asian countries (South Korea, Taiwan) and Canada. During the pandemic, a high SI resulted in an increase in the proportion of optimal adherence versus the pre-COVID-19 period ($p<0.001$). Seven of the eight countries with a high SI showed an absolute increase of >5% in the proportion of patients with optimal adherence: +17% in Colombia, +13% in Guatemala, +8% in Ireland and the UK, and +7% in Argentina, Chile and Italy. None of the 11 countries with a low SI showed an increase of >5% (range: -4 to 5%).

Conclusion: Stringent lockdown regulations during the COVID-19 pandemic appear to have had a positive impact on the proportion of patients with optimal adherence to r-hGH therapy supported by the easypod™ connect ecosystem. Residing at home more often may have contributed to the habit of administering a daily injection.

exposure to supraphysiological doses of growth hormone (GH) in children born small for gestational age (SGA).

Methods: This observational, non-interventional study (NCT01578135) included GH-naïve and non-naïve SGA children treated with GH at 126 sites in France. The inclusion period was 2005–2010 with follow-up until 2018 or until final adult (FA) height (height velocity <2 cm/year). The primary endpoints were proportion of patients with normal (>-2) height standard deviation score (HSDS) at last visit, and with normal FA HSDS. Secondary endpoints included change from baseline in HSDS and safety. Multivariate logistic regression analysis with stepwise elimination was used to identify factors associated with achieving normal HSDS.

Results: Of the 1408 registered patients, every fifth child was randomly selected ($n=291$) for inclusion in this long-term follow-up study. For the full population and subpopulation, mean (SD) baseline age was 8.79 (3.53) and 8.08 (3.32) years; HSDS was -2.55 (0.95) and -3.07 (0.86); 48.4% and 46.0% were female, respectively.

Normal HSDS was reached in 193/291 children (66.3%). Among the 24.7% of patients who achieved FA height at last visit, 66.7% had FA HSDS >-2. Mean change from start of treatment to last visit in HSDS was +1.35 (0.97). Factors associated with reaching normal HSDS were: baseline HSDS (taller better; odds ratio [95% confidence interval]: 5.65 [3.22;9.92], $p<0.0001$); age at treatment start (younger better; 0.88 [0.79;0.98], $p=0.0166$); treatment duration excluding discontinuation periods (longer better; 1.20 [1.04;1.38], $p=0.0166$); and absence of a chronic disease (0.43 [0.21;0.87], $p=0.0188$).

The majority (70.0%) of adverse events (AEs) were non-serious; 39.0% of all AEs and 7.0% of serious AEs were considered possibly/probably related to GH treatment. The most common AEs (% of patients) were increased insulin-like growth factor-I (IGF-I; 17.2%), headache (9.3%) and arthralgia (4.5%). Sixteen patients (5.5%) discontinued treatment prematurely, most commonly because of increased IGF-I ($n=4$). One malignant tumour (nephroblastoma) with a fatal outcome was reported, and considered unrelated to GH treatment.

Conclusions: GH therapy was effective in most short children born SGA. No new safety concerns were observed. The likelihood of achieving normal HSDS with GH therapy increased with greater baseline HSDS, longer duration of GH treatment, absence of a chronic disease and younger baseline age, reinforcing the importance of early identification and treatment of short patients born SGA.

P1-132

Use of growth hormone therapy in short patients born small for gestational age: data from real-life French clinical practice

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Background: A national French registry was created to address the absence of data on final height and safety following long-term

P1-133

Efficacy and safety profile of recombinant insulin like growth factor 1 (rhIGF1) therapy: A long term follow up study at a single tertiary centre

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Background and Objective: Recombinant human insulin like growth factor 1 (rhIGF1) therapy is the only treatment available for primary IGF1 deficiency and related disorders. However, its efficacy in promoting growth is controversial and needs cautious monitoring for adverse effects.

The aim of this study was to determine the long-term efficacy and safety profile of rhIGF1 therapy.

Methods: Retrospective review of all patients on rhIGF1 therapy over the last 13 years (2008 -2021) at a single tertiary centre.

Results: Eleven patients (8 male) on rhIGF1 therapy were identified. Seven harboured genetic mutations: *GH receptor gene mutation* (3/7), *STAT5B* (2/7), *STAT1* (1/7), *GH1 gene deletion* (1/7). Four had no identified mutation but were GH insensitive. Seven patients had an escalating IGF-1 generation test with no significant response.

Median age at presentation was 3.7 (1.57- 13.97) years and median age at start of treatment was 4.12 (2- 22.9) years. Starting dose of rhIGF1 was 77-85 mcg/kg/day (mean=79.89 mcg/kg/day) which was gradually increased to 151- 242 mcg/kg/day (mean=206 mcg/kg/day). Post-treatment follow-up ranged from 1.3 to 12.5 years.

Mean pre-treatment height velocity (HV) was 3.33 (0.85-6.47) cm/year. All cases showed post-treatment HV increment. Maximum HV was seen at 1-year post-treatment (7.54cm/year), followed by 6.13cm/year at 2 years, 5.7cm/year at 3 years, 5.8cm/year at 4 years, and 5cm/year at 6 years. The group with known genetic mutations showed a higher mean 1-year post-treatment HV (8.49 cm/year) as compared to the group with no identified mutation (4.11cm/year). Mean pre-treatment height was -4.60 (-2.66 to -7.31) SD. Post-treatment height improved to -3.11 (-1.85 to -4.33) SD.

Hypoglycaemia was observed in 9/11 patients. 4/9 patients developed hypoglycaemia after the first dose and needed overnight feeding via gastrostomy, with good effect. Three of these patients had a genetic mutation and showed the best response to rhIGF1 (HV 9.95(7.25-11.8) cm/year). Five patients developed hypoglycaemia after increasing IGF-1 dose and needed dose reduction with or without cornstarch and overnight feeds. Three patients developed tonsillar hypertrophy (OSA) within 4-10 months post-treatment (2 needed tonsillectomy). One patient developed left ventricular hypertrophy 2-years post-treatment. No patients developed benign intracranial hypertension.

Conclusion: Recombinant IGF1 therapy promotes growth in primary IGF1 deficiency, especially in patients with known underlying genetic mutations. Hypoglycaemia is the most common adverse effect, and its severity is associated with the response to rhIGF1 therapy. Gastrostomy feeds were highly effective at preventing hypoglycaemia.

P1-134

Starting recombinant human growth hormone treatment at an early age improves adherence and catch-up growth in patients with growth disorders, and highlights the importance of the new guideline on referral of short children to paediatric care

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Background: The new preventive child health care guideline for referral of short/tall children facilitates early detection of growth disorders. Understanding the impact of early treatment initiation on recombinant human growth hormone (rhGH) adherence and catch-up growth can support the use of the guideline.

Aim: To evaluate the impact of age at rhGH treatment start on adherence ($\geq 85\%$ vs $< 85\%$ of prescribed doses administered) and catch-up growth (Δ Height Standard Deviation Score [HSDS]) in patients with growth disorders.

Patients and Methods: Adherence data were extracted from the easypod™ electromechanical injection device in combination with the easypod™ connect system, which electronically records and transmits objective records of the date, time and dose injected for patients receiving rhGH. Height data from patients receiving rhGH during the easypod™ connect observational study¹ were analysed. For these patients, additional height measurements from easypod™ connect were also included. Adherence and height data were extracted for those patients aged 2-15 years (yr) at treatment start, with height data also extracted for treatment-naïve patients aged 2-18yr with GH deficiency (GHD), small for gestational age (SGA) or Turner syndrome (TS), HSDS < -1 at start and ≥ 1 height measurement between 0.5-3.5yr of treatment. Regression analyses were applied to study the impact of age at treatment start on adherence and HSDS between 0.5-3.5yr of treatment, adjusted for HSDS at start. Δ HSDS was expressed as predicted HSDS (using the model from the regression analyses) minus HSDS at start.

Results: Adherence and height data were available for 18,562 and 1,212 patients, respectively, (885 GHD, 243 SGA, 84 TS) with 7,485 height measurements. An early age at treatment start was associated with higher adherence ($p < 0.001$). In the age groups 2-7, 8-11 and 12-15yr at treatment start, adherence was 85%, 83% and 79% at 1yr, 76%, 72% and 70% at 2yr and 73%, 70% and 64% at 3yr of treatment, respectively. An early age at treatment start resulted

in a higher Δ HSDS ($p < 0.001$). Starting from 2yr of age, the predicted Δ HSDS decreased by 0.05 SD with every year of delayed treatment start until the patient reached 10yr, remaining stable thereafter.

Conclusion: Our real-world data show that an early age at treatment start has a positive effect on adherence and catch-up growth. This highlights the importance of early referral of children with growth failure, which is facilitated by using the evidence-based referral criteria for children aged 0-9yr in the guideline.

Reference

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P1-135

Long-term safety of growth hormone in adults and adolescents with growth hormone deficiency: An overview of the full-cohort in KIMS

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Objective: KIMS (Pfizer International Metabolic Survey) was a postmarketing surveillance study of growth hormone (GH) replacement in adults and adolescents with GH deficiency (GHD) that concluded in October 2012. This analysis aimed to evaluate the overall safety outcomes from the full cohort of GH-treated patients of KIMS.

Methods: Data were collected on adults and adolescents with confirmed GHD and closed epiphyses treated with GH (Genotropin® [somatropin]; Pfizer, NY) and followed through routine clinical practice. Adverse events (AEs), serious adverse events (SAEs), and clinical characteristics (eg, lipid profile, glucose) are summarized.

Results: The analysis included 15,809 GH-treated patients with a mean follow up of 5.3 years (maximum 18.3 years and total 83,128 patient-years). Mean age at study entry was 43.9 years (standard deviation 15.3 years). Most patients had pituitary/hypothalamic tumors (62.6%) as the cause of their GHD, while 21.5% due to idiopathic/congenital GHD, and 15.2% due to other etiologies. GHD was adult-onset (AO-GHD) in 77.4 % of patients. AEs were reported in 51.2% of patients (treatment-related in 18.8%) during KIMS follow up; the most frequent being arthralgia (4.6%),

while the most frequent SAE being pituitary tumor growth or recurrence (2.0%). A total of 606 deaths (3.8%) were reported, most commonly caused by neoplasms ($n=146$). Other common death causes were cardiac or vascular disorders ($n=71$) and infections/infestations ($n=60$). Overall cancer incidence among patients without a prior history of cancer was comparable to that of the general population (standard incidence ratios [SIR] 0.92; 95% CI 0.83-1.01). Cancer SIRs were decreased in patients with idiopathic/congenital GHD (0.64; 95% CI 0.43-0.91), but were similar to the general population in those with pituitary/hypothalamic tumors (0.96; 95% CI 0.87-1.07) or other etiologies (0.80; 95% CI 0.56-1.10). Neither AO-GHD (0.90; 95% CI 0.81-1.00) nor childhood-onset GHD (1.21; 95% CI 0.81-1.74) was associated with elevated cancer risks. Mean (standard deviation) IGF-1 standard deviation score was -1.3 (2.2) at baseline, increased to +0.2 (1.73) at year 1, and reached +0.7 (1.47) at year 18. Neutral effects were observed for lipids and fasting blood glucose levels.

Conclusion: The present KIMS analysis of the full cohort of GH-treated adults, in one of the largest and longest real-world safety surveys, confirms and reinforces the favorable safety profile of GH replacement in adults and adolescents with GHD, with no new safety signals observed. The results support that GH replacement is safe and tolerable as currently prescribed in routine clinical practice.

P1-136

Comparison of actual GH dose with labeled dose in children with short stature based on the LG Growth Study

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Objectives: This study aimed to analyze dosing patterns of recombinant human growth hormone (rhGH) (Eutropin® Inj., Eutropin®Pen Inj., and Eutropin®AQ Inj. for daily injection, and Eutropin®Plus Inj. for weekly injection, LG Chem, Ltd.) using the collected data of the LG Growth Study (LGS) in Korean pediatric patients with growth disorders including growth hormone deficiency (GHD), idiopathic short stature (ISS), small for gestational age (SGA), and Turner Syndrome (TS).

Methods: The LGS, an open-label, multicenter (total 76 sites), observational study has begun in November 2011, and the data collected until March 2020 was used for this analysis.

GH dosing was compared descriptively across indications and to labeled dose per each indication in Korea. All reported adverse events (AEs) across indications were also assessed. Also the literary comparison of GH dosing data with those from other observational studies in USA and European countries (NordiNet® IOS and ANSWER Program) was done.

Results: During the 8-year study, a total of 3,813 patients were enrolled, and dosing data from total 3,590 patients were used for analysis. Of those patients, 2,328 (64.8%) had GHD, 523 (14.6%) were diagnosed with ISS, 483 (13.5%) were born SGA, and 246 (6.9%) had TS. The mean treatment duration was 3.5 years.

In patients with GHD, mean GH dose of daily injection products (0.24 mg/kg/week) was slightly higher than its labeled dose (0.17 to 0.21 mg/kg/week) in Korea, and the same trend was shown in weekly injection product (0.59 mg/kg/week over the labeled dose of 0.50 mg/kg/week). But the mean doses in ISS (0.26 mg/kg/week), SGA (0.28 mg/kg/week), and TS (0.30 mg/kg/week) were less than those corresponding labeled/recommended doses. This is similar pattern with other observational studies in USA and European countries even though their clinical practice guideline are different from Korea.

Among total 1,035 subjects who reported adverse events (AEs), there were 672 (28.9%) patients in GHD, 122 (23.3%) in ISS, 123 (25.5%) in SGA, and 112 (45.5%) in TS. Most of the reported AEs were mild in severity, and 5.3% of them were related with rhGH treatment.

Conclusions: In this study, GHD patients received a slightly higher doses than labeled recommendations, but patients with ISS, SGA and TS used lower doses of GH than the labeled dose. And the incidence rate of AEs was not correlated with the dosing pattern across the indications.

P1-137

Persistently increased IGF-I levels and excellent auxological response despite low doses of recombinant growth hormone in a GH-deficient patient with a heterozygous variant of the growth hormone receptor (GHR) gene

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ABSTRACT

Introduction: Homozygous loss-of-function mutations of the growth hormone receptor (*GHR*) gene result in GH insensitivity due to a dysfunctional receptor protein. Heterozygous mutations may result in a variable clinical *spectrum* ranging from normal height to severe short stature. Gain-of-function variants have been reported rarely.

Case Report: We hereby report the case of a Russian boy who was referred to our endocrine outpatient clinic for faltering growth at the age of 7.25 years. Since he was adopted, neither mid-parental height nor birth weight and length were available. Upon the time of consultation, his height was -3.17 SDS – WHO growth charts.

The combination of a remarkably delayed bone age (2.7 years), baseline IGF-I levels equal to -1.57 SDS, a pathological response to two GH-stimulation tests (GH peaks: 4.7 and 3.4 ng/mL, respectively) and the findings of severe pituitary hypoplasia with intrasellar arachnoid diverticulum prompted the diagnosis of GH deficiency.

As a consequence, treatment with recombinant human GH (rhGH) was undertaken at a daily starting dose of 0.029 mg/Kg. The patient showed an excellent auxological response, with an overall height gain of 1.57 SDS in 24 months.

However, after the first year of treatment, IGF-I levels showed a persistent increase above +2 SDS (maximum value recorded +10.64 SDS), irrespectively of a stepwise down-titration to a daily dose of 0.018 mg/kg. Treatment was therefore discontinued resulting in a timely normalization of IGF-I levels (-1.24 SDS).

Given this unexplained responsiveness to rhGH, the patient underwent a genetical assessment: a novel heterozygous *c.535C>T (p.Arg179Cys)* variant involving the *GHR* gene was demonstrated in the proband. The mutation involved a functional domain and it was therefore predicted to be likely disease-causing by bioinformatic pathogenicity prediction tools.

Discussion: The overall response to rhGH treatment in GH-deficient patients is the result of both genetic and non-genetic factors. Increased responsiveness to rhGH associated to polymorphisms of the *GHR* gene has already been described in patients with idiopathic short stature. The novel variant hereby described may positively affect the sensitivity to treatment.

Conclusions: Growth hormone-deficient patients presenting with an excellent auxological response and persistent IGF-I levels above +2 SDS despite low rhGH doses may be carriers of *GHR* gene polymorphisms. *GHR* genotype influences sensitivity to GH; therefore, GH doses should be customized on the basis of IGF-I levels and clinical response. Further studies should be performed to define the optimal GHR genotype-based dose.

Safety and effectiveness of pediatric growth hormone therapy: Results from the full cohort in KIGS

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Objective: KIGS (Pfizer International Growth Survey) was a large, international database of pediatric patients who received recombinant human growth hormone (rhGH) as prescribed in real-world clinical settings. This analysis evaluated the long-term safety and efficacy data from all participants until KIGS close in 2012.

Methods: Children with growth disorders and treated with rhGH (Genotropin® [somatropin]; Pfizer, NY) were enrolled. Under informed consent/assent, safety and growth data were collected during their visits. Safety was evaluated in all rhGH-treated patients, and effectiveness in those who had ≥ 1 year of treatment and completed height assessment at year 1. The near-adult-height (NAH) subgroup included patients who received rhGH for ≥ 5 years (≥ 2 years of prepubertal treatment) and achieved NAH, defined by height velocity < 2 cm/year during the last year and age > 14 years (females) or > 16 years (males). Adverse events (AEs), serious AEs (SAEs), and auxological data were collected. Height standard deviation score (Ht-SDS) and Ht-SDS minus mid-parental height SDS (DiffSDS) were based on the Prader reference. Continuous variables are presented as mean $\pm$ SD.

Results: Globally, 83,803 patients (58% male, 42% female) were enrolled in KIGS. Indications for treatment included idiopathic GH deficiency (IGHD; 46.9%), small for gestational age (SGA; 9.5%), Turner syndrome (TS; 9.2%), idiopathic short stature (ISS; 8.2%), and other syndromes or growth disorders (26.2%). Patients were 10.2 ± 4.0 years old and received rhGH at 24.3 ± 10.0 to 42.9 ± 17.1 mg/kg/day for different indications at treatment start. Duration of rhGH treatment was 3.3 ± 2.8 years (0.0-19.8 years), with 3.8 ± 3.1 years of follow-up (0.0-24.1 years). AEs were reported for 12,055 (14.4%) patients and SAEs for 3108 (3.7%). The most common SAEs included craniopharyngioma recurrence (n=151),

neoplasm recurrence (n=99), scoliosis (n=91), and recurrent malignancy (n=91). Death was reported for 307 (0.4%) patients, most commonly caused by neoplasms (n=84). Increases in height SDS with rhGH were observed. In particular, in the effectiveness cohort (n=55,284), delta Ht-SDS at year 1 versus treatment start was 0.63 ± 0.51 , 0.67 ± 0.43 , 0.54 ± 0.43 , and 0.48 ± 0.38 for patients with IGHD, SGA, TS, and ISS, respectively, and total gain to NAH Ht-SDS was 2.08 ± 1.23 , 1.54 ± 0.92 , 1.09 ± 0.79 , and 1.51 ± 0.90 , respectively, in the NAH subgroup. DiffSDS increased at NAH versus treatment start for all diagnoses.

Conclusion: Data from KIGS, the largest and longest running database of rhGH-treated children, confirm the safety and effectiveness of pediatric rhGH therapy as used in clinical practice.

The effect of growth hormone therapy on linear growth and weight gain in children with growth hormone deficiency vs idiopathic short stature (ISS); a controlled study

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Introduction: Controversy still exists about the effect of GH treatment on linear growth and weight gain (WG) in children with ISS.

Aim: To study linear growth and weight gain in children with ISS treated with GH vs those not treated in comparison with treated children with GHD.

Methodology: We conducted a longitudinal controlled study on 78 children presented to a pediatric clinic with short stature (January - December 2017). Children were classified to ISS and GHD based on the GH provocation test. ISS children were randomly stratified into two groups. Group 1 (N=19) treated with GH 0.035 mg/kg/day and group 2 (N= 30) was not treated with GH. Both groups were compared to GHD children (N=29) treated with growth hormone (0.03-0.05 mg/kg/day). The dose was tailored to keep IGF-1 SD between (0 to +2).

Anthropometrics data (HtSDS, the difference from MPH, BMISDS, and WG), bone age, and IGF-1 level were studied in the 3 groups for 1 year.

Results: At presentation, there was no difference in age, HTSDS, BMISDS, the difference from MPHSDS, bone age and IGF-1 SD among the three groups. ($P > 0.05$). After 1 year, there was a significant increase in HtSDS in GH-treated groups $P < 0.01$. The increase in HtSDS, change in BMISDS, and the difference in HtSDS from MPHSDS did not differ among the two treated groups. Comparison between treated and non-treated ISS showed that BMISDS and WG increased significantly ($P=0.02$) in the treated vs. nontreated group whereas the increase in HtSDS was not significant in the non-treated ISS group.

Conclusion: Growth hormone therapy improved the HtSDS, BMISDS, and daily weight gain during the first year of treatment of ISS which was comparable to the response of GH treatment in GHD children.

		Age 1	HtSDS1	BMI SDS1	Age 2	HtSDS2	BMI SDS2	WGD	Delta BMISDS	DeLta HtSDS
GH def N (29)	Mean	9.77	-2.24	-0.49	11.08	-1.92	-0.26	12.51	0.06	0.34
	SD	3.58	0.63	1.29	3.65	0.69	1.23	7.30	0.40	0.48
ISS treated N (19)	Mean	10.58	-2.20	-0.53	11.78	-1.83	-0.07	13.89	0.25	0.27
	SD	2.30	0.64	1.09	2.14	0.47	0.92	6.57	0.46	0.32
ISS not treated N (30)	p 1	0.34	0.84	0.90	0.47	0.63	0.59	0.55	0.21	0.57
	Mean	10.25	-2.20	-0.92	11.10	-1.98	-0.94	9.85	0.21	0.11
	SD	3.00	0.50	0.89	3.30	0.56	1.02	7.53	0.64	0.36
	p2	0.68	0.99	0.18	0.51	0.41	0.02	0.02*	0.87	0.21

P1-140

Linear growth response top Growth hormone therapy in underweight versus normal-weight children with idiopathic short stature (ISS)

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Introduction: A multicenter clinical trial in the US showed that underweight small for gestation (SGA) children responded to GH treatment like non-underweight SGA children. However, data on GH response in short underweight children with the normal birth size is not studied well.

Aim: To measure growth response to GH therapy in underweight children versus short normal-weight children with idiopathic short stature (ISS) born appropriate for gestational age (AGA)

Methods: We studied 52 short prepubertal children (HtSDS <-2 born AGA (i.e. normal birth weight and/or length for their gestational age) with normal growth hormone peak to provocation, thyroid, hepatic and renal function, and hemogram and negative celiac screening. 15 were underweight at presentation (BMI SDS <-2) and 37 had normal (BMISDS >-1.5). Both groups received rhGH at 0.03: 0.05 mg/kg/day for 1 year. In addition, underweight children had nutritional counseling and supplementation. Anthropometric data {height (Ht), weight (W), HtSDS and BMISDS} and insulin-like growth factor 1 (IGF1) were evaluated and recorded for all the children before and after GH therapy.

Results: Before treatment with GH the age, HtSDS, and bone age did not differ between the 2 groups. The difference between HtSDS and Mid-parental HtSDS (MPHSDS) did not vary between the two groups. IGF1 was significantly lower in the underweight group versus the normal weight group. After a year of GH treatment, the BMISDS did not change significantly in both groups. The HtSDS and IGFSD increased significantly in the normal weight group but not in the underweight group. The difference between the HtSDS and MPHSDS decreased significantly in the normal weight versus the underweight group.

Conclusion: GH therapy increased significantly the IGF1 concentration and HtSDS in prepubertal children with ISS and normal BMI but not in underweight short children (BMI<-1.5). Underweight children with ISS who received GH therapy grew at a normal growth rate without catch-up in height.

	low BMI	Normal BMI
	N=15	N = 37
BMISD1	-1.36*	-0.14
	0.63	0.88
BMSDI2	-1.43*	-0.20
	0.68	0.88
HSDS1	-2.37	-2.03
	0.25	0.27
HSDS2	-2.13	-1.83*
	0.29	0.25
HtSDS-MPHtSDS1	-1	-1.33
	0.64	-0.66
HtSDS-MPHtSDS2	-0.7	-0.8
	0.8	1

1 = at presentation, 2 = after 1 year of GH therapy

*p<0.05 between the two groups.

Sex Endocrinology and Gonads B

P1-141

Screening of serum differential proteins in girls with rapidly progressing central precocious puberty with TMT quantitative proteomics

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Objective: To screen and identify serum differentially expressed proteins in girls with rapidly progressing central precocious puberty and healthy girls by proteomics.

Methods: 15 idiopathic central precocious puberty girls and 15 healthy children were admitted to the Children's Hospital of Suzhou University from August 2017 to October 2018. After mixing in the group, the high-abundance protein was removed and quantified with proteomics tandem mass tag (TMT) labeling

technique. Gene functional clustering (GO) analysis and pathway enrichment analysis were performed on the identified differential proteins to screen for proteins associated with the development of rapidly progressive central precocious puberty.

Results: Mass spectrometry identified 504 proteins with >95% confidence, of which 83 were differentially expressed. Compared with the control group, 31 of the 83 differential proteins were up-regulated and 52 were down-regulated. GO analysis showed that most of the differential proteins were in the extracellular region (36%); KEGG pathway enrichment analysis showed that the pathway with the largest number of differential proteins was the protein digestion and absorption pathway.

Conclusion: The differential proteins associated with protein digestion and absorption pathways have been identified in the serum of girls with rapidly progressing central precocious puberty, and their specific functions need further study.

P1-142

Investigation of primary adrenal insufficiency (PAI) in children with 46,XY differences in sex development (DSD)

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Background: When a baby presents with atypical genitalia, the most important diagnosis to consider is 21-hydroxylase deficiency (21OHD, CAH, 46,XX). However, primary adrenal insufficiency (PAI) can also occur in 46,XY children with differences in sex

development (DSD), although this is less common. Known causes of 46,XY DSD-PAI include high blocks in steroidogenesis (*STAR*, *CYP11A1*); steroidogenic enzyme defects (*HSD3B2*, *CYP17A1*, *POR*); syndromic associations (Smith-Lemli-Opitz, *DHC7R*; IMAGe, *CDKN1C*; MIRAGE, *SAMD9*), and very rarely, defects in steroidogenic factor-1 (*NR5A1*). The relative prevalence of these conditions is not known, nor how best to investigate for them in 46,XY DSD.

Methods: Case notes were reviewed of 316 children with 46,XY DSD presenting to a single tertiary centre multidisciplinary team over 25 years. Children were identified who had been diagnosed with PAI and treated with steroid replacement. Clinical, biochemical, and genetic data were obtained. Basal cortisol, standard synacthen-stimulated peak cortisol and incremental rise, and basal ACTH were analysed for those children with PAI, and compared to a "control" group of children being investigated for 46,XY DSD with normal adrenal function (n=57).

Results: A total of 10 out of 316 (10/316, 3.2%) children with 46,XY DSD were diagnosed with PAI. Five of these children (1.6%) were diagnosed with PAI first: three of them were 46,XY phenotypic girls in whom DSD was not suspected (two with congenital lipoid adrenal hyperplasia (*STAR*), one with complete 17 α -hydroxylase/17,20 lyase deficiency (*CYP17A1*)) and two of them had syndromic features that led to the diagnosis (Antley-Bixler Syndrome (*POR*), IMAGe Syndrome (*CDKN1C*)). Five children (1.6%) presented with 46,XY DSD/genital differences and were diagnosed with PAI through adrenal investigations: two of them had 3 β -hydroxysteroid dehydrogenase deficiency type 2 (*HSD3B2*), two had partial 17 α -hydroxylase/17,20 lyase deficiency (*CYP17A1*), and one had fetal growth restriction/PAI of unknown aetiology. For these five children, basal ACTH (>60 ng/L) had a sensitivity of 100% and specificity of 88%. Specificity was higher if basal cortisol was <150 nmol/L, and if synacthen-stimulated peak or incremental cortisol was suboptimal. Hyperpigmentation, salt loss and ancestral background provided additional clues. Urine steroid profiles and genetic testing were usually diagnostic.

Conclusion: PAI in 46,XY DSD is an important diagnosis to consider with short- and long-term consequences, but it is uncommon (3.2% of our cohort). For those children presenting primarily with DSD/genital differences, basal ACTH is a useful investigation if turn-around time is quick.

Current clinical practice of prenatal dexamethasone treatment in at risk pregnancies for classic 21-hydroxylase deficiency in Europe

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Background: Prenatal dexamethasone treatment (Pdex) has been used since the 1980s to prevent virilization in female offspring suspected to have congenital adrenal hyperplasia (CAH).

However, due to lack of strong evidence for its best practice as well as limited data regarding long-term adverse effects, use of dex is highly controversial. This study reveals the current medical practice regarding Pdex in female fetuses at risk of CAH due to 21-hydroxylase deficiency (21OHD) in Europe.

Methods: A questionnaire was designed and distributed using Microsoft Forms, including 17 questions collecting quantitative and qualitative data. Thirty-six medical centres from 14 European countries responded and 28 out of 36 centres were reference centres of the European Reference Network on Rare Endocrine Conditions, EndoERN.

Results: 36% (13/36) of the surveyed centres are currently providing Pdex. The treatment is initiated by different specialties i.e. pediatricians, obstetricians/gynecologists or geneticists. Regarding the starting point of Pdex, 15% of centres stated to initiate therapy as early as pregnancy is confirmed, 23% at 4 to 5 wpc, 31% at 6 wpc, and the rest at 7 wpc at the latest. A dose of 20µg/kg/d is used and dose distribution among the centres varies between once to thrice daily. Prenatal diagnostics are conducted at 72% (26/36) of centres, which however mainly includes chorionic villous sampling ± genotyping of the sex-determining region Y from maternal blood (SRY-typing) or amniocentesis and CYP21A2 genotyping. Non-invasive genetic testing from maternal blood is currently offered by one centre.

The total number of pregnant women who received Pdex during the first trimester of pregnancy varied from 3 to 44 per centre (median=10, total number of treated cases n=197), while 0 to 13 cases (median=5, total number of treated cases n=70) were treated for the entire gestational period. A mean of 1.6 cases are treated at each centre per year. Registries for long-term follow-up are only available at 46% of the centres that are using Pdex. National registries are only available in 2 of the 14 corresponding countries.

Conclusion: This study reveals a high international variability and discrepancy on the use of Pdex across Europe. It highlights the importance of a European cooperation initiative for a joint international prospective trial to establish evidence-based guidelines on prenatal diagnostics, treatment and follow-up of pregnancies at risk for CAH. Evaluation of outcome and long-term health of already treated cases across Europe is highly recommended.

P1-144

Ovarian AMH production is transiently affected in pubertal and prepubertal girls with acute lymphoblastic leukaemia and non-Hodgkin lymphoma receiving chemotherapy: a prospective, longitudinal study

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Introduction: Improvements in the treatment of acute lymphoblastic leukaemia (ALL) and non-Hodgkin lymphoma (NHL) have increased survival, with the consequent concern about the long-term effects that childhood chemotherapy may have on ovarian function. AMH constitutes an indirect, reliable biomarker of the ovarian reserve, useful for the assessment of cancer therapy-related ovarian damage.

Aim: To evaluate small ovarian follicle status in girls and adolescents with hematologic malignancies during and after treatment (Post Tx).

Methods: prospective cohort study in children with ALL or NHL. Serum AMH was measured (EIA Immunotech-Beckmann-Coulter) at diagnosis, during chemotherapy and until 3 year after treatment completion. Secondly, FSH levels were analysed. Results were interpreted according to age or pubertal stage as appropriate and expressed as median (range).

Results: Twenty-three girls aged 7,3 yr (1-15,7) were included; 15 were prepubertal and 8 were pubertal at diagnosis. NHL was diagnosed in 4 (17,4%) and ALL in 19 (82,6%), of which 6/19 (31,6%) were high risk and 13 (68,4%), intermediate or standard risk. Total follow-up was 4,7 yr (3-5,1).

AMH was low (<3rd centile) in 20 patients (86,9%) at some point during treatment. In 4 girls AMH was low since diagnosis. In the others, a marked decrease in AMH was observed between 6 and 12 months of treatment.

Fifteen out of 20 (75%) patients recovered normal serum AMH. (Table); 4 of the 5 girls who did not recover AMH had basal AMH <25th centile and a diagnosis of high-risk ALL or NHL, receiving more aggressive chemotherapy.

AMH	Basal	3m	6m	9m	12m	15m	18m	24m	12m Post Tx	24m Post Tx	36m Post Tx
pmol/L	13.0 (1.2-55)	6.7 (1.2-38)	1.9 (1.2-21)	5.1 (1.2-25.6)	4.8 (1.2-49)	9.0 (1.2-71.2)	14.7 (1.2-40.5)	15.2 (3-29.7)	17.7 (3-58.4)	14.9 (1.2-46.2)	17.6 (1.2-41.7)
< 3rd Pcn (%)	4 (17.4)	8 (34.8)	14 (63.3)	12 (60.0)	10 (50.0)	5 (26.3)	5 (27.7)	2 (10.5)	3 (13.0)	3 (13.0)	5 (21.7)

A mild and transient increased FSH was seen in 12 (52,1%), 7 prepubertal and 5 pubertal,

All girls who received pubertal inhibition treatment recovered their sexual cycles within 7 months of suspension.

Conclusion: These preliminary results suggest that most girls with ALL or NHL suffered a transient impairment of the small ovarian follicle pool during chemotherapy, with recovery in a large majority of them in the long-term. Most of the girls with persistently low AMH had received more aggressive chemotherapy.

P1-145

Serum anti-Müllerian hormone as a marker of ovarian reserve among childhood cancer survivors

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Introduction: Female patients treated with alkylating agents in childhood are at risk for ovarian impairment. We aimed at describing the pattern of residual ovarian function in a cohort of hematological cancer survivors, assessing the relationship between the cumulative dose of alkylating agents administered (expressed as Cyclophosphamide Equivalent Dose - CED) and Anti-Müllerian Hormone (AMH) levels.

Methods: Gonadal health was assessed in 81 post-menarchal survivors treated for pediatric lymphoma or leukemia at a mean age of 11.75 ± 5.02 years and aged 20.05 ± 4.13 years upon data collection. Clinical and biochemical (LH, FSH, AMH) data were gathered in all the patients enrolled.

Results: Eighty-one patients were treated with alkylating agents with a CED (mg/m^2) < 4000, between 4000 and 8000 and > 8000 in 39%, 57% and 4% of patients, respectively. Abdomino-pelvic irradiation was administered to 11/81 patients (13.4%).

Seventy-eight patients presented with regular menses (96.3%), whereas 3 (3.7%) showed secondary amenorrhea, raised FSH and undetectable AMH levels, profiling an overt “premature ovarian insufficiency” (POI). Among 78 women with retained menses and normal FSH levels, milder “diminished ovarian reserve” (DOR), identified by AMH-SDS below -1.65 (5th centile) was detected in 18 patients (22.2% of the whole cohort). Mean AMH-SDS values were -0.48 ± 1.43 SDS.

Among not irradiated patients, increasing CED values were associated with lower AMH-SDS (p 0.05), with the threshold of $7200 \text{ g}/\text{m}^2$ being the best discriminator between impaired and normal ovarian function (AUC: 0.75 on ROC analysis) and with an observed decrease of 0.14 AMH-SDS for each CED increase of $1 \text{ gr}/\text{m}^2$. In addition, pelvic irradiation played a detrimental role on ovarian reserve (p 0.0297).

At last, age at diagnosis below 10 years was associated with normal ovarian function in 100% of cases and with greater AMH values than those of patients diagnosed beyond 10 years ($p < 0.0001$), with an observed decrease of 0.11 AMH-SDS for each 1-year increase (p value=0.004).

Conclusions: In the present study we used an AMH-driven approach to identify the cut off of CED that best discriminates between women with diminished *versus* normal ovarian reserve ($7200 \text{ mg}/\text{m}^2$). This value is consistent with the threshold already reported in Literature ($8000 \text{ mg}/\text{m}^2$), beyond which the incidence of POI is increased. The harmony between these two values supports the reliability of age-standardized AMH as a tool for the earlier detection of ovarian impairment. In addition, our findings suggest that younger age at diagnosis plays a protective role on ovarian reserve.

P1-146

Reaching a definitive diagnosis of hypogonadotropic hypogonadism – experience of a multidisciplinary diagnostic service

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Introduction: Hypogonadotropic hypogonadism (HH) is a rare condition, where a definitive diagnosis is often hard to reach.

Objectives: To describe the clinical, biochemical and genetic findings in cases with suspected HH in the West of Scotland who were referred for genetic analysis between 2016 and 2020.

Methods: Information was collected on clinical assessment including family history, biochemical and molecular genetic analysis using a panel of 21 HH genes.

Results: Thirty cases (19 male, 11 female) were included in this study with a median age at genetic testing of 18.3 yrs (range, 1.8, 48.3). This cohort included 11 (37%) with Kallmann syndrome (KS) defined as anosmic HH, 14 (47%) with idiopathic HH with normosmia (nHH), 1 (3%) with uncertain sense of smell (uHH), 3 (10%) with multiple pituitary hormone deficiency (MPHD) and 1 (4%) with CHARGE syndrome. A positive family history related to HH was present in 9 (30%). Of the 22 that had neuroimaging, 5 (23%) had hypoplasia or agenesis of the olfactory system. Diagnostic biochemistry was available in 23/30 cases (77%) at the median age of 17.5 years (0.25, 35.4). The median basal and peak stimulated LH were $0.2 \text{ IU}/\text{L}$ (0.1, 4.3) and $1.7 \text{ IU}/\text{L}$ (0.2, 18.9), respectively. The median basal and peak stimulated FSH were $0.7 \text{ IU}/\text{L}$ (0.2, 6.7)

and 2.8IU/L (0.1, 12.1), respectively. The median basal testosterone was 0.5nmol/L (0.4, 10.3) in 12 male participants. In total, 19 gene variants were identified in 14/30 cases (47%); this included 10 variants of uncertain significance in 5 genes in 7 cases (six *FGFR1*, one *CHD7*, one *FGF8*, one *PROKR2* and one *SPRY4*), 4 likely-pathogenic variants in 3 genes in 4 cases (one *CHD7*, one *PROK2*, two *FGFR1*), 5 pathogenic in 4 cases (one each in *FGFR1*, *PROK2*, *ANOS1*, 2 *GNRHR*). Of these 14 cases, 7 were KS, 5 were nHH and there was one each of uHH and CHARGE syndrome. Of the 16 cases with no gene variants identified, 4 were KS, 9 were nHH and 3 were MPHD. There was no clear relationship between the presence of classic features of HH and the likelihood of detecting a gene variant.

Conclusions: Over 40% of patients with HH who had undergone targeted genetic analysis had a variant identified. A low threshold is required to suspect a diagnosis of HH even if classic features of HH do not exist.

P1-147

A pre-analytical challenge to determine estradiol in children: A monovette systematically causing increased estradiol-concentrations in LC-MS/MS analysis

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Introduction: In children, estradiol (E2) concentrations are 1000-times lower in comparison to their precursors, the androgens. Depending on sex, age, and pathology, plasma concentrations vary in a broad range. The sensitive and specific determination of E2 is a particular challenge in pediatric endocrinology. Here we report a female patient aged 12 6/12 years and Tanner stage B1 with a presumed diagnosis of ovarian insufficiency. She showed a very high E2 concentration of 296 pmol/L fitting with the age reference (ref. 10-430 pmol/L, 12-14 years) but not with the clinical diagnosis and Tanner B1. The aim of our study was to identify possible interfering factors.

Methods: First, E2 was determined by LC-MS/MS. Secondly, two new blood samples of the patient were collected independently in two different types of monovettes. One monovette was the same used beforehand (Kabe Labortechnik) and the other one typically preferred by our pediatric laboratory (Sarstedt). In a third approach, monovettes were broken down into their components (gel, pellets, and hole monovette). The components were incubated independently with either aqua dest. or strip-plasma for one week.

Results: On average, ten times higher E2 concentrations were determined in the patient using the Kabe monovette (average: 147.94 pmol/L, SD: 81.57, N=5) compared with the Sarstedt monovette (average: 15.13 pmol/L, SD: 6.86, N=3). Further on, an

unusual broad peak was noticed at the typical position of the E2 peak using the Kabe monovettes. After incubating each component of the monovettes, a similar wide peak could be identified after incubation with the gel of the Kabe monovette. Possible isomeric interference could be excluded by chromatographic separation of 17- α and 17- β -E2 into two separated peaks.

Conclusion: In addition to classic interfering factors like lipemia and haemolysis, monovettes are pre-analytical factors which need to be considered in the sensitive analysis of E2 via LC-MS/MS. Therefore, automated evaluation should not be used for E2 determination in LC-MS/MS. Paediatric hormonal measurements should involve pediatric endocrine validation to notice discrepancies.

P1-148

Central precocious puberty and sleep patterns in COVID-19 outbreak

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Background: epidemiological studies reported an increased incidence of central precocious puberty (CPP) during the last year compared to previous year. Confinement measures and consequent daily routine modifications applied to contain coronavirus infectious disease-19 (COVID-19) contagion have been proposed as a cause of this phenomenon. Our study aims in investigating changes in CPP rates in a tertiary paediatric endocrinology outpatient clinic of South Italy, where school closure and lockdown measures were particularly severe, compared to past year. Moreover, we evaluated sleep patterns and disturbances differences between girls with CPP and healthy controls paying attention to changes before and during lockdown.

Methods: CPP cases were retrospectively evaluated in the period from April 2020 to April 2021. Clinical and biochemical characteristics of lockdown cases were compared to those before lockdown from April 2019 to April 2020. Parents of girls diagnosed with CPP during lockdown and of matched healthy controls filled out a questionnaire about sleep disturbances (SDSC questionnaire) and sleep schedules.

Results: thirty-five girls were diagnosed with CPP during lockdown, whereas the previous year only 14 cases were registered. Clinical and biochemical characteristics did not differ between the two groups. A total of 72 parents-girls' pairs (35 CPP and 37 controls) completed the survey. Sleep disturbance rates did not differ between CPP and controls before lockdown (all $p > 0.05$). Conversely, during lockdown, parents of girls with CPP reported higher rates of sleep disturbs compared to controls: global score 31.4% versus 5.3% ($p = 0.005$), excessive somnolence (DES) 17.1% versus 2.6% ($p = 0.049$), sleep breathing disorders (SBD) 17.1% versus 2.6% ($p = 0.049$), and sleep-wake transition disorders (SWTD) 25.7% versus 2.63 ($p = 0.005$). No differences were found for disorders in initiating and maintaining sleep (DIMS), disorders of arousal (DOA), and sleep hyperidrosis (SH). Moreover, CPP

group showed significant higher rates in shifting toward later bedtime (40.3% vs 17.7%, respectively, $p=0.03$) during lockdown compared to controls. Conversely, total hours of sleep and smartphone exposure around bedtime did not differ significantly between the two groups.

Conclusions: our study confirms the observation of increased incidence of CPP after lockdown measures. Additionally, in our population, girls with CPP showed higher rates of sleep disturbances and later bedtime compared to controls. Puberty timing is a complex phenomenon and sleep hormones play a role in hypothalamus-pituitary-gonadal axis maturation. The causality link between sleep disturbances and CPP should be further investigated to gain knowledge in this association.

P1-149

QUERY by TELARQUIA: Has there been an increase due to the SARS-COV19 pandemic?

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Have a real increase in precocious and advanced puberty with COVID19? Retrospective observational analytical study in which we compared the incidence of first consultations made by early thelarchies between the months of March to December 2019 and between March and December 2020 at the Pediatric Endocrinology (PE) consultation in our hospital, and the increase in diagnosis of precocious puberty (PP) and advanced puberty (PA) in the cases evaluated for this reason, with the aim of demonstrating that the feeling that there has been in Primary Care as well as in the PD service about the increase in the incidence of these pathologies during confinement and the COVID season is real. 77 patients who consulted for early thelarchy in 2019 (group1) and 99 in 2020 (group2). first consultation, difference between chronological age and bone age, sex hormone values (FSH, LH and estradiol) in the first analysis, if a functional test was performed to study the gonadal axis (Procrin) and result of the same, abdominal ultrasound, if they had received stopping treatment, if they had had contact with disruptors, if they had gained at least 3kg in weight in the last 6 months and the final diagnosis given. Comparing both years, in 2020 there were 28% more first consultations by early thelarchies than, in 2019 ($p:0.0001$ average comparison). We therefore understand that there is a significant difference, observing a higher frequency of first consultations by early thelarchies in 2020 compared to 2019. In 2019 of the 77 consultations for precocious thelarchy, 18 were advanced puberty and 12 were precocious puberty, that is, 38.95% of the consultations for precocious thelarchy were diagnosed of an anticipation of physiological puberty; While in 2020 of the 99 consultations for this diagnosis, 35 were advanced puberty and 25 were precocious puberty, that is, of the total of patients with advanced thelarchies, 60.6% had an anticipation of normal puberty; which implies an OR of 1.55. 0.002 Student's t for samples.

We could say that in 2020 an acceleration of puberty has been seen regardless of age, increasing the incidence statistically

significantly in both PP and AP. But we can also observe that in 2020 there are more children who consult with a higher BMI and with an increase in weight gain in the last 6 months. This increase in weight could suggest a trigger effect due to an increase in fat mass and a greater number of advanced puberty.

P1-150

Androgen insensitivity without an androgen receptor mutation: results from a large cohort study

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Introduction: Androgen insensitivity syndrome (AIS) is a 46,XY difference of sex development (DSD) classically caused by mutations in the X-chromosomal androgen receptor (AR) gene. Nevertheless, in over 50% of individuals with clinical AIS no AR coding gene mutation can be found. We previously established an assay (apolipoprotein D (APOD) assay) that measures androgen dependent AR-activity in genital skin fibroblasts (GFs). Using this assay we identified a group of GFs with reduced AR function in the absence of an AR coding gene mutation, called AIS type II.

Objective: Investigation of the prevalence of AIS type II based on GFs derived from a large cohort of patients with DSD and clinically presumed AIS and further characterization of this group of AR mutation-negative AIS.

Methods: Assessment of AR function in GFs from individuals with clinical AIS but no AR coding gene mutation ($n=95$). AR mRNA and protein expression measurement in GFs with reduced AR function and male control GFs. DNA-methylation analysis on the AR promotor in GFs with reduced AR mRNA expression and male control GFs. Exome-sequencing of AIS type II GFs.

Results: 31 out of 95 GFs (33%) from individuals with clinical AIS but no mutation in the AR gene fell in the group AIS type II. Three of them (9.6%) showed normal AR mRNA but reduced AR protein expression levels, nine (29%) showed reduced AR mRNA and protein expression levels and 19 (61%) showed normal AR

mRNA and protein expression. Out of the nine GFs with reduced AR mRNA expression, four showed significantly higher AR promoter methylation levels explaining the reduced AR expression. Exome-sequencing of 26 AIS type II GF revealed in 12 cases likely pathogenic variants in known DSD-genes other than the AR and in 10 cases likely pathogenic variants in genes so far unrelated to DSD. In four cases no candidate genes were identified.

Conclusion: One third of individuals clinically diagnosed with AIS but without a mutation in the AR coding gene show a reduced expression and/or function of the AR (AIS type II). Exome sequencing of AIS type II GFs revealed both known and unknown candidate DSD-genes as potential cofactors of AR-activity. Two thirds of examined cases show a normal APOD induction. In these cases either transcriptional targets downstream of the AR could be affected or the underlying DSD diagnosis is not AIS due to insufficient specificity of the clinical and hormonal findings.

Fetal Endocrinology and Multisystem Disorders B

P1-151

Duration of Fasting Studies Required to Demonstrate a Cure for Patients with Focal Congenital Hyperinsulinism

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Introduction: Focal disease of the pancreas causing hyperinsulinism (FHI) has 2 essential characteristics 1) the inheritance of a paternally derived mutation in *ABCC8* or *KCNJ11* in conjunction with loss of a region of the maternal chromosome 11p13.1 and 2) the ability to be cured by resection of the focal lesion while sparing the majority of the pancreas. At the time of surgery the surgeon resects the focal lesion until clear margins are available. We perform a fasting study postoperatively to determine if the patient is cured or not. In our multidisciplinary team approach we terminate our fasting studies when either a plasma glucose is < 2.7mmol/L, beta-hydroxybutyrate (BOHB) is >1.7mmol/L or a max fasting duration appropriate for the patient's age has been reached. There is current debate as to how long one should fast an infant to demonstrate cure of FHI.

The Aim: of this study is to demonstrate the length of time to either hypoglycemia <2.7mmol/L or BOHB to >1.7mmol/L in order to prove cure in patients with FHI in whom surgery has been deemed successful at the time of frozen section.

Methods: We conducted a retrospective analysis on 36 patients with focal disease. Patients were divided into 3 groups. Group 1: those not cured, Group 2 those cured and fasted until glucose < 2.7mmol/L or BOHB >1.7mmol/L and group 3 those cured and fasted based on time.

Results: Group 1 N= 7, Group 2 N = 22 and Group 3 N= 7. The mean duration of fasting in: group 1 was 11.4 h with 5 fasting more than 9 hours and 4 fasting >12 h, Group 2 was 16.6 h (range 13 to

22h) with 8/22 patients fasting ≥18 hrs and Group 3 was 20.6 h (range 15-30 h) and 7/7 were >18 hours. Of the patients determined cured (group 2 and 3) the 9 hour glucose was above 3.88mmol/L in 26/29 patients whereas it was only >3.88mmol/L in 1 who was not cured. Extending fasting studies to 18-24 hours will add 0.37 to 0.62 extra days of hospitalization. In our case an average length of stay for cured focal patients is 22.1 days.

Conclusion: We recommend that fasting studies to demonstrate cure in patients with FHI be performed until either the glucose is <2.7mmol/L, the BOHB >1.7mmol/L or 18 hours for those <6m or 24 hours for those >6m, whichever comes first.

P1-152

Impact of gestational weight gain on methylation of imprinted genes in umbilical cord and its relationship with postnatal growth and metabolism

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Introduction: Imprinted genes are critical for placental function and normal fetal growth and development. Very little is known about the impact of maternal obesity on imprinted genes and their role in postnatal growth and metabolism.

Objectives: 1) To identify umbilical cord DNA methylation sites (CpG) associated with gestational weight gain (GWG); 2) to identify which of these CpGs lie within imprinting control regions (ICRs); and 3) to study the association of these CpGs with offspring's growth and metabolism.

Materials and Methods: A pilot study was conducted in 16 pregnant women with different degrees of GWG. The newborns were followed up from birth to 6 years of age. Umbilical cord DNA methylation was assessed using microarray Infinium Methylation EPICBeadChip (Illumina). Beta regression models (false discovery rate (FDR)<0.05 and odds ratio>1.5 or <0.67) were performed to identify the CpGs associated with GWG. The CpGs that lied within ICRs were selected and correlated with anthropometric and metabolic parameters of the offspring.

Results: 2773 differentially methylated CpG were identified, out of which 8 lied within ICRs. The top 5 CpGs, which annotated for *KCNQ1OT1*, *GNAS A/B*, *MEST*, *PLAGL1* and *FAM50B* (FDR<0.001 and odds ratio>1.03), were chosen for the study. The methylation of all these CpGs was positively correlated with GWG (r from 0.603 to 0.826; all p<0.02). The CpGs that annotated for *KCNQ1OT1* and *GNAS A/B* were negatively associated with the levels of glycated haemoglobin (HbA1C) and glucose in the offspring at 6 years of age (r=-0.610, p=0.016 and r=-0.705, p=0.003, respectively). The CpGs that annotated for *MEST* and *FAM50B* were negatively associated with visceral (renal) fat at 6 years of age (r = -0.627, p = 0.012 and r = -0.634, p = 0.011, respectively).

Finally, the CpG annotated for *PLAGL1* were associated with height and glucose at 6 years of age ($r = -0.661$ $p = 0.005$ and $r = -0.714$, $p = 0.004$, respectively).

Conclusions: This preliminary study suggests that excessive gestational weight gain can cause changes in DNA methylation of imprinted genes and thereby regulate postnatal growth and metabolism in the offspring.

P1-153

Different faces of minipuberty in preterm twin girls

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Background: minipuberty (MP) consists in a postnatal activation of hypothalamic-pituitary-gonadal (HPG) axis, which occurs physiologically in both sexes during the first months of life. FSH and LH peak between 1 and 3 months, stimulating sex hormones secretion. In preterm infants, MP might lead to a stronger and more protracted hormonal stimulation, even if specific literature data are limited and not univocal. Immaturity of the hypothalamic feedback has been suggested as a possible mechanism for this phenomenon, although its biological meaning is still unknown. We present a case of MP observed in a preterm girl, in comparison to her twin sister.

Case report: a girl born at 31 weeks of gestation presented with severe edema in the vulva and swelling labia major and minor, appeared at one month of life. She was the second twin of a mono-chorionic diamniotic pregnancy, born by cesarean section (Apgar scores 8-9) and adequate for gestational age (AGA). She was admitted to NICU for prematurity, mild distress respiratory syndrome and neonatal jaundice. She had no family history for precocious puberty and no personal history of any hormonal therapy.

Laboratory evaluations highlighted central activation of the HPG axis, with elevated LH (4.66 mUI/ml) and FSH (2.74 mIU/ml) and increased estradiol levels (1152.1 pmol/l). Adrenal steroidogenesis and serum electrolytes were within the normal range, thus excluding congenital adrenal hyperplasia. Thyroid function, prolactin, alpha-fetoprotein, and beta-human chorionic gonadotropin levels were normal. Pelvic ultrasonography and MRI showed increased uterine length (4.5 cm), endometrial thickness of 4 mm, enlarged ovaries with multiple follicles bilaterally and three ovarian cysts (measuring 8 mm, 16 mm and 9 mm of diameter, respectively). Brain imaging was unremarkable.

Repeated hormonal workup over the course of 6 months showed decreasing trend of gonadotropin and estradiol levels. Clinical and sonographic pubertal signs also spontaneously regressed over time.

The same hormonal evaluation was performed in her twin sister, displaying mildly elevated levels of FSH (3.23 mUI/ml), LH (2.23 mUI/ml) and estradiol (289.6 pmol/l), without evidence of pubertal clinical signs.

Conclusion: preterm birth does not seem to influence the timing of MP occurrence. The amplitude of postnatal HPG activation might be exacerbated in preterm babies, with evidence of puberty changes in clinical, laboratory and sonography data. The spontaneous resolution, together with the exclusion of other causes, is suggestive for MP of infancy.

P1-154

The Evaluation of Accuracy and Effectiveness of Newborn Screening for Congenital Adrenal Hyperplasia in Lithuania

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Introduction: The main reason for Newborn screening (NBS) for congenital adrenal hyperplasia (CAH) is to prevent adrenal insufficiency that can lead to life-threatening conditions. On the other hand, screening programmes are not always sensitive and effective enough to detect the disease. We aimed to evaluate the specificity, sensitivity and efficiency of the national NBS for CAH in Lithuania.

Methods: retrospective study was performed on the data of 88 patients with CAH from 1989 to 2020. Patients with confirmed CAH were divided into two groups: 1) 75 patients diagnosed before NBS: 52 cases with salt-wasting (SW), 21 with simple virilising (SV) and 2 with non-classical (NC) form; 2) 13 patients diagnosed with NBS: 12 cases with SW and 1 case with SV form. For the evaluation of NBS effectiveness, data of only male infants with salt-wasting CAH were analyzed ($n=36$, 25 unscreened and 9 screened). Data on gestational age, birth weight, weight, symptoms, and laboratory tests (serum potassium and sodium levels) on the day of diagnosis, were analyzed.

Results: The 158 482 neonates were screened for CAH from 2015 to 2020 in Lithuania. After the establishment of NBS since 2015, CAH was confirmed in 13 patients (12 SW, 1 – SV form), no false negative cases were found. The sensitivity and specificity of NBS programme were 100%. There were no significant differences between unscreened and screened male infant groups in terms of age at diagnosis (19.13 ± 7.156 d. vs. 15.44 ± 7.79 d., $p=0.189$), serum potassium (7.7 ± 1.5 mmol/l vs. 6.89 ± 1.5 mmol/l, $p=0.180$) and serum sodium (124.5 ± 9.7 mmol/l vs. 126.31 ± 8.99 mmol/l, $p=0.64$) levels. Significant differences were found in weight at diagnosis between the groups (-1.67 ± 1.12 SDS vs. 0.046 ± 1.01 SDS of unscreened and screened patients respectively, $p=0.001$). Eight (32%) of 25 unscreened patients and 2 (22.2%) of 9 screened patients were treated in the Neonatal intensive care unit ($p=0.58$).

Conclusion: During NBS for CAH, the sensitivity and specificity of the programme increased to 100% and there were no false-negative cases. Weight loss was significantly lower and the weight SDS at diagnosis was significantly higher in the group of screened patients.

P1-155

Pediatric Inflammatory Multisystemic Syndrome in Brazil: sociodemographic characteristics and risk factors to death

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Background: A virus initially considered benign in this age group, SARS-COV-2 has recently been associated with Pediatric Multisystemic Inflammatory Syndrome (PIMS), temporarily associated with COVID-19, a syndrome whose diagnostic determination has a vital relevance since it imposes unfavorable outcomes. This study aims to describe the sociodemographic characteristics of PIMS in Brazil and the factors associated with death by this syndrome.

Methods: This research is an observational and retrospective cohort study of cases of PIMS associated with Covid-19 in the Brazilian population between 04/01/2020 and 04/17/2021.

Data from the Ministry of Health's epidemiological bulletin, obtained from the compulsory notifications from PIMS and Covid-19 carried out up to the 15th epidemiological week of 2021, were used. The analyses were descriptive through absolute and relative frequencies, and also relative risks of PIMS cases were calculated between the exposure variables (age groups, genders, and regions of the Brazilian territory) and the outcome (deaths by PIMS). The work was carried out at the significance level of 5% in Stata 16.0 package.

Results: Between 04/01/2020 and 04/17/2021 (15th epidemiological of 2021), 903 cases of PIMS associated with Covid-19 were notified in Brazil, of which, the largest part (55.26%) were male, between 0 and 4 years old (45.29%), from the Southeast region (38.76%). The deaths were higher in the female gender, between 0 and 4 years old (47.54%) and in the Southeast region (34.43%). It was identified that the risk of death by PIMS related to Covid-19 is 5.29 (CI= 2.83; 9.87 and P-value= <0.001) times higher in adolescents from 15-19 years old than in other age groups when compared to 0-4 years old children. Also, the residency in North region was as risk factor to death (RR= 3.72, IC= 1.29; 10.74 e P-value= 0.008).

Conclusion: In this study, despite the numbers showing more deaths from zero to 4 years old, the risk for teenagers is notably higher. In addition, Brazil's North region is a risk factor that reaffirms social inequality and poor access to health. Understanding PIMS's epidemiology in the age group is essential for planning public health policies and raising public awareness to avoid tragic outcomes in Brazil, which already suffers from COVID-19.

P1-156

Molecular and phenotypic profile of Alstrom syndrome in Chinese patients: results from a Chinese cohort

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Introduction: Alstrom syndrome, inherited in autosomal-recessive manner, is a complex multi-system disease including obesity, sensorineural hearing loss, retinal dystrophy, cardiomyopathy, type 2 diabetes mellitus, and multiple organ fibrosis. ALMS1 is the defective protein of Alstrom syndrome. The protein is located in the basal body of the primary cilia and involved in ciliary function. Large cohorts of Alstrom syndrome lack around the world, especially in East Asia.

Methods: 50 patients were included in this study, aged from 0.47 years to 21.66 years old. Detail phenotypic data and genetic data were obtained from all affected individuals. Truncated mutations were confirmed in all patients through genetic sequencing with Alstrom syndrome. And all Chinese patients reported previously were reviewed.

Results: 82% of the patients with Alstrom syndrome in our cohort were under 10 age years old, in which 37% were under 5 and 45% were during 5-10. Most of the patients in China were from East China, Centra China and South China. 61 different ALMS1 variants (59 truncating and 2 exon deletion) in 50 patients from 47 different families were confirmed, including 22 novel variants. The variant c.2090C>A was the most frequency variants in Chinese cohort. Retinal dystrophy was observed in all patients. Obesity and hepatic symptom were shown in over 50% of the patients.

Conclusions: This is the largest cohort of Chinese patients with Alstrom syndrome and it is the youngest cohort in the world. This study enriched the spectrum of genotypes and phenotypes.

P1-157

Endocrine Monitoring and Outcome After Therapy in Childhood Survivors of Central Nervous System Tumours

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Background: Childhood cancer survivors (CCS) are at increased risk of endocrinopathies; as a consequence of cranial/craniospinal radiotherapy and alkylating agents. Hypothalamic-pituitary dysfunction, thyroid dysfunction and gonadal failure are frequently seen.

Aim: To explore the endocrine monitoring following completion of treatment for central nervous system (CNS) tumours within a regional paediatric oncology service.

Methods: Children who received radiotherapy as part of treatment of CNS tumours, 2004-2019, were included. Records of growth hormone (GH) stimulation tests, thyroid function tests (TFT), ACTH stimulation tests, gonadotrophins, oestradiol/AMH (girls) and testosterone (boys) were collected.

Results: Of 100 CCS (38 treated for medulloblastoma, 62 for other CNS tumours), 43 (43%, 20 males) completed treatment successfully [19 (50%) for medulloblastoma and 24 (39%) for other CNS tumours ($p=0.303$)]. Median age at diagnosis was 7.6 years (0.69-16.28). Median time since completion of treatment was 6.25 years (1.25-14.41). Median dose of total radiotherapy received was 5540cGy (4420-8000) for medulloblastoma and 5400cGy (50-6000) for other CNS tumours ($p=0.002$). GH stimulation test was performed in 33/43 (76.7%) at a median time of 1.29 years (0.08-6.5) post-treatment. TFT were performed in 36/43 (83.7%), at a median time of 1.44 years (0.08-6.92) post-treatment. ACTH stimulation test was performed in 33/43 (76.7%), at a median time of 2.25 years (0.67-8.75) post-treatment. Gonadotrophins were tested in 33/43 (76.7%) children, at a median time of 1.69 years (0.14-6.89) post-treatment. Gonadal function was tested, in 24/43 (55.81%) children [15/19 (78.9%) with medulloblastoma and in 9/24 (37.5%) with other CNS tumours ($p=0.013$)], at a median time of 3.02 years (0.14-6.62) post-treatment [2.9 years (0.1-6.6) and 4.9 years (1.0-6.6) for medulloblastoma and other tumours respectively ($p=0.022$)]. GH deficiency was diagnosed in all 14/14 (100%) children tested with medulloblastoma and 16/19 (84.2%) with other CNS tumours ($p=0.887$). Hypothyroidism was seen in 11/16 (68.8%) children with medulloblastoma and in 5/20 (25%) with other CNS tumours ($p=0.018$). Inadequate cortisol response was noted in 1/15 (6.7%) for medulloblastoma and 4/19 (21.1%) for others ($p=0.577$). Hypogonadism was diagnosed in 2/16 (12.5%) children for medulloblastoma and 8/17 (47.1%) with other CNS tumours ($p=0.057$).

Conclusions: The majority of children had appropriate monitoring for endocrine sequelae following treatment of CNS tumours, however, there was variability in those endocrine axes included and timing of the initial endocrine evaluation with potential clinical compromise resulting from either delay or missing investigations. A systematic approach to monitoring would ensure timely management and treatment of all endocrine complications.

P1-158

Low adrenal androgen levels in patients with and without primary adrenal insufficiency in APECED (APS1)

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Objective: Treatment of primary adrenal insufficiency (PAI) is often challenging in patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED or APS1). In addition, electrolyte levels often fluctuate in APECED patients. This study aimed to describe adrenal steroid and electrolyte levels in patients with APECED.

Design: This cross-sectional study included 43 Finnish patients with APECED (27 females, 7 under 18 years of age) and 68 age- and gender-matched healthy adult control subjects (43 females). We determined serum adrenal steroids, plasma renin, sodium, potassium, and creatinine concentrations, as well as blood pressure in all study participants. Mann-Whitney U-test was used to determine differences between the groups.

Results: Patients' median age was 39.1 years (range 7.0-70.1); 35 (81%) had PAI. Patients with PAI had, in comparison with non-PAI patients, significantly lower serum cortisol, cortisone, aldosterone, DHEA, androstenedione, and cortisol-to-cortisone ratio. Plasma renin and electrolyte levels did not differ between PAI and non-PAI patients. When we compared adults with PAI with adult control subjects, we found that serum concentrations of all adrenal steroids, plasma potassium ($p<0.001$), and cortisol-to-cortisone ratio ($p=0.014$) were significantly lower in PAI patients. Plasma sodium ($p<0.001$) and creatinine ($p=0.003$) were significantly higher in patients with PAI compared with controls. When we compared adult non-PAI patients ($n=6$) with adult controls, we found that concentrations of cortisone [median (range); 46.0 (2.3-72.5) vs 66.5 (40.0-89.0) nmol/l, $p=0.004$], DHEA [6.0 (0.6-20.2) vs 17.3 (3.1-61.7) nmol/l, $p=0.011$], and potassium [3.5 (3.0-4.0) vs 3.7 (3.1-4.3) mmol/l, $p=0.036$] were lower in patients. Their plasma creatinine was also higher ($p=0.013$) compared with controls. Three non-PAI patients with low levels of DHEA and/or DHEAS had autoantibodies against 21-hydroxylase at the age of 23.0-62.7 years, and none had antibodies against side-chain cleavage enzyme. Blood pressure levels did not differ between any groups.

Conclusions: Concentrations of adrenal steroids and electrolytes differed between PAI and non-PAI patients but also between non-PAI patients and healthy controls. We found significantly lower concentrations of serum DHEA and plasma potassium in patients without PAI in comparison with the controls. Low adrenal androgens associated with autoantibodies against 21-hydroxylase in three patients without PAI, possibly reflect eventual gradual development of adrenal insufficiency.

Clinical features and body mineral density in Italian patients with rapid onset obesity with hypoventilation, hypothalamic dysfunction, autonomic dysregulation and neural tumor (ROHHADNET): a single center observational study

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Background: ROHHAD (rapid-onset obesity with hypoventilation, hypothalamic dysfunction, autonomic dysregulation) syndrome is a rare and underdiagnosed disease with high mortality rate. When a neural crest tumor (NET) is detected (56% of patients) the acronym used is ROHHADNET.

Aim: To analyze the relationship between clinical variables, hypothalamic-pituitary disorders, DXA parameters and neural tumors, in ROHHADNET patients.

Methods: We included individuals with ROHHAD(NET), who were followed at our centre (Pediatric Endocrine Unit, IRCCS Istituto Giannina Gaslini, Genoa, Italy) between January 2008 and December 2020 (median follow up 7.82years, 4.12-8.80y). They were selected by clinical criteria, after excluding Prader-Willi Syndrome and Congenital Central Hypoventilation Syndrome. Medical history, anthropometric, hormonal and densitometric data were collected for the two groups of patients (ROHHAD and ROHHADNET) and analyzed.

Results: In our cohort of 14 patients (9 females - 64,3%), NET were reported in 4 females (28,5%). Median age at rapid weight gain onset was 3 years in both groups (2.5 – 3 vs 1.5 – 4). Median BMI SDS at diagnosis was +4.13 vs +4.6. Seven patients have pubertal disorder (either precocious puberty or central hypogonadism), 4 patients with NET(57,1%) and 3 without NET(42,9%)(p=0.2). Nine patients have GHD, 4 with NET(44,4%) and 5 without NET(p=0.22). Ten patients have central hypothyroidism, 2 with NET (20%) and 8 without NET(p=0.52). Eight patients have adrenal insufficiency, 2 with NET (25%) and 6 without NET(p=1.00). Prolactin level was elevated in all patients with NET, and 8 patients without NET. Five patients have strabismus, 3 patients with NET (60%), and 2 without NET(p=0.1). Nine patients have autonomic dysfunction, 1 with NET (11,1%), and 8 without NET (p=0.1). Back to data from birth, there was no difference in birth length between the two groups, while patients with NET showed a lower median birth weight SDS(-0,26 vs 0,84,p=0.06). Regarding DXA parameters, there was no difference in BMD SDS total body between patients with NET and without NET, while patients with NET showed a higher BMD SDS L1-L4(1.55 vs 0.7) (p=0.06).

Conclusion: Our patients with ROHHAD who developed NET are females (100%), they tend to have a lower birth weight, higher

BMD SDS L1-L4, and greater incidence of strabismus and autonomic dysfunction. None of these associations are significant because of low numbers. Multicentric cohorts need to be analyzed in order to better understand the clinical characteristics of this rare and severe disease.

Congenital Central Hypothyroidism (CeH) due to a new variant in IGSF1 gene: clinical case of 2 siblings

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Congenital Central Hypothyroidism (CeH) is a rare and heterogeneous disease that can be part of a combined pituitary hormone deficit (CPHD) condition. The immunoglobulin superfamily member 1 (*IGSF1*) is the gene more frequently involved in these inherited forms and responsible for the so called X-linked *IGSF1* deficiency syndrome, characterized by an estimated incidence of 1:100.000. The main features are CeH, delayed/disharmonic pubertal development, macroorchidism, variable prolactin and occasionally transient/partial GH deficiencies. Here we report the case of two siblings affected by this peculiar form of CeH. The younger brother was referred to our center at 7 years of age with a previous diagnosis of CeH and treated with Levothyroxine (L-T4). He presented suggestive phenotypic features including a relative macrocrania, disharmonic growth, BMI of 21 kg/mq (+1.55SDS), 3-4 cc testicles (+1.3-2.2SDS) with infant penis. Blood tests showed an inhibited TSH with normal FT4 values (1.02 ng/dl, vn 0.93-1.7 ng/dl) on treatment with 1.79 mcg/kg/day L-T4; testosterone and basal gonadotropins were compatible with pre-pubertal stage. IGF1 and prolactin values resulted within normal range. Genetic analysis for CeH-related genes revealed the presence of a p.T614A (c.1804A>G) hemizygote genetic variant on exon 12 of *IGSF1* gene. This is a newly described allelic variant of uncertain significance (VUS) inherited from the mother. The older brother was evaluated at our center at the age of 8. He had a BMI of 20.8 kg/mq (1.27 SDS), 4-5 cc testicles (+2.2-2.8 SDS) with infantile penis. Blood tests showed: TSH 1.98 mU/L, FT4 0.96 ng/dl (vn 0.93-1.7 ng/dl), prolactin and IGF-1 within normal limits, basal gonadotropins and testosterone values as in pre-pubertal stage. The TRH test documented a valid response in TSH and FT4 values after specific stimulus. Brain MRI was normal. After the discharge, he presented persistently low FT4 levels, therefore L-T4 treatment was started at a dose of 1.6 mcg/kg/day. The therapy was progressively increased (up to 2 mcg/kg/day) maintaining free hormones in the upper part of the reference range.

Patients with CeCH typically present with mild symptoms and biochemical diagnosis can be challenging. We advise genetic evaluation of *IGSF1* gene in all patients with CeH of unknown cause especially in presence of a typical X-linked inheritance and/or peculiar clinical signs such as macrocrania and/or macroorchidism. Indeed, genetic analysis may allow an early diagnosis and a prompt therapeutic approach in order to avoid possible sequelae of untreated CeH.

Growth B

P1-161

Continued Safety and Efficacy of Weekly Lonaepsomatropin (TransCon hGH) for up to Two Years in Children with Growth Hormone Deficiency (GHD)

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Lonaepsomatropin (TransCon hGH) is an investigational once-weekly prodrug of somatropin for the treatment of GHD. Previous trials in treatment-naïve (52-week heiGHt Trial) and treatment-experienced children (26-week fliGHt Trial) have reported the efficacy and safety of lonaepsomatropin.

Subjects were eligible to enter the open-label extension enliGHten Trial, which continues to evaluate weekly lonaepsomatropin in pediatric GHD. In heiGHt, treatment-naïve subjects received lonaepsomatropin (Group A; vial/syringe) or daily somatropin (Group B; pen device). In fliGHt, treatment-experienced subjects switched to lonaepsomatropin from daily somatropin (Group C; vial/syringe). Lonaepsomatropin was administered at a starting dose of 0.24 mg hGH/kg/wk. Upon entry into enliGHten, all subjects received lonaepsomatropin (vial/syringe), and switched to TransCon hGH Auto-Injector pending regional availability. A total of 298 (of 303 eligible) subjects continued into enliGHten (A: n=103; B: n=55; C: n=140). The mean dose remained approximately 0.24 mg hGH/kg/wk for Group A/B at Week 104 and was 0.20 mg hGH/kg/wk for Group C at Week 78.

Subjects starting heiGHt on daily somatropin who switched to lonaepsomatropin continued to approach their average parental height, with height standard deviation score (SDS) improving from -3.0 at baseline to -1.52 at Week 104. Subjects from the fliGHt Trial also continued to approach their average parental height,

with height SDS improving from -1.42 at fliGHt baseline to -0.69 at Week 78. Observed Mean annualized height velocity (AHV) at Week 78 was 8.4 cm/year. heiGHt subjects starting lonaepsomatropin continued to approach their average parental height, with height SDS improving from -2.89 at baseline to -1.37 at Week 104.

As of the data cut (01 June 2020), 5 subjects have met or exceeded their target height and 11 subjects have grown to within 2 cm of their target height.

Mean (SD) average IGF-1 SDS remained stable and generally within the expected range for all groups (Week 104, A:0.95 [1.22], B:1.04 [1.25]; Week 78, C:1.81 [1.08]). Across all phase 3 trials, lonaepsomatropin produced a dose linear IGF-1 response. With lonaepsomatropin treatment, the adverse event (AE) profile remained consistent with what was observed in the parent trials, with no new safety signals, comparable tolerability, and a mean body mass index (BMI) SDS approaching zero.

Across the broad population of the phase 3 program, subjects treated with lonaepsomatropin for up to 2 years continued to approach their average parental height, with a safety profile comparable to daily somatropin, including a similar AE profile, tolerability, and stable BMI.

P1-162

Evaluation of growth patterns from the Edinburgh and Gothenburg cohorts by the QEPS model

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Background: The QEPS-growth-model, developed and validated in GrowUpGothenburg cohorts, used for developing growth references and investigating healthy/pathological growth, lacks external validation from other longitudinal cohorts of healthy individuals.

Objective: To investigate if the QEPS-model fits the longitudinal Edinburgh growth study of another design than GrowUpGothenburg cohorts. To compare growth patterns in two longitudinal growth cohorts born in mid-1970s in North-Western Europe.

Methods: Longitudinal growth data was obtained from the Edinburgh and the GrowUp1974Gothenburg cohorts. The QEPS-model was used to describe length/height from birth to adult height with confidence intervals and multivariate regression was performed to estimate the contribution of different QEPS-functions to adult height.

Results: The main QEPS-height estimates (Emax/Qmax/Pmax) had confidence intervals of 1.1-2.1cm in the Edinburgh cohort compared to 1.9-4.3cm in the Gothenburg group. Despite

2.8cm shorter stature (due to less QE-function growth) in the Scottish cohort, the growth patterns were similar. Timing of pubertal growth, showed no statistical differences between the study groups (Table 1).

A. Gothenburg cohort, girls (n1165)   Edinburgh cohort, girls (n68)

Variable	Mean Gothenburg	Mean Edinburgh	Difference	p-value
E _{max} (cm)	62.85	61.40	1.45	<.0001
Q _{max} (cm)	97.59	96.21	1.38	0.14
AgeP5% ¹ (years)	9.87	9.97	0.10	0.49
Age at PHV(years)	11.84	11.92	-0.08	0.61
P _{max} (cm)	12.80	12.90	-0.10	0.83
Pubertal height gain(cm)	26.37	25.80	0.57	0.24
T _{max} ² (cm)	167.26	164.44	2.82	<.0001

B. Gothenburg cohort, boys (n1174)   Edinburgh cohort, boys (n89)

Variable	Mean Gothenburg	Mean Edinburgh	Difference	p-value
E _{max} (cm)	65.07	63.95	1.12	<.0001
Q _{max} (cm)	104.05	102.26	1.79	0.042
AgeP5% ¹ (years)	11.82	11.98	-0.16	0.13
Age at PHV(years)	13.69	13.86	-0.17	0.12
P _{max} (cm)	17.38	16.98	0.40	0.31
Pubertal height gain(cm)	28.97	28.09	0.88	0.026
T _{max} ² (cm)	180.53	177.66	2.87	<.0001

1=Age at onset of pubertal growth. 2=Calculated adult height by QEPS.

The contribution to adult height (percentage explained variance) from QEPS-functions was similar (Table 2).

	E _{max}	E _{max} Q _{max}	E _{max} Q _{max} P _{max}	E _{max} Q _{max} P _{max} AgeP50% ¹
Girls Gothenburg	12.3	67.7	86.5	99.5
Girls Edinburgh	4.9	58.9	77.9	98.4
Boys Gothenburg	9.0	69.7	89.9	99.5
Boys Edinburgh	11.8	66.9	91.1	99.5

1=Age at 50% of the pubertal growth.

Conclusion: The QEPS-model now validated for the first time in another longitudinal study of healthy individuals, fitted the Edinburgh cohort well, with high accuracy and narrow confidence intervals indicating high precision. Both cohorts born in mid-1970s showed for both sexes similar growth patterns, especially for pubertal growth.

P1-163

The etiology of extreme tall stature above +3 SDS in a screened Finnish population

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Background: Most comprehensive guidelines on tall stature suggest that extremely tall children (defined as height above +3 SDS) should be referred to specialized health care for comprehensive diagnostic work-up. However, currently the etiology of tall stature is poorly characterized and no systematic studies focusing on extreme tall stature exist.

Methods: We identified all subjects with height above +3 SDS after the age of three years from the Helsinki University Hospital district that is subjected to growth monitoring and screening rules. The district covers a population of 1.2 million with a yearly birth-rate of approximately 13500. Subjects born prior to 1990 or subjects with missing or erroneous data were excluded. We report the diagnoses underlying extreme tall stature and describe auxological clues and clinical features indicative of underlying growth disorders.

Results: We identified 424 extremely tall subjects that fulfilled all our inclusion criteria. Extreme tall stature was equally frequent in females (n=214) and males (n=210). A pathological cause for tall stature (i.e. primary or secondary growth disorder) was diagnosed in 61 patients: in 17% of the girls and 12% of the boys (P=NS). Secondary causes were diagnosed in 42 (10%) patients and the two most frequent secondary diagnoses, premature adrenarche (n=16) and central precocious puberty (n=11) were more frequent in girls. Primary causes for tall stature were diagnosed in 19 (4%) patients: Marfan syndrome (n=10) was the most common primary cause, followed by Sotos syndrome (n=5). Overall, the most frequent diagnosis was idiopathic tall stature (ITS) diagnosed in 363 (86%) subjects, 141 of whom had a tall parent (parental height above 2 SDS). Features associated with syndromic tall stature (i.e. dysmorphic feature or neurodevelopmental disorder) were noted in almost all patients with a primary cause (95%) and were common among subjects with ITS (29%). The probability of primary growth disorders increased with increasing degree of tall stature. Height SDS cut-off of +3.7 SDS resulted in 81% sensitivity and 63% specificity in detecting a syndromic growth disorder, with a positive likelihood ratio of 2.2 and a negative likelihood ratio of 0.30.

Conclusions: A considerable proportion of extremely tall children have an underlying pathological cause. Syndromic causes were more frequent in subjects with greater height SDS. Clinical features related to syndromic causes of tall stature were surprisingly frequent in subjects with ITS. Our results support comprehensive diagnostic work-up in extremely tall children.

P1-164

Long-term efficacy and safety of rhGH in children with SHOX deficiency: preliminary data of a national Italian survey (on behalf of ISPED Study Group on Growth Factors and Puberty)

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Background: The phenotypic spectrum of short stature homeobox-containing gene deficiency disorders (SHOX-D) ranges from non-specific short stature to Leri-Weill dyschondrosteosis. Current guidelines support rhGH in SHOX-D children, but long-term data are still lacking. Moreover, no correlation has been established yet between the severity of phenotype, including the response to rhGH, and the underlying SHOX pathogenic variant.

Aims: To evaluate long-term efficacy and safety of rhGH in children with SHOX-D and to identify potential predictive factors influencing response to rhGH therapy.

Methods: This is an Italian multicentric, observational study collecting anamnestic, anthropometric [height SDS (H-SDS), arm span/height ratio (AS/H), sitting height/height ratio (S/H), pubertal status, growth velocity (GV) SDS, target height (TH)], clinical (Rappold score), instrumental (bone age) and therapeutic data (rhGH dose, side effects) in children and adolescents with a genetic confirmation of SHOX-D treated on rhGH. Data were collected at the beginning of rhGH (T0), yearly during the first 4 years of rhGH (T1, T2, T3, T4) and at final height (T5), when available. Statistical analysis was carried out on STATISTICA (StatSoft Inc, Tulsa, OK, USA).

Results: 67 SHOX-D children (93% Caucasian, 85% prepubertal) started rhGH (initial dose 0.24±0.04 mg/kg/week) at a mean age of 8.27±3.06 years. During rhGH (mean follow-up 6.64±1.47 years), H-SDS and GV SDS improved significantly (H-SDS: T0 -2.46±0.66, T1 -1.97±0.66, T2 -1.70±0.74, T3 -1.52±0.55,

T4 -1.47±0.49, T5 -1.72±0.60, X^2 64.54, $p < 0.05$ and GV SDS: T0 -1.04±1.87, T1 2.02±1.99, T2 1.37±2.39, T3 1.27±1.67, T4 0.76±2.72, X^2 43.51, $p < 0.05$) without changes in AS/H ratio (X^2 1.02, p 0.90), S/H ratio (X^2 7.61, p 0.17) and Rappold score (X^2 2.80, p 0.59). Mean H-SDS gain at T5 vs. T0 was +0.96±0.80. H-SDS at T4 positively correlated with H-SDS at T0 (r 0.64, $p < 0.05$) and H-SDS at T5 with TH-SDS (r 0.52, $p < 0.05$). No differences in clinical and therapeutic data were detected between patients carrying mutations involving enhancers (35/67) and ones with no-sense and missense mutations in SHOX gene, both at the beginning of rhGH and along follow-up. No adverse effects were reported apart from transient impaired glucose metabolism (2/67 cases) and transient headache (1 case).

Conclusions: Our preliminary data confirm the efficacy and safety of rhGH in SHOX-D children. Besides wide phenotypic spectrum, all SHOX-D genotypes seem to adequately respond to rhGH.

P1-165

Effects of age at start growth hormone treatment in children with Prader-Willi syndrome: The earlier the better?

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Context: Clinical findings characterizing PWS are muscular hypotonia, abnormal body composition, developmental delay, behavioral problems, hyperphagia with obesity when food intake is not restricted and short stature. Endocrine problems are described, like hypogonadism, hypothyroidism and adrenal insufficiency and growth hormone (GH) deficiency. Hypothalamic dysfunction may be responsible for many features of PWS. Randomized controlled studies showed that GH treatment in children with PWS improves linear growth, body composition, bone mineral density, lipid profiles, cognition and physical strength. Over the years, the age at start of GH treatment has become younger. Studies evaluating the long-term effects and safety of starting GH during infancy versus at later age are very limited.

Objective: To investigate whether the age at start of GH treatment is associated with body composition, anthropometric parameters, cognitive functioning and scoliosis after 8 years of GH and to determine the safety of starting GH treatment in the first year of life.

Methods: Prospective study in 76* children with PWS, who used GH during 8 years and started GH before the age of 5. DXA-scans, X-rays, IQ-tests (WISC) and anthropometric measurements were annually performed and blood samples were analysed.

Results: 20 children started GH between 0-1 years (group A), 39 between 1-3 years (group B) and 17 between 3-5 years (group C). There were no differences in gender or genetic subtype between

the groups. At GH start, the older children had a higher weight ($p<0.001$) and a higher fat percentage ($p=0.016$). After 8 years of GH treatment, group A tended to have the lowest fat mass % SDS and trunk fat/peripheral fat ratio ($p=0.072$ and $p=0.057$, resp.). Median (IQR) estimated total IQ in groups A to C was 74.0 (69.4;81.0), 68.2 (59.5;80.5) and 59.4 (50.7;87.8), resp. ($p=0.25$). No differences were found on Cobb angle of the spine or metabolic parameters.

Conclusion: Starting GH in the first year of life was, after 8 years of treatment, tended to be associated with a better body composition. There were no safety issues. In children with PWS it is, therefore, beneficial to start GH treatment as early as possible, preferably during the first year of life.

*7 visits still coming up in the next weeks.

P1-166

The BoneXpert adult height prediction method outperforms the Bayley and Pinneau method in tall male adolescents

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Background and Aim: Adult height predictions by the manual Bayley and Pinneau (BP) method in tall boys have shown large confidence intervals up to a bone age of 15 years. The adult height (AH) BoneXpert prediction method, which is based on an automated bone age reading, has not been evaluated in tall adolescents. We therefore compared the bias between the manual BP method and the BoneXpert (BE) method in tall male Flemish adolescents.

Patients and Method: In 20 untreated young adult (age > 19 years) men, who had been evaluated for non-pathological tall (height SDS > 2) stature during adolescence at three Flemish University hospitals, AH was obtained by a recent measurement at the hospital or by self-measurement. X-rays of the left hand and wrist, which had been obtained digitally at initial evaluation, were scored again using the Greulich and Pyle atlas by the same experienced examiner (JDS) as well as by the BE software (version 3.0). AH was compared with the BP and BE AH (version 2.23) height prediction methods.

Results: At initial assessment, standing height SDS ranged between 2 and 5.2 (median 3.0). Chronological age varied between 11.0 and 16.0 years (median 13.3 years), while GP bone age and BE bone age varied between 12 and 17 and 11.84 and 16.76 years respectively, resulting in a non-significant (median (range)) difference of 0.05 (-0.83 and 0.79) years. BE advancement ranged between -1.2 and 1.9 years (median 0.43 years). Measured AH varied between 191 and 208 cm (median 197 cm) and correlated significantly with the BP ($r = 0.582$; $p = 0.007$) and the BE ($r = 0.774$; $p < 0.0005$) AH predictions. Bias was +1.8 cm for the BP method and -0.3 cm for BE method, while the limits of agreement were respectively -6.9 and +10.4 cm and -5.5 and +4.9 cm. The BE bias was not significant correlated with age, bone age, bone age

advancement and height SDS at the moment of prediction, while the BP bias correlated negatively with age ($r = -0.462$; $p < 0.05$) and bone age ($r = -0.609$; $p < 0.0005$).

Conclusion: In tall adolescent males aged between 11 to 16 years and with moderate bone age advancement, the BE AH prediction method performs better than the classic BP method, given its higher correlation with AH, smaller limits of agreement and lower bias.

P1-167

Sex differences in growth response to GH treatment: more prepubertal and less pubertal gain in girls diagnosed with IGHD, ISS, SGA. Analysis of data from GH-SAFETY-database, including all children treated with rhGH- 1986-2009 in Sweden, in National-GH-Registry and rhGH-clinical-trials

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Background: Due to fewer girls than boys being GH-treated, after 50yrs the knowledge about sex-differences in both GH-response and GH-responsiveness before and during puberty remains limited.

Aim: To describe factors explaining growth response to GH-treatment, separately in girls and boys from GHstart to adult height (AH).

Methods: Children diagnosed with IGHD/ISS/SGA from GH-SAFETY-database¹.

Complete data was required: gestational age (GA) ≥ 32 weeks; birth-size > -4 SDS²; from birth-to-AH longitudinal heights/weights, pubertal stage (B2/testis ≥ 4 ml); mid-parental-height (MPH); GH_{max}AITT/12-24h-GHprofile; rhGHstart ≥ 3 yrs; available rhGH-dose (μ g/kg/day).

Growth-response outcomes were: change vs population³ (Δ height_{SDS}), vs parents (DiffH-MPH_{SDS}) for prepubertal 1styr, 2yr < prepubertal (GHstart-to-last-prepubertal visit using prepubertal reference), pubertal (last-prepubertal visit-to-AH using 18yrs reference), and total (GHstart-to-AH) GH-treatment periods. Fisher's non-parametric permutation-test and linear regression was applied.

Results: Girls, compared to boys of similar GA/birth-size, grew less during infancy, resulting in more pre-treatment deficit to both parents and population. Girls responded, on higher GH-doses, with more prepubertal 1st-growth and more prepubertal growth. During puberty, on similar GH-doses, mean Δ height_{SDS} was reduced for girls while maintained in boys until AH. Thus, the total gain, on similar GH-doses, became similar for girls vs boys.

Birth/infancy	Boys=420 Mean(SD)	Girls=184 Mean(SD)	p-value
BirthLength _{SDS}	-1.60(1.14)	-1.70(1.15)	0.31
BirthWeight _{SDS}	-1.06(1.09)	-0.98(1.18)	0.42
InfancyΔHeight _{SDS} 0-2yrs	-0.51(1.11)	-0.82(1.09)	0.0019
DiffH-MPH _{SDS} 2yrs	-1.12(1.03)	-1.38(1.02)	0.0042
Pre-treatment			
ΔHeight _{SDS} Pre-treatment	-0.03(0.23)	0.02(0.23)	0.015
GH _{max} AITT/GHprofile	16.1(19.1)	15.7(14.4)	0.81
at GHstart Age(yr)	8.65(2.12)	7.86(2.17)	<.0001
Height _{SDS} GHstart	-2.72(0.52)	-2.97(0.58)	<.0001
Outcome			
ΔHeight _{SDS} 1 ^{yr}	0.71(0.26)	0.80(0.29)	0.0011
ΔHeight_{SDS}Prepubertal	1.48(0.65)	1.63(1.12)	0.012
GHdose(μg/kg/day)Prepubertal	35.8(8.0)	39.0(11.6)	0.0002
ΔHeight_{SDS}Pubertal	-0.005(0.69)	-0.36(0.68)	<.0001
GHdose(μg/kg/day)Pubertal	30.1(10.0)	30.3(9.8)	0.80
ΔHeight_{SDS}GHstart-AH	1.47(0.80)	1.27(0.80)	0.0037
GHdose(μg/kg/day)GHstart-AH	32.5(7.9)	33.9(8.8)	0.051
At AH			
Height(cm)	172.2(6.0)	157.2(5.4)	<.0001
Height _{SDS}	-1.25(0.92)	-1.70(0.89)	<.0001
DiffH-MPH _{SDS}	-0.26(0.93)	-0.57(0.83)	0.0002

Conclusion: This group of girls responded more than the boys did before puberty, being more GH-responsive⁴ as they were younger and shorter vs parents and population at GHstart; in addition, they received higher GH-doses. In girls, 20% of the prepubertal gain was lost during puberty whereas maintained in boys on similar GH-doses.

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P1-168

Mother's smoking during pregnancy influence intrauterine and postnatal growth - the GrowUp 1990 Gothenburg cohort population

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Background/Objective: Smoking during pregnancy is known to influence prenatal/postnatal growth of the offspring. We investigated the impact of smoking in the Swedish reference population

for new reference for height, weight and BMI, the GrowUp-1990Gothenburg cohort.

Material/Methods: The study was based on 1907 healthy children (918girls/989boys) born at term in Sweden with Nordic parents and longitudinal growth measurements. 155girls/180boys was born to mothers smoking during pregnancy. Both traditional measures and estimates from the QEPS-growth model were used for comparisons.

Results: Individuals of both sexes with smoking mothers were shorter/lighter at birth, came earlier into puberty, had earlier peak height velocity (AgeTPHV) and were 1.8-1.9cm shorter at adult height as seen in the table. The girls median weight/BMI remained lighter during infancy and childhood, whereas along +2SDS became greater from 10yrs onwards, resulting in broader ranges. The boys' median weight/BMI remained lighter during infancy, from 2.5yrs of age heavier and with greater BMI during childhood and adolescence.

NS=non smoking mothers, S=smoking mothers. E,Q,Pmax= maximum of E,Q,P-functions by the QEPS-model. AgeP5=onset of pubertal growth.

Conclusion: Growth and maturation in children born to mothers smoking during pregnancy were influenced: they were shorter, lighter at birth/during infancy than those born to non-smoking mothers, with shorter stature and increased BMI during childhood. Omitting children born to mothers smoking during pregnancy narrowing the range of ±2SDS. We therefore recommend omitting children to smoking mothers when developing new growth references1, 2,3.

Variable	Mean NS, girls	Mean S, girls	Diff.	P-value	Mean NS, boys	Mean S, boys	Diff.	P-value
Gestational age, days	281.1	281.7	-0.6	0.4369	281.0	280.7	0.3	0.6804
Birth weight, gram	3563	3379	184	<.0001	3691	3530	161	<.0001
Birth length, cm	50.2	49.4	0.83	<.0001	51.0	50.3	0.70	<.0001
E _{max} , cm	62.8	62.72	0.10	0.6877	65.1	65.1	-0.04	0.8376
Q _{max} , cm	98.7	97.3	1.39	0.0453	105.6	104.3	1.30	0.0491
AgeP5, yrs	9.8	9.6	-0.21	0.0130	11.8	11.6	0.24	0.0028
AgeTPHV, yrs	11.8	11.6	-0.22	0.0141	13.7	13.4	0.24	0.0028
P _{max} , cm	13.0	13.1	-0.13	0.6885	17.3	17.0	0.26	0.4059
Adult height, cm	168.6	166.8	1.76	0.0020	182.0	180.1	1.90	0.0004
Mother, cm	167.2	167.1	0.10	0.8279	167.4	166.7	0.70	0.1373
Father, cm	181.7	180.3	1.38	0.0285	181.2	180.2	1.00	0.0941

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P1-169

Safety of growth hormone and cardiovascular outcomes in patients with Noonan syndrome enrolled in NordiNet® International Outcome Study (IOS) and the ANSWER Program

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Introduction: Growth hormone (GH) treatment has been shown to increase height velocity and adult height in patients with Noonan syndrome (NS). NS is also associated with cardiovascular (CV) anomalies, namely pulmonary stenosis and hypertrophic cardiomyopathy. Concerns persist about the role of GH in progression of CV conditions despite data, albeit limited, showing

low rates of CV events and left ventricular wall thickness remaining normal. This pooled analysis of data from two non-interventional, multicentre studies, NordiNet® IOS (NCT00960128) and the ANSWER Program (NCT01009905), describes real-world use of GH treatment in NS.

Methods: The studies evaluated long-term effectiveness and safety of Norditropin® (somatropin; Novo Nordisk A/S) as prescribed by physicians in a clinical setting. NS-related genotyping, concomitant medications, safety and CV outcomes were evaluated in GH-treated patients with NS.

Results: The full analysis set (FAS) comprised 412 children with NS (29.1% females), with a mean (standard deviation) age of 9.48 (3.92) years and height standard deviation score of -2.65 (0.95) at baseline. There were 66 gene variants among the 61 patients with available genotypes: *PTPN11* (n=56), *RAF1* (n=5), *KRAS* (n=2), *SOS1* (n=2) and *SHOC2* (n=1). Three patients had mutations in multiple genes, all including *PTPN11*. Forty-eight (11.7%) patients reported a cardiac lesion at baseline.

Baseline GH dose was 43.9 (13.7) µg/kg/day; average GH dose during childhood was 46.6 (13.6) µg/kg/day. The most common concomitant medications were central nervous system stimulants (12.4%), antihistamines (6.6%) and thyroxine replacement (5.1%).

There were no substantial differences in baseline characteristics between patients in the FAS and those experiencing safety events (n=22). Of the 24 non-serious adverse reactions, the most common were headache (eight events in seven patients) and arthralgia (five events in three patients). One patient experienced two serious adverse reactions (brain neoplasm and metastases to spine) after 2.5 years of treatment, possibly related to GH. No cardiovascular safety events were recorded during the study.

Pulmonary valve stenosis (PVS) and atrial septal defects were the most common CV comorbidities at baseline. Additionally, five CV comorbidities were reported after initiation of GH treatment: three cases of unspecified CV disease, one PVS and one ruptured abdominal aortic aneurysm.

Conclusions: The data suggest that GH was well tolerated in patients with Noonan syndrome, including those with CV

comorbidities and those receiving concomitant medications. Prospective studies are warranted to systematically assess the response of the CV system to GH treatment in patients with Noonan syndrome.

P1-170

Facilitating Telehealth In A Tertiary Paediatric Endocrine Service: A Quality Improvement Initiative To Reduce The Discrepancy Between Parent-reported And Auxologist Height Measurements

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Background: The COVID-19 crisis required paediatric endocrinologists to rapidly adopt telehealth into their clinical practice. Accurate auxology is a cornerstone of paediatric endocrinology care and is needed to monitor growth and guide medication changes. Remote consultations depend upon parent-reported measurements. However, home height measurements are often inaccurate.

Aim: We designed a quality improvement study with the aim of reducing the mean percentage difference between auxologist and parent-reported home measurements from 2.6% to 0.5% over a 2-month period.

Methods: Patients between the ages of 2 and 18 years attending face-to-face appointments at paediatric endocrinology clinics over a 2-month period (August-October 2020) were included. We compared the mean percentage difference between parent-reported height measurements taken prior to clinic to the "gold standard" height measurements taken on the day of clinic review by a single paediatric auxologist. We conducted a baseline audit over a two-week period which demonstrated that the mean percentage difference between parent-reported and auxologist height measurements was 2.6% (SD 4.1), with the proportion of parents providing home height measurements being 57.4%. Three Plan-Do-Study-Act (PDSA) cycles followed. The mean percentage difference between home and auxologist height measurements was tracked prospectively on a run chart. Data were also collected on the proportion of parents providing home height measurements.

Results: A total of 59 children were included (61.0% male, n=36) with a mean age of 12.1 years (SD 3.8). During the first PDSA cycle, parents were provided with verbal reminders and brief instructions on how to measure their child a week prior to clinic review. The second cycle focused on ensuring all families were registered on the patient communication portal of the hospital's electronic healthcare record system. Parents were then sent an electronic reminder via the portal two days before their clinic review. Parents were also called by a clinical team member to discuss the home

height measurement process in detail, facilitated by departmental guidelines. The third PDSA cycle focused on sustainability; parent reminders and home height measurements instructions were embedded into standard pre-visit electronic hospital communications. Mean percentage difference between home and auxologist height measurements was reduced to 0.4% (SD 0.4), with 91.6% of parents providing home height measurements.

Conclusions: Change interventions focusing on simple reminders and parental empowerment resulted in improved reliability of parent-reported height measurements. This will facilitate clinical care decisions during teleconsultations, which are likely to remain a part of routine paediatric endocrinology practice going forward.

Growth Hormone and IGFs B

P1-171

Diagnosing growth hormone deficiency - Can a combined arginine and clonidine stimulation test replace two separate tests?

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Objective: Given a large number of false-positive growth hormone deficiency (GHD) diagnoses from a single GH stimulation test in normal children, two different pharmacological tests, performed on separate days or sequentially, are required. This study aims to assess the reliability and safety of a combined clonidine-arginine stimulation test (CACST).

Design: Retrospective, single-center, observational study.

Methods: During 2017-2019, 515 children aged > 8 years underwent GH stimulation tests [CACST-362 or clonidine-first stimulation test (CST)-153]. The main outcome measures used to compare the tests were GH response (sufficiency/deficiency) and amplitude and timing of peak GH and safety parameters.

Results: Population characteristics: median age-12.2 years (IQR 10.7, 13.4), boys -331 (64%), prepubertal-282 (54.8%). GHD rate was comparable with 12.7% for CACST and 14.4% for CST followed by confirmatory test (glucagon/arginine), P=0.609. Peak GH was higher and occurred later in response to CACST compared to CST [14.6 ng/ml (IQR 10.6, 19.4) vs. 11.4 ng/ml (IQR 7.0, 15.8), P < 0.001; 90 min (IQR 60, 90) vs. 60 min (IQR 60,90), P < 0.001, respectively]. Peak GH in response to CACST was not modified by pubertal stage. No serious adverse events occurred following CACST.

Conclusion: Our findings demonstrate the reliability and safety of CACST in detecting GHD in late childhood and adolescence, suggesting that it may replace separate or sequential GHSTs. By diminishing the need for a second GHST, CACST saves time, is more cost-effective, and reduces discomfort for children, their caregivers, and medical staff.

Glucagon Testing of Childhood-Onset Growth Hormone Deficiency during Transition

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Objectives: To reassess growth hormone (GH) status by the means of Insulin (ITT) and Glucagon tests (GL) in young adults with childhood-onset GHD.

Methods: We present preliminary data of 67 subjects (25F, 42M) recruited from a single Center, in whom anthropometrics, ITT and GL stimulation tests and IGF-1 evaluations were undertaken at adult height achievement, at a mean age of 17.3±2.2 (range: 13.3-25.7). Subjects were classified as idiopathic isolated GHD (I-GHD N=33), organic GHD (0, 1 or 2 hormone deficiencies=O-GHD, n=18), congenital/genetic defects/organic GHD (≥3 hormone deficiencies, CGO-GHD, n=16) based on the American Association of Clinical Endocrinologists guidelines 2019. Diagnosis of permanent GHD was compatible with a peak GH value <6μg/L after ITT.

Results: GH peak to ITT (1.7±1.7 μg/L) and GL (1.7±1.7 μg/L, range 0.0-5.3) were lower in CGO-GHD compared to I-GHD subjects (19.4±10.8 to ITT and 15.1±6, range 5.3-31.5 μg/L to GL, P's <0.0001); similarly, GH peak to ITT (3.7±4.3 μg/L) and GL (4.2±5.3 μg/L, range 0.4-17.8) were lower in O-GHD compared to I-GHD subjects (P's <0.0001). Mean IGF-1 were also lower in CGO-GHD (-3.2±2.3 SDS; P<0.0001) and in O-GHD (-2.0±1.6 SDS; P<0.0001) compared to I-GHD subjects (0.1±1.1 SDS). In contrast, there were no differences in GH peak responses to ITT or GL and IGF-1 SDS values between O-GHD and CGO-GHD. A GH peak <6 μg/L for ITT was found in 29/67 of whom 13 O-GHD (72% of O-GHD) and 16 CGO-GHD (100% CGO-GHD); a GH peak <5.4 μg/L after GL was obtained in 31/67 of whom 14 O-GHD (77% of O-GHD), 16 CGO-GHD (100% CGO-GHD patients) and 1 I-GHD patient (GH peak to GL 5.26 μg/L, to ITT 7.13 μg/L; 3% I-GHD). Mean BMI SDS was higher in patients with CGO-GHD (1.2±1.4, P<0.001) and O-GHD (1.1±1.0, P<0.001) compared to I-GHD (-0.2±1.2). GH peak to glucagon was not correlated with BMI SDS (all P's n.s.).

Conclusions: Our preliminary results suggest that GL test is accurate in detecting CGO-GHD during transition independently of BMI SDS.

Growth hormone receptor 6Ω pseudoexon activation: a novel cause of severe growth hormone insensitivity

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Context: Severe forms of growth hormone insensitivity (GHI) are characterised by extreme short stature, dysmorphism and metabolic anomalies. They are classically caused by homozygous or compound heterozygous mutations of the growth hormone receptor gene (*GHR*). Genetic analysis traditionally focuses on the exonic regions of genes that encode proteins rather than the intervening non-coding sequences. These seldom explored non-coding regions may harbour numerous disease-causing mutations that are not yet well recognised or understood.

Objective: Identification of the genetic cause of severe postnatal growth failure in 3 'classical' GHI subjects. Characterisation of the novel *GHR* 6Ω pseudoexon variant identified.

Design: A novel intronic *GHR* variant was identified by our GHI targeted whole genome custom-made gene panel. *In vitro* splicing assays were performed to confirm the *in silico* prediction of aberrant splicing. Patient fibroblast analysis determined the presence of the *GHR* 6Ω pseudoexon in the cDNA transcripts. A *GHR* 6Ω pseudoexon vector, created by Gibson assembly, enabled functional assessment of the 6Ω pseudoexon inclusion.

Results: We identified a novel homozygous intronic *GHR* variant (g.5:42700940T>G, c.618+836T>G), 44bp downstream of the previously recognised intronic *GHR* 6Ψ pseudoexon mutation, in the index patient. In the second kindred, two siblings were found to harbour the same novel intronic *GHR* 6Ω pseudoexon variant in compound heterozygosity with the known *GHR* c.181C>T (R43X) mutation. RT-PCR of patient fibroblasts demonstrated presence of the 6Ω pseudoexon transcript in the patient cDNA. *In vitro* splicing analysis confirmed inclusion of a 151bp mutant 6Ω pseudoexon not identified in wild-type constructs. Inclusion of the 6Ω pseudoexon causes a frameshift resulting in a non-functional truncated *GHR* lacking the transmembrane and intracellular domains. HEK293 cells transfected with the 6Ω pseudoexon Gibson construct demonstrated extracellular accumulation of the mutant

truncated GHR protein and diminished activation of STAT5B signalling following growth hormone stimulation.

Conclusion: Novel *GHR* 6Ω pseudoexon inclusion results in loss of GHR function consistent with a severe GHI phenotype. This represents a novel mechanism of growth hormone insensitivity/Laron syndrome and is the first deep intronic variant identified causing severe postnatal growth failure. The two kindreds originate from the same town in Campania, Southern Italy, implying common ancestry. Our findings highlight the importance of studying variation in deep intronic regions as a cause of monogenic disorders.

P1-174
High incidence and male predominance of transient form of isolated growth hormone (GH) deficiency in children. What is the optimal time for GH therapy withdrawal and retesting?

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Introduction: Normal growth hormone (GH) secretion after the attainment of final height (FH) is observed in the majority of GH-treated children with GH deficiency (GHD), however it is unclear when such normalization of GH secretion occurs.

The Aim: of the study was to assess the incidence of transient GHD in retesting with respect to pediatric criteria in the patients with isolated GHD diagnosed in childhood, depending on the moment of GH therapy withdrawal.

Material and Methods: 260 children with isolated GHD (height SDS <-2.0, GH peak in 2 stimulation tests <10.0 µg/l), who completed GH therapy before (Group PRE) or after (Group POST) the attainment of near-FH (bone age >16 years in boys, >14 years in girls, height velocity <2.5 cm/year) and have performed retesting (insulin tolerance test followed by 2nd pharmacological test if GH

peak <10.0 µg/l); GH peak >10.0 µg/l in retesting was diagnostic for transient GHD.

Results: Significant increase (p<0.001) of GH peak in retesting with respect to pre-treatment values was found, with only a weak correlation between GH peaks before treatment and in retesting (r = 0.195, p<0.05). Male predominance (66.54%) among treated patients was observed. Transient GHD was diagnosed significantly more frequently (p=0.0008) in boys than in girls, while there was no significant difference in the incidence of transient GHD between Groups PRE and POST (p=0.57). Special attention should be paid to non-responders (mainly the patients with transient GHD in POST Group) and to the patients with GH peak in retesting <3.0 µg/l (9 cases in PRE, only 1 in POST Group).

Conclusions: In the majority of children with isolated GHD normalization of GH secretion with respect to pediatric criteria occurs before the attainment of near-FH. Overrepresentation of boys and higher incidence of transient GHD in them suggests the possibility of overdiagnosing GHD in boys. Earlier retesting of GH secretion could help to avoid overtreatment of patients with transient GHD.

P1-175
Growth without growth hormone. A tertiary care hospital's experience

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Introduction: Growth without growth hormone (GWGH) is a rare phenomenon described in patients with hypothalamic structural pathology who present a normal growth rate in spite of growth hormone (GH) deficiency and low concentrations of insulin-like growth factor-1 (IGF-1). Possible aetiologies involve hyperinsulinaemia, hyperprolactinaemia or hyperleptinaemia; however, the exact mechanism is still unknown.

Group		All	PRE	POST
No of patients (boys/girls)		260 (173/87)	121 (92/29)	139 (81/58)
	GH peak [µg/l]			
	before treatment	6.69±2.04	6.63± 2.13	6.73± 1.97
	in retesting	14.23± 8.42	13.85± 8.99	14.55± 7.91
Increase of height SDS during treatment		1.80± 0.85	2.09± 0.75	1.55± 0.85
Patients with transient GHD (boys/girls)		168 (124/44)	76 (63/13)	92 (61/31)
Incidence of transient GHD	total	64.62%	62.81%	66.19%
	in boys	71.68%	68.48%	75.31%
	in girls	50.57%	44.83%	53.45%

Objective: We aimed to analyse clinical and biochemical parameters and imaging studies in patients who have been diagnosed with GWGH.

Patients and Methods: A single-centre, retrospective and descriptive study in paediatric patients diagnosed with GWGH within the last 20 years in a tertiary care hospital was carried-out.

Results: Eight patients (four boys and four girls) were studied, all of them with structural pathology in the central nervous system (four craniopharyngiomas, two dysgerminomas, one pilomyxoid astrocytoma, and one multisystem Langerhans cell histiocytosis). The median age at diagnosis of the underlying pathology was 6.5 years (interquartile range (IQR) 3.2-9.8) and the median age at the diagnosis of GH deficiency was 6.77 years (IQR 4.37-9.12).

Both IGF-1 and IGFBP-3 were low in all the patients upon diagnosis of GH deficiency. Despite this, all patients had a normal growth rate. GH stimulation tests were performed in 6/8 patients, confirming the deficiency in all cases. Bone age was delayed in all patients and the median delay with respect to chronological age was 1.35 years (IQR 0.92-1.73). None of the patients developed acromegaloïd features. Six patients presented with obesity at some point during their follow-up. Slightly elevated prolactin concentrations were observed in four patients (maximum value: 77 ng/ml); in two of these, the concentrations normalised within the first two years after the diagnosis of GH deficiency. Basal insulin concentrations were elevated in three patients, with a median of 14.4 mcg/ml (IQR: 5.4-24.1), and one patient had a maximum insulin concentration of 117 mcg/ml at 120 minutes during an oral glucose tolerance test. Five patients started treatment with recombinant human GH, at a median age of 12.6 years (IQR 9.5-12.9). Final height was available in three patients, all of whom reached a normal height, according to their mid-parental target height. All patients developed deficiency of TSH, ADH and ACTH. Five had reached an age compatible with onset of puberty, with four of them developing gonadotropin deficiency.

Conclusions: Excess weight, with or without hyperinsulinaemia and hyperprolactinaemia may contribute to GWGH. However, not all patients presented these characteristics. Hence, other factors could be involved.

P1-176

Irisin in the growth hormone deficient children: before and on rhGH therapy

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Introduction: In recent years, one of the most frequently studied focuses is the pathophysiology of adipose and muscle tissue; however, in the literature there is no report about regulatory proteins (myokines/adipomyokines), which expression affects the body's metabolism and communication between tissues especially in children population. Irisin (Ir) is one of the adipomyokines, which induces the conversion of white adipocytes into beige adipose tissue, and Ir deficiency may be a factor contributing to the development of metabolic diseases.

The Aim: of the project is to evaluate the effect of rhGH treatment on Ir concentration in children with GHD in relation to the selected bone parameters.

Participants and Methods: 78 patients (33 girls and 45 boys) with growth hormone deficiency (GHD) qualified for recombinant growth hormone (rhGH) therapy and treated with rhGH for 6 months were prospectively studied.

The diagnosis of GHD was confirmed by a peak GH secretion below 10 mg/dl during three tests performed. All patients were examined with magnetic resonance imaging of the pituitary gland.

The exclusion criteria were: a tumor of the hypothalamic-pituitary region, multiple pituitary hormone deficiency and other comorbidities that can affect metabolism.

All children received rhGH daily injections in the evening at a dose of 0.023 mg per kg body weight.

The control group consisted of 24 healthy children (14 girls and 10 boys) without growth problems, autoimmune diseases or other diseases affecting the growth process selected according to age, and sex of the study group.

The fasting blood samples were taken to determine concentrations of: Ir, HbA1c, IGF-1, IGFBP-3, PTH, AP, P, Ca, 25OHD3, Mg, K, and Na. In a group of children with GHD a twice determinations were done (before treatment, and after 6 month therapy).

The obtained data was subjected to statistical analysis.

Results: We did not find statistically important difference in Ir concentration between GHD children and control group. Of the 78 children with GHD (mean age 7.43) we did not observed any significant difference in Ir levels between neither the age groups nor the sex (boys and girls). We did not find any association between Ir and BMI or bones markers.

Conclusions: The replacement doses of rhGH applied in children with GHD do not significantly affect the concentration of Ir. It seems valuable to extend the observation period during rhGH therapy.

P1-177

Immunogenicity of recombinant growth hormone and relationship its growth-promoting effect in the children with short stature

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Background/Aim: Although there are many well-known components that affect the growth response to recombine growth hormone (rGH), its effect on total height gain is still not fully predictable. Current knowledge on the relationship between growth response to rGH and its immunogenicity is limited. The aim of the study was to reveal its relationship with the antibody formation against rGH and growth-promoting effect.

Materials and Methods: This was a cross-sectional study involving 193 children presenting with short stature, 111 of whom were treated for GH due to growth hormone deficiency (GHD), 45 for non-endocrin, and 37 for idiopathic short stature (ISS). The distribution of the participants according to treatment years was as follows: 24, 34, 46, 39, 21, 29 children; at onset, first, second, third, 4th, and $\geq 5^{\text{th}}$ years on treatment. GH antibody (GH-Ab) and total

IgE assays were studied from all and 97 participants, respectively. The relationship between clinical features associated with growth response and antibody seropositivity was evaluated.

Results: Seropositivities for GH-Ab and total IgE were detected in 103 (53.3%) and 25 (25.7%), respectively. The number of GH-Ab positive patients was higher in the ISS group (67.5%) ($p=0.013$). In 15 of 24 (62.5%) patients whose test was studied, GH-Ab seropositivity was detected before treatment. In all three groups, first-year height velocity was found to be lower in GH-Ab positive patients than in GH-Ab negative patients (GHD; 8.62 ± 2.97 vs. 10.91 ± 3.63 cm/year, ISS; 5.63 ± 0.11 vs. 8.30 ± 1.79 cm/year, non-endocrin; 7.75 ± 1.26 vs. 10.12 ± 2.26 cm/year; $p=0.003$, $p=0.003$, and $p=0.001$, respectively). Similarly, first-year height velocity was found to be lower in IgE positive patients (7.01 ± 3.25 vs. 8.93 ± 2.16 ; $p=0.032$). In the non-endocrin group, first-year height velocity was negatively correlated with mean GH-Ab and total IgE levels ($r=-0.468$, $p=0.039$; $r=-0.448$, $p=0.042$, respectively).

Conclusion: This study showed that GH-Ab formation is common in children with short stature, especially those with ISS, before and during rGH treatment, and also GH-Ab positivity is associated with lower first-year height velocity. It also indicates

that GH-Abs both could play a role in the etiology of GH-related short stature and that immunogenicity against rGH could have an impact on first-year height velocity.

P1-178

Study on linear growth of children with idiopathic short children (ISS) with Low Insulin-like growth factor 1 (IGFI) at diagnosis: Growth hormone (GH) treatment versus no treatment

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ISS is a condition in which the height of the individual is more than 2SD below the corresponding mean height for a given age, sex, and population, in whom no identifiable disorder is present. At presentation, some of these children have relatively low IGF-I

1= at presentation

ISS low IGF1 (No GH treatment) N = 12		Age1	HtSDS 1	BMI SDS1	MPHSDS	HtSDS- MPHSDS1	IGF-I1	IGF1SDS1	Bone age
Mean		10.1	-2.22	-1.18	-0.87	-1.12	100	-1.97	-0.88
SD		2.58	0.43	0.60	0.56	0.34	35.3	0.37	0.81
ISS low IGF1 treated with GH n=10									
Mean		10.3	-2.53	-0.65	-1.14	-1.54	101.	-2.00	-1.15
SD		2.16	0.30	0.80	0.60	0.44	31.7	0.19	0.77
P value		0.42	0.07	0.09	0.24	0.10	0.48	0.38	0.26

2 = after 1 year of follow up

ISS low IGF1 (No GH treatment)		Duration of F/U	GH-P	HtSDS2	BMI SD2	D IGFSD	wt gain g/ day	Delta BMISDS	Delta HtSDS	HTSDS2- MPHSD
Mean		15.3	14.	-2.20	-1.30	0.3	9.32	0.45	0.07	-1.76
SD		2.99	4.0	0.34	0.60	0.3	3.70	0.53	0.13	0.24
ISS low IGF1 treated with GH										
Mean		13.82	14.	-1.96	-0.24#	1.04#	16.73	0.13	0.41	0.22
SD		2.65	5.5	0.22	0.71	0.7	4.53	0.20	0.14	0.85
P value		0.38	0.5	0.14	0.02*	0.001	0.02*	0.14	0.001	0.004

* = significant treated versus not treated groups

= significant after versus before treatment

levels which theoretically can affect their response to GH therapy. The question is: does GH treatment of these children improve their linear growth compared to no treatment?

Aim: We studied effect of GH therapy (0.035 mg/kg/day) on linear growth and weight gain in ISS children who have low IGF-I (IGF SDS < -1.5) (n=12) at the presentation in comparison with a similar group (n=10) who did not receive GH therapy.

Results: At presentation, the age, HtSDS, BMI, BMISDS, IGFISDS, peak GH response to clonidine provocation, and bone age didn't differ between the two groups (ISS and low IGF-I). After a year of treatment with GH (0.035 mg/kg/day) the HtSDS, daily weight gain and BMI improved significantly in the GH treated group ($P < 0.05$). The IGFISDS, BMISDS, HtSDS, and difference between HtSDS and mid-parental HtSDS were significantly higher in treated versus not treated group.

Conclusions: GH therapy improved linear growth and weight gain in children with ISS who had low IGF1 at presentation compared to the non-treated control group.

P1-179

Novel dominant negative GH receptor variants provide important insights into GH receptor physiology

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Background: Growth hormone insensitivity (GHI) encompasses normal/elevated growth hormone (GH), low IGF-I levels and growth restriction. Non-classical/mild-moderate GHI is an emerging entity which is poorly characterised, and, in many subjects, the underlying cause is unclear. Heterozygous dominant negative (DN) variants located in the intracellular/transmembrane domain of the GH receptor (GHR) cause a 'non-classical' GHI phenotype.

Hypothesis/Objective: Detailed characterisation of novel, naturally occurring *GHR* variants will improve our understanding of the physiology of human growth and lead to improved diagnosis/enhanced patient care.

Methods: Two novel heterozygous *GHR* variants were identified in 2 GHI patients by our short stature whole genome panel. *In vitro* splicing assays were performed using an exon trap vector. Gibson assembly created *GHR* wild type (WT) and variant (MUT 1 & 2) constructs. Additional WT and MUT constructs with either NanoLuc® Large BiT (LgBiT; 17.6kDa) or Small BiT (SmBiT; 11 amino acids) subunits were generated. These constructs were transfected into HEK293T cells and western blotting (WB) was performed using anti-STAT5b, anti-pSTAT5, anti-GHBP and anti-NanoLuc® Luciferase antibodies (anti-beta-actin/GAPDH as controls). NanoBiT complementation assays allowed quantitative assessment of WT and MUT GHR homo/hetero dimerization.

Results: Heterozygous *GHR* variants (c.876-15T>G (MUT 1) and c.902T>G (MUT 2) in intron 8/exon 9, respectively) were identified in 2 GHI subjects. Segregation studies confirmed MUT

1 was maternally inherited (mother's height SDS -2.4) and MUT 2 arose *de-novo*. *In-vitro* splicing assays confirmed both *GHR* variants activate the same alternative splice acceptor site resulting in abnormal splicing and exclusion of 26 base pairs of *GHR* exon 9. Wildtype (WT) and MUT constructs were co-transfected to mimic the heterozygous state of patients. WB analysis confirmed the production of truncated MUT variants and reduced GH-induced STAT5B phosphorylation. WB analysis of the supernatant of cells transfected with the NanoLuc®-*GHR* constructs, showed increased GH binding protein (GHBP) production in MUT:MUT and WT:MUT compared to WT:WT *GHR*. Novel NanoBiT complementation assays showed increased luminescence readings of MUT:MUT and WT:MUT *GHR* homo/heterodimers compared to WT:WT homodimers suggesting increased cell surface expression of MUT:MUT and WT:MUT *GHR* receptor dimers.

Conclusion: Heterozygous defects in the intracellular domain of *GHR* should be considered in cases with a non-classical GHI phenotype. Our novel truncated *GHR* variants exert a dominant negative effect with blunted *GHR* signalling. The creation of NanoLuc®-*GHR* constructs provide a novel, innovative methodology for characterising the functional role of *GHR* variants.

P1-180

The miRNA network and the interplay between growth and cancer regulating pathways in prepubertal patients with idiopathic isolated growth hormone deficiency (IGHD) on growth hormone (GH) treatment

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GH and IGF1 regulate cell proliferation, differentiation and apoptosis playing a key role in growth, and leading to consider potential oncogenic effects of GH. To evaluate possible oncogenic risks in GHD patients who underwent GH replacement therapy, the SAGhE consortium was created. The data collected have not yielded definite conclusions and continuous surveillance is yet required. MiRNAs are regulators of gene expression, and are involved in many biological processes. We aimed at identifying miRNAs varying on GH treatment using a profiling approach, and at evaluating whether these miRNAs had an impact on pathways involved in cancer.

Ten prepubertal normal weight patients with IGHD were enrolled (5 Males, 5 Females-CA: 8.79±0.82yr). miRNA profiles were evaluated at -3,0 and at +3 months on treatment. miRNA expression levels at -3 and 0 months were compared and miRNAs showing a p-value≤0.05 were excluded allowing to identify

those miRNAs changing only in response to treatment. MiRNAs were analysed by the DDCt method and only the ones differing by either a factor $2^{-DDCt} > 1.5$ or $2^{-DDCt} < 1.5$ (up- or down-regulated, respectively) were considered of interest. MiRNetv.2.0 platform was used for gene target and pathway analyses.

Sixteen miRNAs were up-regulated and 2 down-regulated. Pathway analysis showed that they were significantly involved in the regulation of 100 different pathways. Among these, the most significant were: *Oncogene-induced senescence*, *SHC-related events triggered by IGF1R*, and *Cyclin D associated events in G1 pathways*. The first involved CDK6, MDM2, MAPK1, and TNRC6A genes; the second IGF1R, KRAS, and MAPK1 genes; the third CCND1, CDK6, and CDKN1A genes. These are all involved both in longitudinal growth and cancer. Specifically, CDK6/CCND1 regulate chondrocyte maturation and cell cycle progression. MDM2 increases bone mineralization and is a negative regulator of p53. MAPK1(ERK2) and TNRC6A are involved in many cancers. IGF1R is pivotal for growth but is overexpressed in breast, colon, melanoma and prostate cancers among others. KRAS is an oncogene mutated in RASopathies which present both short stature and increased risk of cancer. CDKN1A(p21) regulates chondrocyte development but is also expressed in malignancies.

Concluding, GH regulates miRNAs that in turn modulate genes and pathways commonly dysregulated in cancer. Interestingly, 16 out of 18 miRNAs were up-regulated suggesting inhibition of gene expression which is encouraging in terms of safety for treatment. We have validated two up-regulated miRNAs in 25 treated subjects, and are performing specific experiments in bone cell lines to provide new insight into these aspects yet unclear in clinical practice.

Pituitary B

P1-181

Continuous versus discontinuous administration of gonadotropin in neonates with congenital hypogonadotropic hypogonadism

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Context: Newborns with Congenital hypogonadotropic hypogonadism (CHH) have an impaired postnatal activation of the gonadotropic axis. Substitutive therapy with recombinant gonadotropins can be proposed to mimic physiological male mini-puberty during the first months of life.

Objective: To retrospectively compare the clinical (penile size, volume and testicular descent) and biological efficacy (serum concentrations of testosterone, AMH and Inhibin B) of two treatment modalities of gonadotropins administration during mini-puberty in CHH neonates.

Patients: Thirty-five patients were included, 18 with continuous administration of recombinant gonadotropins by pump (P group) and 17 with subcutaneous injections (I group). The mean age at treatment initiation in the P group was 5.2 +/-3.5 months compared to 13 +/-17.8 months in the I group.

Results: A significantly higher increase in penile length and testosterone level were observed in the I group compared to the P group (+ 0.16 +/-0.02 mm vs + 0.10 +/-0.02 mm per day and + 0.04 +/-0.007 ng/ml vs + 0.01 +/-0.008 ng/ml per day). In both groups, significant increase in penile width, testicular volume, height, AMH, Inhibin B and FSH levels were observed, as well as improved testicular descent (OR of not being in a scrotal position at the end of treatment = 0.97 [0.96; 0.99]).

Conclusions: Early postnatal administration of recombinant gonadotropins in CHH boys is effective in stimulating penile growth, gonadal development, Sertoli cell proliferation and testicular descent, independently from treatment modalities. Based on our clinical and biological results the best option could be continuous administration of optimized dosages of recombinant gonadotropins.

P1-182

Sequence of MKRN3 and DLK1 genes in cases with familial central precocious puberty

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Background: Approximately one-third of the central precocious puberty (CPP) cases have familial transitions. Although more than 30 genes related to puberty have been reported to date, only a few (*KISS1*, *KISS1R*, *MKRN3*, *DLK1* and *PROKR2*) were associated with CPP. This study aims to reveal the associated sequence variants of *MKRN3* and *DLK1* genes in cases with familial CPP and their etiology.

Method: This study includes 18 cases (16F, 2M) from different families, whose past medical history, physical examination, laboratory and follow-up records were evaluated. SDS calculation was performed according to national standards; bone-age (BA) was assessed by Greulich-Pyle-method, and predicted adult height (PAH) was calculated according to Bayley-Pinneau-method. Family pedigrees were drawn for each case, and informed consents from all families were obtained before genetic testing. Sanger sequencing was performed in regions coding *MKRN3*(NM_005664.3) and *DLK1*(NM_003836.6). Segregation analyses were performed in families with pathogenic variants.

Results: The mean onset of pubertal age was 7.3 years (6.38-7.58) in females; 6.7 and 8.8 years in two males. The mean birth weight SDS was -0.6 (-1.3-0.9). At presentation, height and BMI SDS were 0.3 (-1.2-2.6) and -0.5 (-1.1-3.2) respectively. The mean BA was 8.8 years (7.8-10.5), and chronological age-BA difference

was 3 years (1.6-4.9). Mean PAH was 156.7cm (-0.78 SDS) (147-171.6) in females; 167.9 and 181.7cm in males. The mean target height SDS was -0.7 (-2.18 and -0.1) in females; -0.7 and 0.32 in males. Cranial-pituitary MRI of all cases was normal. Fifteen cases received GnRHa. Two different novel heterozygous variants in the *DLK1* gene in two different families and a mutation in the *MRKN3* gene in one case were detected. The first variant of *DLK1* gene was c.357C>G(p.Tyr119Ter) in exon 4, and the second variant was c.67+78C>T in intron1. Segregation-analyses of these families had shown a paternal origin for the variants. The heterozygous variant in *MRKN3* gene was c.982C>T(p.Arg328Cys, which is also paternal derived.

Conclusions: Although more frequent in literature, mutation in *MKN3* gene was detected only in one case in our study. Two-variants in the *DLK1* gene were found to be compatible with the paternal imprinted gene model. In-silico analysis predicted that the first would lead to clipping error and the second to protein truncation. Transcription level study was planned for the clipping region change in the intronic region. We suggest that performing WES analysis in cases without pathogenic variant may help to explain the new genes and their relationships in familial CPP.

P1-183

Hypoandrogenism degree and lipid profile in boys with delayed puberty

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In recent years, the problem of androgen deficiency as a factor in the formation of dyslipidemia, endothelial dysfunction, insulin resistance and systemic inflammation has been studied mainly in adult men, because the main cause of mortality and disability in this cohort is cardiovascular disease. However, there are practically no data on the relationships of sex hormones with lipid metabolism during hypoandrogenism (HA) during puberty.

Aim of Research: was to analyze the effect of the degree of HA during puberty on lipid profile in boys with delayed puberty (DP).

Materials and methods: A comprehensive study of 75 boys aged 13-17 years with DP, including with the study of T in the blood by enzyme-linked immunosorbent assay, the level of which was determined by the degree of HA (ranging from 12.0 to 8.0 nmol/l - 1, in the range from 7.9 to 4.0 nmol/l - 2; less than 4.0 nmol/l - 3). The blood lipid spectrum was studied: total cholesterol (TC), β -lipoproteins (β LP), triglycerides (TG), high density lipoprotein cholesterol (HDL) in blood serum with the calculation of low density lipoprotein cholesterol (LDL) and atherogenicity coefficient (AC).

Results: In 59.1% of the examined, the presence of pathological changes in lipid parameters of atherogenic orientation (mainly type IIa dyslipidemia), an increase in the level of TC in 46.5%, β LP in 66.2%, LDL in 25.3%, and TG in 15.5%, which led to an increase in AC in 32.4% of patients. Changes in the atherogenic orientation in the lipid profile increased in proportion to the deficiency

of androgens, with an increase in the degree of HA, a significant increase in the average values of TC, β LP, and LDL was noted. An analysis of the correlation relationships showed the existence of reliable negative relationships between the content of T and TC ($r = -0.32$, $p = 0.008$), β LP ($r = -0.26$, $p = 0.03$), which also confirms the effect of HA on the lipid profile.

Conclusion: In 59.1% of boys with DP, changes in the lipid profile were recorded, mainly due to the growth of proatherogenic lipid fractions, more pronounced with an increase in the degree of HA, which may indicate the effect of androgen deficiency in adolescents on lipid metabolism and is important for early diagnosis of disorders lipid metabolism, prevention of disorders of the cardiovascular system in future men.

P1-184

The pituitary gonadal axis is not responsive to GnRH administration in PCSK 1 dysfunction

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Introduction: Patients homozygous for mutation in the PCSK-1 gene present clinically with severe congenital diarrhea and variable hormonal defects due to lack of enzyme/prohormone processing by Prohormone Convertase 1/3 (PC1/3). Although absence of spontaneous puberty has been reported in patients with PCSK-1 mutations, no peptide hormone(s) in the hypothalamus-pituitary-gonadal axis (HPG) have been reported to be dependent on PC1/3 cleavage. Here we studied the effect of GnRH administration in a patient with PCSK-1 loss of function.

Methods and Results: Genetic evaluation of a consanguineous kindred presenting with congenital diarrhea and hormonal deficiencies, revealed them to be homozygous for the malfunctioning N309K mutation in the PCSK-1 gene. The oldest patient an 18 years old female presented classically with congenital diarrhea followed by obesity, cortisol, growth hormone and thyroid hormone insufficiency. Pubertal development, secondary sexual characteristics and regular menstruation were achieved only following hormone replacement therapy. Repeated GnRH stimulation tests between 13-15 years of age showed a prepubertal pattern with only minimal increase of LH.

Aiming to study the response of pituitary gonadotrophic cells at 18 years of age, hormonal replacement therapy was discontinued for 60 days. GnRH stimulation test was then performed prior and post a week of pituitary "priming" by 300ng/Kg/d of GnRH. Prepriming GnRH test results indicated no significant increase in gonadotropin response compared to almost undetectable basal levels (basal: LH 0.04 IU/L FSH 1.12 IU/L, Peak LH 0.79 IU/L FSH - 3.38 IU/L). Interestingly post priming GnRH stimulation test did not show a significantly improved gonadotrophic cell response in basal or in peak levels of gonadotropins (LH 0.09-1.36 IU/L and FSH 1.08-4.56 IU/L).

Conclusion: The homozygous N309K mutation in the PCSK-1 gene causes hypogonadotrophic hypogonadism, absence of spontaneous puberty and primary amenorrhea responsive to estrogen

replacement therapy. Significant priming with GnRH failed to stimulate gonadotropin secretion in response to acute GnRH stimulation, indicating a novel crucial role of PC1/3 in production and processing of gonadotropins within pituitary gonadotrophic cells. Further studies to dissect specific pituitary related PC1/3 function are underway.

P1-185

Puberty and pituitary-gonadal axis function after treatment for a childhood brain tumor

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Introduction: Primary brain tumors are the second most common childhood malignancies, with an increasing survival rate over the years. Late effects on puberty and fertility alter survivors' quality of life.

Methods: We included 204 patients diagnosed with a primary brain tumor before 18 years, followed in pediatric endocrinology at the University Hospital "Necker-Enfants Malades" in Paris between January 2010 and December 2015. Data was retrieved from medical records to analyze pubertal timing and the effects of the tumor and its treatments.

Results: The total cohort of 204 patients was studied for early puberty (EP) and gonadal toxicity (GT), and 187 patients (≥ 13 years (girls) or ≥ 14 years (boys) were analyzed for hypogonadotropic hypogonadism (HH). Among these 187 patients, only 53 (28.3%) had spontaneous puberty at the same time as their peers, with no significant sex ratio.

Of 32 patients with a suprasellar glioma, 19 had EP, with a positive predictive value (PPV): 59.4%, $p=0.001$. Risk for EP was lower when radiotherapy dose was high, >40 Gy ($n=2/6$, PPV: 33.3%, $p=0.02$), and it increased with doses <40 Gy or when the child had not been treated by radiotherapy ($n=17/26$, PPV: 65.4%). There was a trend for higher PPV for EP in younger children (diagnosis <5 years), but this was not statistically significant.

Thirty out of 43 patients with medulloblastoma treated by high-risk chemotherapy developed GT on average 7.6 ± 3.7 years after the end of treatment (PPV=69.7%, $p=0.001$); patients who were not treated by chemotherapy ($n=17$) did not develop GT (PPV: 0%, $p=0.001$). Children diagnosed <5 years of age had a higher risk of GT after chemotherapy ($n=14/16$, PPV=87.5%, $p=0.001$).

Craniopharyngioma was associated with an increased risk of HH regardless of treatment ($n=39/56$, PPV 69.6%, $p=0.001$). Growth hormone deficiency (GHD) increased the risk of HH to 79.2%, whereas in absence of GHD, the PPV was 0% ($p=0.001$).

Conclusions: The type of tumor, its location and treatment are the main factors that drive the type of pituitary-gonadal axis dysfunction. Craniopharyngioma is associated with a risk of HH, glioma with EP and medulloblastoma (through high-risk chemotherapy) with GT. Awareness of potential secondary effects and their mechanism is essential to assess pubertal status of these patients, to guide parental information, and to decide of an adequate and timely hormone replacement therapy.

P1-186

Additive effect of androgens and estrogens on pubertal growth acceleration

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Objective: The influence of androgens and estrogens on growth is complex, and understanding their relative roles is important for optimizing the treatment of children with various disorders of growth and puberty.

Design: We examined the proportional roles of androgens and estrogens in the regulation of pubertal growth in boys with constitutional delay of growth and puberty (CDGP). The study compared 6-month low-dose intramuscular testosterone (T) treatment (1 mg/kg/month) (n=14) with peroral letrozole (Lz) treatment (2.5 mg/day) (n=14) which inhibits conversion of androgens to estrogen.

Patients: Boys with CDGP were recruited to a randomized, controlled, open-label trial between 2013 and 2017 (NCT01797718)¹.

Measurements: The patients were evaluated at 0-, 3-, and 6-month visits, and morning blood samples were drawn. Linear regression models were used for data analyses.

Results: In the T-group, serum testosterone concentration correlated with serum estradiol concentration at the beginning of the study and at 3 months, whereas in the Lz-group the sex steroids correlated only at baseline. Association between serum T level and growth velocity differed between the T- and Lz-groups, as each nmol/l increase in serum T increased growth velocity 2.6 times more in the former group. Serum T was the best predictor of growth velocity in both treatment groups. In the Lz-group, adding serum estradiol to the model significantly improved the growth estimate. Only the boys with serum estradiol above 10 pmol/l had a growth velocity above 8 cm/year.

Conclusions: During puberty promoting treatment with T or aromatase inhibitor Lz, growth response is tightly correlated with serum T level. A threshold level of estrogen appears to be needed for optimal growth rate that corresponds to normal male peak height velocity of puberty. Serum T one week after the injection and serum T and estradiol 3 months after aromatase inhibitor treatment onset can be used as biomarkers for treatment response in terms of growth.

Reference

1. Data on primary endpoints, i.e. changes in testicular volume and hormonal markers of puberty have been published before. Varimo T, Huopio H, Kariola L, et al. Letrozole versus testosterone for promotion of endogenous puberty in boys with constitutional delay of growth and puberty: A randomised controlled phase 3 trial. *Lancet Child Adolesc Health*. 2019;3(2):109–120. doi: S2352-4642(18)30377-8.

P1-187

The Adrenal Steroid Profile in Adolescent Depression: A Valuable Bio-Readout?

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Background: There is preliminary evidence that adrenal steroids other than cortisol may be valuable biomarkers for major depressive disorder (MDD). So far, studies have been conducted in adults only, and conclusions are limited, mainly due to small sample sizes. Therefore, the present study was intended to assess whether adrenal steroids (progesterone, 17-hydroxyprogesterone, 21-deoxycortisol, 11-deoxycortisol, cortisol, cortisone, deoxycorticosterone, corticosterone) serve as biomarkers for adolescent MDD.

Methods: In 261 depressed adolescents ($N_{\text{females}} = 170$), treated at a single psychiatric hospital between 2016 and 2019, serum adrenal steroids were determined by liquid chromatography-tandem mass spectrometry. Findings were compared to that of an age- and sex-matched reference cohort ($N = 255$) by nonparametric analysis of variance. Nonparametric receiver operating characteristics (ROC) analyses were conducted to evaluate the diagnostic performance of single steroids and steroid ratios to classify depression status. Sensitivity analyses considered important confounders of adrenal functioning, and ROC results were additionally verified by cross-validation.

Results: Compared to the reference cohort, levels of deoxycorticosterone and 21-deoxycortisol were decreased ($P < .001$). All other glucocorticoid- and mineralocorticoid-related steroids were increased ($P < .001$). The corticosterone to deoxycorticosterone ratio evidenced excellent classification characteristics, especially in females (Area Under the Curve (AUC): 0.957; sensitivity: 0.902; specificity: 0.891).

Conclusion: The adrenal steroid metabolome qualifies as a bio-readout reflecting adolescent MDD by a distinct steroid pattern that indicates dysfunction of the hypothalamus-pituitary-adrenal axis. Moreover, the corticosterone to deoxycorticosterone ratio may prospectively qualify to contribute to precision medicine in psychiatry by identifying those patients who might benefit from antiglucocorticoid treatment or those at risk for recurrence when adrenal dysfunction has not resolved.

P1-188

Congenital hypogonadotropic hypogonadism in a large French cohort: New genetic findings

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Congenital hypogonadotropic hypogonadism (CHH) is a rare condition caused by a dysfunction of the GnRH Axis. The clinical variability of the disease is accompanied by genetic heterogeneity. Indeed, more than 40 genes are implicated in the pathogenesis of this condition.

The main goal of this present study was to characterize genetic defects in a large cohort of French CHH patients using a targeted NGS panel.

Patients: a cohort of 120 unrelated patients (77 males / 43 females) with CHH (24 Kallmann syndrome, 1 Gordon-Holmes syndrome, 1 Woodhouse-Sakati Syndrome, one 4-Syndrome and 93 normosmic CHH) were studied using a panel of 54 genes.

Results: Pathogenic or probably pathogenic variants were identified in 34 (28%) CHH patients, 13 (11%) of these variants are novel. The most affected genes are *CHD7*, *FGFR1*, *IGSF10*, *GNRHR*, *TACR4* and *WDR11*. Thirty one patients (26%) had rare variants including variants of uncertain significance (VUS) in more than one candidate gene. The CNV analysis identified two duplications in *ANOS1* and a large deletion in *GNRHR*. The achieved diagnostic rate of the NGS panel was comparable to other genetics studies of CHH.

Conclusion: This is one of the largest genetic study in a french cohort of CHH patients that provide new genetics findings of a rare and heterogeneous disease. The use of a targeted NGS panel is an effective tool to diagnosis CHH patients but it must be completed in some cases with exome and whole genome analysis in order to unravel the complexity of this condition and to move a step closer to a personalised medicine.

P1-189

Dimensional changes in structures of craniofacial and brain in precocious puberty: Developmental surrogate markers of the brain as a secondary sex characteristic in puberty

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Background/Aim: Sex hormones drive organizational and activational changes in craniofacial structures and various regions of the brain and establish a sexual dimorphism in the re-shaping of the brain and related structures during puberty. Although the evolutionary approach, which accepts the brain and related structures as secondary sex characteristics since they are target organs for sexual selection, increases awareness of the role of sex hormones in sex-specific brain development during the pubertal period, further research is required to improve our understanding of the subject.

This study focused on dimensional changes of craniofacial and various structures of the brain in girls with precocious puberty (PP) characterized by the early onset of pubertal development.

Materials and Methods: The study included a total of 120 participants, 87 PP and 37 healthy girls, aged 6-8 years. In all the participants, following variables were measured: craniofacial structures including nasal bone length, anterior nasal spine, transfer nasal diameter, biparietal distance, bitemporal diameter, intermaxillary diameter, head circumference, and limbic structures including inter-uncal distance, pituitary height, right and left hippocampal dimensions using magnetic resonance imaging (MRI). Basal estradiol (E2), basal/stimulated luteinizing hormone (LH), follicle-stimulating hormone (FSH) values, uterus length, and ovarian volumes were evaluated in the girls with PP.

Results: When compared the measurements in the PP and healthy girls, there were significant differences following variables: nasal bone length, nasal transfer diameter, biparietal diameter, pituitary height, transverse and craniocaudal distances for right hippocampus, craniocaudal distance for left hippocampus (<0.001 , 0.001 , 0.007 , 0.013 , 0.029 , <0.001 , <0.001 , respectively). In girls with PP, there was no correlation of measurement of the craniofacial/limbic structures with following variables: basal E2 and basal/stimulated LH and FSH, while moderate correlation was found between uterine and nasal bone lengths ($r=0.432$). While moderate and/or strong correlations were found between most of the craniofacial and limbic structures with each other in healthy children, most of these correlations were not found in girls with PP.

Conclusion: This study demonstrated that dimensional changes occur in various structures, including the craniofacial and limbic system in girls with PP, pointing to dimensional changes of potential craniofacial/limbic structures as surrogate markers for regions where functional changes occur in the brain. It also showed that there is no significant relationship between craniofacial/limbic and reproductive structures/dimensional measurements of sex hormones, indicating that further studies are needed to elucidate the relationship between pubertal physical changes and brain development.

P1-190

Six novel variants in the MKRN3 gene causing central precocious puberty: characteristics of ten patients and their affected relatives

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Background: In 2013, Abreu et al identified loss-of function mutation in the MKRN3 gene of fifteen patients from five families with idiopathic central precocious puberty (iCPP), highlighting the implication of this maternally imprinted gene in this still poorly understood condition. Since this study, other mutations

have been described and now represent the most common genetic cause of iCPP.

Objective: The objective of the study was to document the clinical course of puberty in nine girls and one boy harbouring pathogenic MKRN3 variants.

Design and Participants: This is an observational case series study of patients with iCPP followed in our center.

Results: We identified eight different variants predicted to be deleterious by in silico analysis in the MKRN3 gene of ten patients with iCPP from eight unrelated families. Six of the eight pathogenic variants were undescribed as far as we know: two of them were missense mutations, three were nonsense mutations and one was a frameshift mutation. In all cases for which we had data, the mutation was inherited from the father. The 4 years-old twin brothers of one patient were also carriers but still prepubescent. Index cases had a very rapid pubertal development and frank peak LH response to the GnRH test. Final height of affected adult relatives were in the target for males but below target height in females.

Conclusion: We identified six novel MKRN3 mutations in children with CPP. One of them had no known family history at the time of the analysis but a very early and rapid pubertal onset. An MKRN3 defect should be considered in all patient with CPP at a very young age or with a history of CPP in the paternal family. Family study of a patient also allowed us to detect a MKRN3 mutation in her two still prepubescent brothers, highlighting the value of regular clinical follow-up of early diagnosed patients without the necessity of a cerebral MRI. iCPP seems to impact adult height in females' adult relatives carrying MKRN3 mutations unlike males, but this remains to be confirmed because only a few adults could be studied.

Thyroid B

P1-191

The Impact of Hospital Surgical Volume on Healthcare Utilisation Outcomes after Paediatric Thyroidectomy

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Background: A positive relationship between an individual surgeon's operative volume and clinical outcomes after paediatric and adult thyroidectomy is well-established. The impact of a hospital's paediatric operative volume on surgical outcomes and

healthcare utilisation, however, are infrequently reported. We investigated associations between hospital volume and healthcare utilisation outcomes following paediatric thyroidectomy in Canada's largest province, Ontario, using population-level data.

Methods: Retrospective analysis of administrative and health-related population-level data from 1993 to 2017; a province-wide single-payor insurance system permits sampling the entire population. A cohort of 1,908 pediatric (<18 years) index thyroidectomies was established. Hospital volume was defined per-case as thyroidectomies performed in the preceding year. Healthcare utilization outcomes: length of stay (LOS), same day surgery (SDS), readmission, and emergency department (ED) visits were measured. Multivariate analysis adjusted for patient-level, disease and hospital-level co-variables.

Results: Mean age at surgery was 10.4 ± 5.4 years, 61% female and 20% had a cancer diagnosis. Hospitals with the lowest volume of paediatric thyroidectomies, accounted for 30% of thyroidectomies province-wide and performed 0-1 thyroidectomies/year. The highest-volume hospitals performed 19-60 cases/year. LOS was 0.64 days longer in the highest, versus the lowest quartile. SDS was 83% less likely at the highest, versus the lowest quartile. Hospital volume was not associated with rate of readmission or ED visits. Increased ED visits were, however, associated with male sex, increased material deprivation, and rurality.

Conclusions: Increased hospital paediatric surgical volume was associated with increased LOS and lower likelihood of SDS. This may reflect patient complexity at such centres. In this cohort, low-volume hospitals were not associated with poorer healthcare utilisation outcomes. Further study of groups disproportionately accessing the ED post-operatively may help direct resources to these populations.

P1-192

Analysis of hypothyroidism NGS test in Korean patients with congenital hypothyroidism in a single center

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Introduction: Thyroid hormone is known as greatly influence on growth and development in fetuses and newborns. If the detection of the disease is delayed, hypothyroidism can cause irreversible damage, so early detection and treatment is very important. Hypothyroidism can be divided into permanent and temporary cases depending on the duration of treatment, but there is no predictor that can completely differentiate those two. However, as genes related to hypothyroidism are revealed, genetic analysis can predict whether hypothyroidism will be permanent.

Method: Among the patients diagnosed with congenital hypothyroidism from July 2017 to December 2020 and being treated at Soonchunhyang University Seoul hospital, patients who want to implement the hypothyroidism NGS panel were enroll the study. A total of 147 patients were tested, and 30 genes (DUOX2, DUOX2, FOXE1, GNAS1, HESX1, IYD, LHX3, NKX2-1, NKX2-5, PAX8, POU1F1, PROP1, SLC16A2, SLC5A5, SLC5A4, TG, THRA, THRB,

TPO, TRH, TRHR, TSHB, TSHR, LHX4, SOX2, GLIS3, OTX2, DUOX1, IGSF1, SOX3) with more related genes were analyzed through hypothyroidism NGS panel.

Results: A total of 22 known pathogenic variants were identified in 20 patients; *DUOX2* 9 times (40.9%), *DUOX2* 8 times (36.4%), and *TSHR* 5 times (22.7%). A total of 42 variants identified as likely pathogenic in 38 patients; *DUOX2* 28 times (66.7%), *TSHR* 7 times (16.7%), *DUOX2* 2 times (4.8%), *TG* 2 times (4.8%), and each *TPO, LHX3, PAX8* 1 time (2.4%) in order of frequency. In addition, 121 VUS variants were identified in 90 patients; *DUOX2* 40 times (33.1%), *TG* 27 times (22.3%), *TPO* 7 times (5.8%), *GLIS3* 6 times (5.0%), *DUOX1, IGSF1* 5 times (4.1%), *GNAS1, LHX3, TSHR* 4 times (3.3%), *TBL1X, PAX8* 3 times (2.5%), *DUOX2, LHX4, OTX2, SLC26A4* twice (1.7%), *HESX1, NKX2-1, TRH, IYD, THRA* once (1.1%). Among 147 patients, 50 patients (34%) had pathogenic or likely pathogenic genes and 33 patients (22.4%) had none of related mutations. There were 9 ectopic thyroid, 4 agenesis, 1 hemiplasia patient and 33 patients could stop treatment until now.

Conclusion: It is expected that causative genetic analysis of congenital hypothyroidism will be helpful in actively stopping the treatment of congenital hypothyroidism according to the clinical condition of the patient, except when the disease is estimated due to pathogenic or likely pathogenic genes.

P1-193

Further evidence that Borealin/CDCA8 is involved in thyroid morphogenesis and aging

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Background: We found *BOREALIN/CDCA8* mutations in patients with Congenital Hypothyroidism and Thyroid Dysgenesis, varying from asymmetric lobes to athyreosis (Carré et al. *Hum Mol Genet* 2017). Borealin is a major component of the Chromosomal Passenger Complex, an essential regulator of mitosis. We demonstrated a new feature of *BOREALIN*: involvement in the adhesion and the migration of the thyrocytes.

Objective: Further understand the role of Borealin in thyroid development and function.

Methods: *Borealin*^{+/−} mice were studied during development, at the adult stage and during old age. *Borealin*^{−/−} mice were

not available because they die at E5.5. We documented thyroid morphology, performed immunohistology with thyroid markers (Nkx2-1, Thyroglobulin, T4) and we analyzed the thyroid function. We used a well-established model with antithyroid drug induced hypothyroidism which was applied to the *Borealin*^{+/−} and wild-type mice.

Results: First of all, *Borealin*^{+/−} mice had no hypothyroidism at the adult stage (4-month-old) but they were significantly more sensitive with a more profound hypothyroidism than wild-type when treated with antithyroid drugs (T4: 41% less for *Borealin*^{+/−} vs wild-type, $P < 0.01$). Thyroids of *Borealin*^{+/−} mice were significantly hyperplastic with larger follicles surfaces in comparison with wild-type ($P < 0.05$). Thus, the *Borealin*^{+/−} mice remain euthyroid because they developed a goiter. For elder mice, thyroid morphology of *Borealin*^{+/−} was altered with heterogeneity in size of follicles with predominantly very large follicles and thyroids that were significantly hyperplastic compared with wild-type (0.34mg/g thyroid weight/animal weight vs 0.23mg/g, $P < 0.05$). We found that thyroids of *Borealin*^{+/−} were significantly hyperplastic at E9.5 in comparison with wild-type, and hypoplastic from E11.5 to E17.5 ($P < 0.05$). Thyroid development thus was abnormal in *Borealin*^{+/−} compared to wild-type.

Summary: Thyroid development is altered in *Borealin*^{+/−} mice. Goiter do develop in adult *Borealin*^{+/−} mice and they are more prone to hypothyroidism when treated with anti-thyroid drugs.

Conclusion: Borealin is involved during crucial steps of the thyroid lifetime cycle. These data demonstrated the involvement of Borealin in the structural organization of the thyroid gland. The role of Borealin in thyroid development and function was strengthened here and supports its involvement in thyroid dysgenesis of patients with congenital hypothyroidism.

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P1-194

Role of Next Generation Sequencing in the etiological diagnosis of congenital hypothyroidism with gland in situ

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The pathogenetic role of genetic factors in congenital hypothyroidism (CH) is now widely known. The constant evolution of diagnostic methods in the field of medical genetics provides the opportunity to obtain an etiological diagnosis in CH patients with genetic defects in candidate genes.

We performed genetic analysis by Next Generation Sequencing (NGS) of 18 candidate genes (*DUOX2, DUOX2, FOXE1,*

GLIS3, IGSF1, IYD, NKX2-1, NKX2-5, PAX8, SLC16A2, SLC26A4, SLC5A5, TG, THRA, THRB, TPO, TSHB, TSHR involved in both morphogenesis and thyroid function in a selected sample of CH patients.

Inclusion Criteria were: CH patients with gland-in-situ (GIS), identified by newborn screening from January 2003 to December 2015 in Emilia-Romagna region, with permanent CH emerging from the re-evaluation of the diagnosis.

Exclusion Criteria were: children with chromosomal abnormalities and the absence of written informed consent.

41 patients (25 males, 16 females) were enrolled.

The NGS analysis was carried out using the Ion Torrent S5 Life Technology instrument.

Allelic variants (AVs) with MAF <0.05 were included and classified using Varsome. Benign and probably benign AVs were excluded.

36 AVs were detected in 23/41 patients (56%): 13 pts presented with one AV, 7 pts with 2 AVs and 3 pts with 3 AVs.

The remaining 18/41 pts were found to be wild-type (WT).

25/36 AVs were found in genes involved in thyroid hormone synthesis: 11 (30.5%) *DUOX2*; 9 (25%) *TG*, 3 (8.3%) *TPO*, 1 *SLC26A4*, 1 *SLC5A5*.

10/36 AVs in genes involved in thyroid morphogenesis: 8 (22.2%) *TSHR*, 1 *GLIS3*, 1 *FOXE1*.

1/36 AV in a gene (*IGSF1*) implicated in the hypothalamic-pituitary function.

50% of the AVs (18/36) were classified as VUS, 28% (10/36) as pathogenic and 22% (8/36) as likely pathogenic, according to the guidelines of the ACMG.

In 7 patients (19,4%) we found an oligogenic CH.

Among patients who harbored more than one AVs, 3/10 (7%) presented with compound heterozygosity on the same gene and these patients showed a more severe CH (higher TSH and lower fT4 at diagnosis) than those with oligogenic CH ($p = 0.017$).

Despite the preliminary nature of the results, in 56% of patients with CH and GIS we found at least 1 AV of probable pathogenic significance.

Further investigations through the search for copy number variations and the analysis of the regulatory regions, currently ongoing, will allow to increase the detection rate and elucidate the mechanisms underlying CH.

P1-195

DNA Methylation at a nutritionally sensitive region of the PAX8 gene is associated with thyroid volume and function in Gambian children

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Background: Thyroid hormones contribute to a wide range of physiological processes and health outcomes. Epigenetic regulation of thyroid development and function has been little explored. PAX8 (Paired Box 8) is a thyroid transcription factor implicated in thyroid gland development and differentiation. PAX8 gene methylation appears to be sensitive to the environment in early pregnancy.

Methods and Findings: Using a recall-by-epigenotype design, 118 Gambian children were recruited from the top and bottom quintiles for PAX8 methylation measured in blood DNA taken at 2-years of age. Participants were assessed for thyroid volume, function, urinary iodine, and body composition and bone measures by whole body DXA scan at age 5-8 years. In multiple linear regression models adjusted for relevant covariates, the low PAX8 methylation group was associated with a 0.61cm^3 [SE=0.15] or 21% increase in thyroid volume ($p < 0.0001$) and a 0.85 pmol/L [0.24] increase in free T4 (a change equivalent to 8.4% of the normal range, $p < 0.001$). Increased free T4 was associated with a decrease in all measures of overall body fat including log fat mass index ($\beta = -0.04$ [0.02], $p = 0.033$), log total fat mass ($\beta = -0.05$ [0.02], $p = 0.041$) and log fat lean ratio ($\beta = -0.05$ [0.02], $p = 0.045$), and with a decrease in log total-body-less-head bone mineral density ($\beta = -0.008$ [0.004], $p = 0.044$) after adjustment for relevant covariates. No fat or bone-related measures were independently associated with PAX8 methylation group.

Infant PAX8 methylation measurements and nutritional biomarker data from maternal blood taken from early pregnancy were available for 303 children. Logit PAX8 methylation z-score was significantly lower in boys ($\beta = -0.24$ [0.09], $p = 0.005$) and was nominally associated with 4 maternal one carbon metabolites: homocysteine (standardised $\beta = -0.11$ [0.05], $p = 0.05$), cysteine ($\beta = -0.16$ [0.05], $p = 0.003$), B12 ($\beta = -0.1$ [0.05], $p = 0.05$) and the vitamin B6 vitamers, PLP ($\beta = -0.12$ [0.06], $p = 0.03$). The association with cysteine remained significant after correction for multiple testing. PAX8 methylation was shown to be stable from age 7 and 17 years ($R = 0.76$, $p < 2.2 \times 10^{-16}$). We observed a strong relationship between cis-genotype and PAX8 methylation variability suggesting sensitivity to environmental exposures may be under partial genetic control.

An inverse relationship between PAX8 antisense expression and methylation at the analysed region was seen in non-malignant thyroid tissue from The Cancer Genome Atlas.

Conclusions: A maternal early nutrition-sensitive DNA methylation signature at the *PAX8* gene was associated with thyroid function and volume in Gambian children. These findings may have significant implications for early embryonic programming of thyroid-related health and disease.

P1-196

Clinical and Molecular Presentation of Congenital Hypothyroidism Caused by Thyroglobulin Gene Mutations

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Background: Congenital hypothyroidism (CH) characterized by a deficient secretion of thyroid hormone in newborn. It is the most common endocrine disease in the children with an incidence rate about 1:3000 live births in Saudi Arabia. Thyroid dysgenesis and dyshormonogenesis are the most common causes. Thyroid dyshormonogenesis commonly inherited as autosomal recessive disorders. Although Thyroglobulin followed by TSHR mutations are the most common genetic defects in Saudi patients, there was no enough data regarding their clinical manifestations and management of these cases.

Method: A retrospective cohort study, conducted at King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia. Including 10 patients who genetically confirmed to have CH secondary to Thyroglobulin gene mutation. Medical Charts were reviewed for clinical, biochemical and radiological data.

Result: 4/10 patients (40%) presented with goiter antenatally and received multiple intra-uterine Thyroxin injection, 8/10 (80%) presented with enlarged goiter and 5/10 (50%) with growth retardation. Biochemically, they all presented with high TSH and low fT4. Interestingly, all patients have persistently high TSH level even with upper-normal level of fT4 ($P=0.0022$) while on excellent dose of L-Thyroxin. We found 3 previously reported homozygous mutation in TG gene. One patient has compound heterozygous likely pathogenic mutation.

Conclusion: This study is the largest cohort series to date describing the clinical and molecular features of CH secondary to Thyroglobulin gene mutation worldwide, as well as their management and prognostic indicators. It will contribute significantly to the understanding of genetic mutations underlying the congenital hypothyroidism related to thyroglobulin mutation in Saudi population.

P1-197

Management of newborns born to mothers with autoimmune hypothyroidism

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Background: Maternal autoimmune hypothyroidism can have negative consequences on the fetus: on the one hand, maternal hypothyrosinemia might affect the fetal brain development in the early stages of pregnancy; on the other, thyroid inhibiting antibodies can pass through the placenta. It is currently unclear if these antibodies may affect the newborn's thyroid function. Consequently, there are no certain indications regarding the management of newborns born to mothers with autoimmune hypothyroidism.

Aims: The purpose of the study is to verify the utility of the serum thyroid function test in newborns born from mothers with autoimmune hypothyroidism.

Methods: All newborns born at term, with mother suffering from autoimmune hypothyroidism and with negative neonatal screening for congenital hypothyroidism (CH), were tested for serum thyroid function by measurement of free thyroxine (fT4) and thyroid stimulating hormone (TSH) in 15th-20th day of life. In the same session a second dried blood spot was collected. Data concerning maternal replacement therapy with L-thyroxine during pregnancy were retrospectively collected.

Results: From November 2019 to March 2020 in Verona (Italy), we found 54 newborns born to mothers with autoimmune hypothyroidism. No extra cases of CH were detected and no infants required replacement therapy. We found a good concordance between the results of serum thyroid function and the dried blood spot at 15-20 days of life.

Conclusions: The prevalence of maternal autoimmune hypothyroidism in our study was 1:29. Therefore, it is not a rare condition and the management of these newborns needs to be carefully defined. We suggest that newborns born to mothers affected by autoimmune hypothyroidism should be submitted to only a second dried blood spot between 2nd and 4th weeks of life. If hormone values result in the normal referring range, no additional test should be performed.

P1-198

Novel single nucleotide variation in DUOX2 and NPTX1 genes in two Sardinian sisters with transient congenital hypothyroidism

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Introduction: Transient congenital hypothyroidism (TCH) refers to a temporary deficiency of thyroid hormone identified after birth, with low thyroxine (T4) and elevated thyrotropin (TSH). Approximately 17%-40% of children diagnosed with CH by newborn screening (NBS), have transient hypothyroidism. Levo-thyroxine (L-T4) early treatment is recommended at the dose 10-15 µg/kg/day. Children with thyroid gland *in situ* should be re-evaluated after the age of 3 in order to differentiate a transient from a permanent form. Several genetic variants, including *dual oxidase 2* (DUOX2), have been described in patients with TCH. DUOX2 (15q15.3) encodes for a glycoprotein member of the NADPH oxidase family required for iodine organification and thyroid hormone synthesis. NPTX1 (Neuronal Pentraxin 1, 17q25.3) is exclusively localized to the nervous system, and probably regulates neural lineage specification from pluripotent stem cells. To date, no association has been reported between NPTX1 and CH.

Case Report: Two sisters were born in 2013 and 2017 from uneventful pregnancies. Prenatal, neonatal medical history were unremarkable. No consanguinity, no other family members affected. CH has diagnosed by NBS. Serum thyroglobulin was normal and the thyroid ultrasound showed a normal gland *in situ*. Thyroid scintigraphy was not performed. They required small doses of L-T4 (≈2 µg/kg/die) to maintain normal serum fT4 and TSH. Next generation sequencing revealed a homozygous DUOX2 missense variant p.A297S (c-G889T) in exon 8 (rs 755241413, MAF<0.01), and a heterozygous NPTX1 missense variant p.L95V (c.C283G) in exon 1 (rs371219313, MAF<0.01). After withdrawal from therapy the older sister presented slightly elevated serum TSH (<10 µUI/ml) with normal fT4. The youngest sister, now 3.2 year old, has just stopped treatment.

Conclusion: Novel missense variants of DUOX2 gene and NPTX1 gene were found in two sisters with CH. While DUOX2 variants are known to be associated with TCH, the significance of the NPTX1 variant and its pathogenic activity are not known and need further investigation.

P1-199

New p.Ser237Asn Activating Mutation At The TSHR Receptor, Causing Familial Non- Autoimmune Hyperthyroidism

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Background: The pathogenesis of hyperthyroidism varies greatly, with familial non-autoimmune autosomal dominant hyperthyroidism being a rare cause. In patients who are genetically related, thyrotoxicosis develops without the clinical features of autoimmunity. In this study, we present five family members with familial hyperthyroidism who have a confirmed mutation of p.Ser237Asn in the TSHR receptor.

Case Report: Our patient, a 13,5- year-old boy, presented with clinical symptoms that were characteristic for diagnosis, including tachycardia, weight loss, unexplained fatigue, muscle tremors, and advanced bone age. Also, abnormal laboratory results were observed [TSH <0,01 uIU/ml (-); fT3 7,79pg/ml (); fT4 2,78ng/ml (); TPO 6,3 IU/ml (N); ATG 15,7 IU/ml (N); anti-TSH <0,3 (N)]. Increased vascular flow in the gland was noted on ultrasound. Treatment began four months ago, and consisted of MMI 0,5mg/kg/day, which he is still taking, and β- blocker 0,5mg/kg/day. No adverse effects were observed.

His mother, a 36-year-old woman, was diagnosed in 2009 with non-autoimmune hyperthyroidism and has been treated with radioactive iodine since. Family history of hyperthyroidism was noted in both her sister and mother. The grandmother of our patient was initially diagnosed and treated with thyroid therapy at the age of 42, followed by radioiodine therapy, which resulted in her developing hypothyroidism. The boy's aunt received a thyroidectomy following an ineffective pharmacological treatment, and also currently presents with hypothyroidism. One of her daughters, although currently in good health, has a pathogenic mutation.

Searching for the genetic basis of hyperthyroidism, blood was taken from the family members and sent to the Biomedicine Department of the University of Turku. A new mutation, p.Ser237Asn, was identified activating at the thyrotropin receptor in all family members, causing the overproduction of thyroid hormones and causing associated clinical features.

Conclusion: In patients who have developed non-autoimmune hyperthyroidism, deepened genetic history should be investigated, along with performing proper tests to possibly identify a gene mutation in the TSHR receptor. Proper radical therapy can be started following a correct diagnosis.

P1-200

Functional studies of *PAX8* gene variants in patients affected by congenital hypothyroidism with eutopic thyroid gland

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Introduction: Thyroid dysmorphogenesis is a heterogeneous group of hereditary diseases produced by the total/partial blockage of the biochemical processes involved in thyroid-hormone synthesis and secretion. Many genes are involved in this process. *PAX8* is a transcription factor essential for thyroid-gland morphogenesis and synthesis of thyroid hormones, since it activates *TG*, *TPO* and *TSHR* gene transcription. More than 50 *PAX8* variants were reported, but most not functionally tested. We identified 4 *PAX8* variants in 5 patients with congenital hypothyroidism (CH).

Objective: To determine if these *PAX8* variants are pathogenic with *in-vitro* functional studies.

Patients and Methods: Patients

Five patients (4 males, 1 female), from the Catalan-CH-screening program (N=70), with an eutopic thyroid. Screening TSH was 68.3±58.4 mU/L and confirmation TSH was 264±168.4 mU/L and T4L 0.94±0.38 ng/dL. Scintigraphy in 4 patients showed an uptake absence in 1, a hypocaptating gland in 2 and a normocaptating gland in another. Four patients were reevaluated at 4.5±2.3 years and diagnosed with permanent hypothyroidism: 2 mild (subclinical) and 2 severe. The fifth had neonatal hyperthyrotropinemia, started levothyroxine (22 months, TSH=13.8 mU/L) and was reevaluated (4 years) confirming permanent mild HC. The discharge test (perchlorate) was negative in 2 and compatible with partial iodine-organization deficit in 3. Massive-sequencing techniques identified *PAX8* heterozygous variants in these patients (3 missense, one deletion): c.117C>A/p.(S59R); c.196_198delTAC; c.397C>T/p.(R133W) and c.398G>A/p.(R133Q) (in 2 patients).

Methods: *In-vitro* functional studies based on transactivating activity of *PAX8* on a *TG*-gene promoter were performed. We obtained a *PAX8* wild-type (WT) expression vector and performed site-directed mutagenesis to obtain mutant-expression constructs of the variants. A *TG* promoter was inserted into a reporter. These vectors (*PAX8*-WT/*PAX8*-mutant + *TG*-reporter) were transiently transfected into HEK293 cells and dual-luciferase assay was performed. Experiments were performed ≥3 times. The transactivating activity of the mutants was compared to WT.

Results: *PAX8* variants had an impaired transcriptional activity of *TG* promoter: c.177C>A retained a 76% activity, c.196_198delTAC a 69%; variant c.397C>T a 52%, and c.398G>A a 71%. Activities were statistically lower than the WT or almost.

Therefore, the variants were considered pathogenic and to be causing the CH in these patients.

Conclusions: *PAX8-in-vitro* functional studies have shown that our patients' variants are pathogenic. These studies have proven their effectiveness in evaluating these types of variants and will continue to be used to analyze the rest of the variants detected in *PAX8* in our patients.

ePoster Category 2

Adrenals and HPA Axis

P2-1

Circadian rhythm of salivary cortisol and cortisone in school-aged children born very preterm and adequate for gestational age

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Introduction: Higher evening cortisol level has been previously described in very preterm infants, possibly reflecting increased Hypothalamic-Pituitary-Adrenal Axis (HPA) tone or alterations in HPA regulation throughout the day. These relatively subtle differences in HPA axis function in preterm compared to full-term children may become meaningful in terms of metabolic risk later in life if sustained over time. Still, only a few studies have investigated whether altered reprogramming of the HPA axis persists beyond toddler age.

Objective: To compare salivary cortisol and cortisone levels and their circadian rhythm between very preterm and term school-aged children, all born adequate for gestational age.

Methods: In this cross-sectional study, 69 very preterm (< 32 gestational weeks) and 42 full-term (> 37 gestational weeks) school-aged children (4.9 to 8.9 years old) were included. Cortisol and cortisone concentrations in saliva, collected in the morning, at mid-day, afternoon, and before bedtime, were measured by mass spectrometry.

Results: Cortisol and cortisone levels and profiles were similar in preterm and full-term children, albeit full terms had slightly higher salivary cortisol at bedtime compared to very preterm children.

	Very preterm infant (n=69)		Full-term infants (n=42)		P-value
Salivary cortisol ug/dl median (SD)					
Morning 08:00 am	0.18 (0.12)	3*	0,19 (0,14)	1*	0.86
Mid-day	0.057 (0.036)	6*	0,075 (0,06)	3*	0.38
Afternoon	0.04 (0.05)	19*	0.048 (0.04)	10*	0.12
Bedtime	0.038 (0.54)	48*	0.059 (0.10)	22*	0.03
Salivary cortisone ug/dl median (SD)					
Morning 08:00 am	0.82 (0.38)	0	0.81 (0.49)	0	0.76
Mid- day	0.39 (0.17)	0	0.42 (0.20)	0	0.51
Afternoon	0.25 (0.20)	0	0.30 (0.18)	1**	0.09
Bedtime	0.18 (0.23)	0	0.23 (0.3)	0	0.09

*Number of participants with low level of cortisol concentration below the limit of detection

** Number of participants with low level of cortisone concentration below the limit of detection

Conversion units to nmol/l = ug/dl x 27.59

Conclusion: According to our data, very preterm and full-term school children adequate for gestational age showed preserved cortisol and cortisone rhythm. Also, both groups had similar levels of these hormones at each evaluated time during the day. Considering that an important proportion of cortisol concentrations in saliva are below the detection limit, cortisone measurement is more suitable for circadian rhythm studies in this type of sample.

P2-2

How do urine steroid metabolites of spot samples correlate with 24 hour urine specimens in children with congenital adrenal hyperplasia?

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Introduction: Steroid profiling in children with congenital adrenal hyperplasia (CAH) is used to monitor the balance between androgen and cortisol metabolites and to decide on the optimal glucocorticoid dosage. Twenty-four hour collection is the gold standard for measurement of steroid metabolites in urine, because steroid production follows a circadian rhythm and is influenced

by short-term stress and steroid drugs. For some children, e.g. those who were diapers, it is not feasible to collect urine over 24h non-invasively, and urine spot steroid assessments might still be an alternative in CAH.

Objective: To investigate whether steroid metabolites in 24h urine collections correlate with those determined in urine spot samples in children with CAH.

Methods: We collected 24h urine and urine spots from children and adolescents with CAH due to 21-hydroxylase deficiency and analysed 40 steroid metabolites using GC-MS (see Table). To assess the strength of correlations between 24h and spot urine metabolites, we calculated Kendall's tau-beta separate for morning and non-morning urine. We set the level to $\alpha=0.005$ to account for multiple testing.

Results: Thirty patients provided both 24h collections and spot urine samples (n=20 morning, n=10 non-morning). Out of the 40 metabolites, there was a strong correlation between 24h and morning spot urine for 17 metabolites, and between 24h and non-morning spot urine for 9 metabolites ($\tau>0.45$, $p<0.005$). Specifically, correlations were noted for progesterones, corticosterones, tetrahydroaldosterone, androgens, estriol, tetrahydro-11-deoxycortisol, but not for the cortisol metabolites (Table).

Conclusions: Urinary steroid profiling in children with CAH revealed correlations between 24h urine specimens and spot urines. Spot urine might suffice to recognize the specific pattern of 21-hydroxylase deficiency for diagnostics (e.g. through marker metabolites 11-oxo-pregnanetriol, TH-11-deoxycortisol). Whether a spot urine can inform about metabolic control of treatment in CAH needs to be further tested in a larger number of specimens.

Table. Correlations between 24h and spot urine metabolites in children with CAH

	24h vs morning n=20	24h vs non-morning n=10
Progesterones		
17-hydroxypregnanolone	+	+
Pregnanediol	+	
Pregnanetriol	+	+
11-oxo-pregnanetriol	+	+
Corticosterones		
TH-deoxycorticosterone	+	
TH-11-DH-corticosterone		
TH-corticosterone	+	
5 α -TH-corticosterone	+	+
TH-Aldosterone	+	
Androgens		
Androsterone	+	+
Etiocholanolone	+	+
Dihydroandrosterone	+	+
11-oxo-etiocholanolone		
11 β -OH-androsterone	+	+
11 β -OH-etiocholanolone	+	
Dehydroepiandrosterone	+	
Androstenediol		
16 α -OH-DHEA		
Androstetriol		
Pregnenetriol	+	
Testosterone		
5 α -dihydrotestosterone		
Estrogens		
Estriol	+	
17 β -estradiol		
TH-11-deoxycortisol	+	+
Cortisols		
Cortisone		
TH-cortisone		
β -cortolone		
20 α -dihydrocortisone		
20 β -dihydrocortisone		
Cortisol		
TH-cortisol		
5 α -TH-cortisol		
α -cortole		
β -cortole		
20 α -dihydrocortisol		
20 β -dihydrocortisol		
6 β -OH-cortisol		
18-OH-cortisol		
α -cortolone		

Legend: +, strong correlation (Kendall's tau >0.45 and p<0.005); empty cells, correlation not significant.

P2-3

Endocrine-disrupting chemicals: an often-forgotten etiology of endocrinological disturbances

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Background: Endocrine disruptors (ED) are chemicals that can mimic hormones and interfere with their receptors, causing endocrinological abnormalities.

Clinical Report: We present the case of a previously healthy, melanodermic, two-year-old female, who had a three-month evolution of clitoromegaly and generalized hypertrichosis. Endocrine blood work showed suppressed serum androgens suggesting steroid exogenous contact. Karyotype, bone age, growth rate, and head and pelvic imaging exams were unremarkable. Detailed medical history revealed exposure to cyclosiloxanes and parabens within an anti-frizz hair product. She totally recovered during the 16 months after its withdrawal.

Discussion: ED have become a matter of concern over the past few years, due to its significant impact on public health, even in low doses. However, besides worldwide regulatory efforts, there are still several known ED in commonly used products, and also others that are not even listed on its labels. Therefore, strict rules should be put on urgently.

P2-4

Serum Sex Hormone Binding Globulin Levels, but not 4-Hour Profile of 17-OH Progesterone, Would be Useful in Monitoring Children with Congenital Adrenal Hyperplasia

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Background: There exists no gold standard for adjustment of treatment in congenital adrenal hyperplasia. Clinicians try to avoid over-and undertreatment by considering various indicators. We aimed to investigate the sampling times of 17-hydroxyprogesterone (17-OHP) and the use of sex hormone-binding globulin (SHBG) as a monitoring parameter, the association of which was not studied with clinical features.

Materials and Methods: This cross-sectional study included 16 children (9 girls, 7 boys; median age 7 years) with salt-wasting congenital adrenal hyperplasia due to 21-hydroxylase deficiency. In addition to standard clinical evaluation, serum levels of 17-OHP, cortisol, androstenedione, SHBG were obtained between 07.00 and 08.00 a.m., prior to morning dose of hydrocortisone and

fludrocortisone, and 17-OHP and cortisol levels 1, 2, and 4 hours after the morning dose. Serum samples of 17-OHP and cortisol were assayed using high-performance liquid chromatography-tandem mass spectrometry. Subjects were divided into good and poor control subgroups according to the presence of hyperandrogenic state, considered when (i) bone age SD score ≥ 2 , (ii) annual change in height SD score was ≥ 0.3 , or (iii) androstenedione >3.3 ng/mL for girls and >3.1 ng/mL for boys. The results are reported as median (interquartile range).

Results: Premedication 17-OHP levels were strongly correlated with 17-OHP levels 1, 2, and 4 hours after the morning dose ($r_s=0.929$, $p<0.01$; $r_s=0.943$, $p<0.01$; $r_s=0.835$, $p<0.01$, respectively). Clinical features, indicators of hyperandrogenic state, and the ratio of reduction of 17-OHP levels after medication were similar in children with premedication serum 17-OHP level >10 ng/mL ($n=9$) vs. <10 ng/mL ($n=7$) while hydrocortisone dose was significantly lower in children with high 17-OHP levels [11 (8) vs. 19 (11) mg/m²/day, $p=0.017$]. Subgroup analyses revealed that clinical and biochemical features were not different except significantly higher SHBG values [92 (59) mmol/L vs. 40 (22), $p=0.036$] in the growth acceleration group ($n=8$) and significantly lower daily hydrocortisone doses in children with growth acceleration [7 (7) vs. 15 (9) mg/m²/day, $p=0.036$] and in those with elevated androstenedione levels [9 (6) vs. 19 (9) mg/m²/day, $p=0.039$].

Conclusions: When over- or undertreatment is suspected, the levels of 17-OHP should not be trusted, it misses the hyperandrogenic state or may falsely suggest unnecessary dose increments. A 4-hour profile of 17-OHP does not add significant data over early morning premedication 17-OHP levels. In general, low doses of hydrocortisone should be avoided. SHBG can be considered as an indicator of hyperandrogenemia.

P2-5

Glucocorticoid side-effects in Duchenne Muscular Dystrophy: Systematic review of side effects in published literature and a survey of the concerns of the patient community

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Background: Long-term use of glucocorticoid for management of Duchenne muscular dystrophy (DMD) has been standard of care for over 20 years with documented improvement in outcomes. Side-effects are common particularly endocrine and bone adverse effects. To date, there is limited information on the perception of glucocorticoid side effects by parents/guardians and those living with DMD.

Aims:

- To identify glucocorticoid side-effects investigated in published literature for boys with DMD.
- To identify the patient perception of glucocorticoid side-effects.

Methods: A systematic literature search was performed using MEDLINE, EMBASE and Cochrane Library (January 2021). An online survey was circulated via UK-based patient groups for a period of 5 weeks. Responders were asked to rate their concern of glucocorticoid side-effects on a scale of 0 to 10 (0: not concerned to 10: extremely concern). Ethics approval was sought from the University of Glasgow Ethics Committee. Continuous data expressed as median (25th, 75th centile).

Results: Sixty-one publications were identified from the systematic search. Fifty-three glucocorticoid side-effects were considered in those publications. The top three side-effects considered were: weight gain/obesity (43/61; 71%), poor growth/short stature (38/61; 62%) and blood pressure abnormalities (25/61; 41%).

Thirty-three parents/guardians responded to the online survey. Median age of the person with DMD was 10 years (6,13) with median age of starting glucocorticoid at 5 years (4, 6). Thirty-one out of 33 are still on glucocorticoid; two had discontinued therapy due to concerns about side-effects and three who are still on treatment were no longer happy to continue glucocorticoid. The top three glucocorticoid side-effects experienced by the young person with DMD as reported by parents/guardians were: poor growth/short stature (25/33; 76%), cushingoid features (21/33; 64%), and weight gain/obesity (19/33; 58%). Glucocorticoid side-effects which concern parents/guardian the most were: long bone fracture [median score 9 (7,10)], vertebral fractures [median score 9 (7, 10)], weight gain/obesity [median score 8(7,9)] and delayed puberty [median score 8 (5,9)]. Glucocorticoid side-effects which concern the young person the most were: short stature [median score 7(2,9)], weight gain/obesity [median score 7(1, 8.8)] and cushingoid features [median score 5.5(1, 8.8)].

Conclusion: This study identified for the first time that endocrine/bone side effects concern parents/guardians and young people with DMD greatly. Research on therapies/DMD treatment that may eliminate or minimize such side effects are needed, strongly supported by concerns raised by the patient community.

P2-6

Single centre experience of Hydrocortisone Granules (Alkindi) in children under 6 years of age with Adrenal Insufficiency

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Introduction: Children with Adrenal insufficiency (AI) are usually managed with glucocorticoid replacement as hydrocortisone. Treatment options in younger patients include administering an aliquot of 10mg hydrocortisone tablets dissolved in water. However, this is time consuming and may be inaccurate. We describe our experience of using Alkindi (www.diurnal.co.uk), the first hydrocortisone preparation licensed for children with AI.

Method: Thirty-one patients with AI (24M, 7F) under 6-years of age in our service were identified over a 30 month period. 18 were diagnosed with congenital adrenal hyperplasia, 11 combined pituitary hormone deficiency and 2 neonatal adrenal haemorrhage.

22 were on hydrocortisone preparations already and 9 were started on Alkindi at the time of diagnosis. Data on growth, episodes of stress dosing and adrenal crisis were documented at clinic visits and a questionnaire captured caregivers experience with their current regimen, with stress-dose information focused around the last 6-months.

Results: The 9 newly-diagnosed patients started directly onto Alkindi all remain on this preparation. 20 of the 22 patients on hydrocortisone 'tablet solution' were switched to Alkindi- 15 (75%) remain on Alkindi 23-30 months later, tolerating and preferring this treatment; 5 (25%) did not tolerate Alkindi and returned to dissolving tablets. In the most recent 6-months, stress dosing varied from 0-4 occasions, with an average of 2.8 episodes per patient per year and with no significant difference between preparations. No patient was admitted with an adrenal crisis. For patients switched to Alkindi (n=15), the height SDS moved closer to the population average after 1-year on Alkindi (mean height SDS pre-treatment -0.42; 1-year post-treatment -0.19). The heights of 12/14 patients were closer to the mid-parental target SDS (0.13). For those starting Alkindi at diagnosis (n=9), height SDS also moved closer to the population average (mean height SDS pre-treatment -1.52; 1-year post-treatment -0.15) and mid-parental height SDS (0.58). E-mail questionnaires were sent to 27 patients and 23 responded. All were satisfied (38% HC; 27% Alkindi) or very satisfied (62% HC; 73% Alkindi) with their current hydrocortisone preparation.

Conclusions: This is the largest single centre report of Alkindi administration over the longest time-period. All newly treated patients remained on Alkindi, although 25% of families who transitioned to Alkindi opted to return to dissolving tablets. There was high patient satisfaction irrespective of the underlying preparation, with no safety issues highlighted and in particular no adrenal crises. Growth parameters were encouraging, with no evidence of toxicity based on height SDS scores.

P2-7

Emotion regulation in congenital adrenal hyperplasia

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Objective: Oral hydrocortisone medication for Congenital Adrenal Hyperplasia (CAH) could lead to suboptimal blood cortisol levels throughout the day. In addition, the HPA-axis is rendered inflexible in patients. Cortisol is crucially involved in the stress response as well as in generating and regulating emotional responses to stimuli. Sub-optimal cortisol levels, in combination with a less flexible HPA-axis, could therefore lead to problems with emotion regulation in patients. The present study aimed to address emotion regulation skills in CAH.

Methods: 32 patients with CAH (20 females) and 37 population controls (23 females) performed an emotion regulation task. During the task, participants were asked to either upregulate, downregulate or maintain their emotional responses to negative or neutral images. During image presentation, a sound burst was presented

to evoke an acoustic startle response. Emotional reactivity to the sound was measured with facial EMG of the left orbicularis oculi muscle to assess amplitude and likelihood of startle responses.

Results: Compared to controls, patients with CAH showed a smaller upregulation of acoustic startle response likelihood when viewing negative stimuli. No other differences were observed.

Conclusion: Patients seemed to have some difficulties with upregulating their emotions. Failure to upregulate startle likelihoods could potentially be associated with altered adrenal medulla function, which could be addressed by future studies. However, the effects were limited and our results rather indicate that CAH is not associated with emotion regulation problems.

P2-8

High-dose steroids in the management of Paediatric Multisystem Inflammatory Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS): Considering the hypothalamic-pituitary-adrenal axis

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Background: Steroid therapy has been used as a therapeutic strategy in the management of Paediatric Multisystem Inflammatory Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS) with good effect. However, as always, exogenous steroid administration carries with it a risk of iatrogenic adrenal insufficiency.

Aim: We characterise steroid therapy use in PIMS-TS and consider implications for hypothalamic-pituitary-adrenal (HPA) axis function.

Methods: We conducted a retrospective review of children (<18 years) admitted to a tertiary paediatric centre with PIMS-TS during the first wave of the COVID-19 pandemic (1st April 2020 to 10th May 2020). We collected data on duration, type, and dosing of steroid therapy used as part of PIMS-TS management. Median total steroid dose is expressed as mg/m²/day, hydrocortisone equivalent. Data are presented as median (interquartile range (IQR)).

Results: A total of 36 patients were included in this study with a median age of 9.5 years (IQR 8.0-13.4) and a median body surface area of 1.20m² (IQR 0.82-1.43). The majority of patients were admitted to the Paediatric Intensive Care Unit (97.2%, n=35) for a median length of stay of 2.8 days (IQR 1.0-5.9). Steroid therapy was commenced in most children (75.0%, n=27). Median total steroid dose was 237mg/m²/day (IQR 122-425) and treatment length was 26 days (IQR 23-35). Dosing regimens predominantly involved a short course of high-dose pulsed methylprednisolone followed by oral prednisone tapered over several weeks. There were no baseline cortisol nor ACTH concentrations available for any patient. Three patients (8.3%, n=3) were referred to endocrinology for advice on steroid management. One of these three patients underwent dynamic testing of the HPA axis (short Synacthen test) which

demonstrated iatrogenic adrenal insufficiency. This patient later recovered endogenous adrenal axis function during paediatric endocrinology follow-up.

Conclusion: Prolonged steroid therapy at supraphysiological doses is often used in the management of PIMS-TS. Patients with PIMS-TS represent a clinical cohort vulnerable to iatrogenic adrenal insufficiency secondary to HPA axis suppression. Steroid therapy should be withdrawn gradually, maintaining a high index of suspicion for adrenal compromise and a low threshold for discussion with paediatric endocrinology teams. If concerns arise at any point during or after the steroid taper, the dose should not be further reduced and dynamic testing of the HPA axis should be arranged. There is a need for advice on steroid management to be incorporated into national and international PIMS-TS guidance.

P2-9

Variability of advice and education for steroid sick day dosing in Duchenne Muscular Dystrophy and the impact of the COVID-19 pandemic: Results of a UK wide patient survey

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Introduction: The use of long-term oral corticosteroid in DMD is associated with a range of side effects including secondary adrenal insufficiency. The updated international care consensus (2018) recognizes this important issue and recommends emergency plans to be in place.

Aim: This online UK-wide patient survey aims to determine the advice and education given for sick day dosing plans and the impact of the COVID-19 pandemic in corticosteroid-treated young people with DMD.

Methods: The survey was circulated between November 2020 and January 2021.

Results: A total of 130 responses were obtained from 129 parents/guardians of a person with DMD. One parent provided responses for twins. Median age of the person with DMD was 11.5 years (Range:5, 26). Eighty-three of 130(64%) were on daily corticosteroid. Sixty of the 130(46%) had access to hydrocortisone for injection with severe and/or vomiting illness. Of the 60 with access

to injectable hydrocortisone, 44/60(73%) also had an oral stress dose plan for mild illness. However, 48/70(69%) with no access to injectable hydrocortisone did not have an oral stress dose plan. Of the 60 with access to injectable hydrocortisone, 42/60(70%) had received some form of training. Twenty-one of the 42(50%) of those who received training performed a practice injection. Thirty-four of the 42(81%) who received training felt confident about administering an injection as opposed to 9/18(50%) who did not receive any training. Forty-one of the 42(98%) who received training were clear on when injectable hydrocortisone is needed as opposed to 14/18(78%) who did not receive training. Prior to the COVID-19 pandemic [February 2020], 43/130(33%) were provided with an oral emergency stress dose plan for mild-moderate acute illness. After February 2020, 66/130(51%) were given an oral emergency stress dose plan for mild-moderate acute illness. A total of seven different oral stress dose plans were identified for those on daily corticosteroid and a greater number of combinations of plans in those on the intermittent regimen.

Conclusion: Despite the risk of adrenal crisis in patients who are treated with long-term corticosteroid and recent international guidance (2018), emergency sick day plans were not consistently in place in this national survey of boys with DMD. Solutions could be challenging but must take a multi-dimensional and multi-disciplinary approach. Guidance at a national level and the development of structured education for hospital clinicians and patients maybe steps towards improving clinical outcomes.

P2-10

Clinical characteristics of cytochrome P450 oxidoreductase deficiency: a nationwide survey in Japan

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Cytochrome P450 oxidoreductase deficiency (PORD) is a disorder of steroidogenesis that causes various symptoms such as skeletal malformations, disorders of sex development, and adrenal insufficiency. The aim of this study was to elucidate the clinical

characteristics, especially age at diagnosis and treatment, of PORD from the perinatal period to adulthood in Japan. The first questionnaire was sent to 183 council members of the Japanese Society for Pediatric Endocrinology on 1 September 2018. The response rate was 65%, and a total of 39 patients with PORD were examined at 20 hospitals. The second questionnaire was sent in November 2018 to the council members examining these 39 patients with PORD. The response rate was 77%, and we received clinical information on 30 of the 39 patients. The two novel clinical findings were the age at diagnosis and the treatment of Japanese patients with PORD. In many cases, PORD can be diagnosed at <3 months of age. Early diagnosis is important for appropriate follow-up in accordance with the natural history of PORD, such as deciding whether to prescribe daily hydrocortisone treatment or administer sex hormone replacement therapy. Because of the lack of guidelines or manuals for PORD treatment, such as the use of hydrocortisone, one of our initial aims in this survey was to reveal how hydrocortisone is administered to patients with PORD. Hydrocortisone as the primary treatment during infancy can be used daily or in stressful situations; however, because patients with PORD generally have mild to moderate adrenal insufficiency, some might be able to avoid hydrocortisone treatment. Patients with PORD should be carefully followed up, and treatment should be optimized as for patients with other types of adrenal insufficiency. Other characteristics in the present study, such as external genitalia, skeletal malformations, genetic analysis, puberty, development, maternal virilization, were similar to those described in previous reports.

P2-11

Rare Presentation of Adrenal Insufficiency in an Infant with Holocarboxylase Synthetase Deficiency

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Introduction: Adrenal insufficiency can be caused by different factors. Biotin deficiency is either nutritional or related to synthesis/recycling defects. We are reporting a rare case of adrenal insufficiency complicating a late diagnosis of holocarboxylase synthetase deficiency in an infant who also had protein-S-deficiency, later thought to be secondary.

Case: Term female infant born, to non-consanguineous parents, in good condition with birth-weight 3.1kg (10th-centile) developed extensive nappy dermatitis that was followed by erythematous scaly patches on her back and excoriation on her abdomen. She gained weight and crossed centiles by 2-month. At 3-month, the rash got worse, therefore she was prescribed

mometasone 1% cream and clotrimazole-betamethasone which the mother continued to apply in large amounts over large body areas for 2-months. At 5-months of age, she presented to the Emergency Department with an acute history of poor activity and respiratory distress. Examination revealed cushingoid appearance, weight 8.3 kg (>99th centile), with dry peeling, depigmented skin and necrosis of her right toe. She had volume and catecholamine refractory shock with severe lactic acidosis, hypoglycemia (1.4mmol/L), hyperlactatemia (10mmol/L), hypokalemia (2.7mmol/L), hyponatremia (155mmol/L), with cortisol (454nmol/L), normal renin (13.8mIU/L) and aldosterone (183pmol/L) levels. Adrenal insufficiency was considered and hydrocortisone (20mg/m²/day) was started. Lactic acidosis peaked to 19mmol/L and started improving a week after hemodynamic stability to a baseline of 2-4mmol/L. Thereafter, she developed hypertension despite halving the steroids. After 2-weeks of stability, she acutely developed irritability and acidotic breathing with similar biochemical derangements but with normal glucose and ammonia levels. However, she was more critical with increasing refractory lactic acidosis up to 21mmol/L needing high inotropic support and hemodialysis to reduce acidosis. At that point, acylcarnitine profile in dried blood spots revealed significantly elevated 3-hydroxyisovaleryl-carnitine 9.23(0.05-0.29umol/L), with elevated free carnitine 496(10.3-56.9umol/L) that was secondary to carnitine supplementation. Significantly elevated 2-hydroxyisovaleric acid was also detected in urine organic acids. Biotin was initiated and the baby improved dramatically within 48-hours. The thrombophilia workup revealed functional protein-S 0.247(0.54-1.18u/mL). Whole exome sequencing revealed compound heterozygous mutations in HLCS gene, consistent with the diagnosis of holocarboxylase synthetase deficiency. No mutations were found to explain protein-S-deficiency.

Conclusion: Very rare presentation of three underlying pathologies, at one time. Hyponatremia, hypokalemia, obesity and hypertension were not reported previously in Biotin/holocarboxylase synthetase deficiency, two disorders notoriously known to be associated with failure to thrive. Steroid use should be restricted in infancy as it caused adrenal insufficiency in this case.

P2-12

Defective Cortisol Secretion in Response to Spontaneous Hypoglycemia but Normal Cortisol Response to ACTH stimulation in neonates with Hyperinsulinemic Hypoglycemia (HH)

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Introduction: Hyperinsulinaemic Hypoglycaemia (HH) is the most common cause of recurrent and persistent hypoglycemia in the neonatal period. Cortisol and GH play an important role as counterregulatory hormones during hypoglycemia. Both antagonize the peripheral effects of insulin and directly influence glucose metabolism.

Patients and Methods: We studied cortisol and GH secretion in newborn infants with HH during spontaneous hypoglycemia. In addition, their basal ACTH level and cortisol response to a standard dose ACTH were performed.

Results: Nine newborns with HH were studied during the first 2 weeks of life. During HH, their mean glucose concentration was 1.42 ± 0.7 mmol/L, mean beta-hydroxybutyrate level was 0.08 ± 0.04 mmol/L, and mean serum insulin level was 17.78 ± 9.7 μ U/mL. Their cortisol and GH levels at the time of spontaneous hypoglycemia were 94.7 ± 83.1 nmol/L and 82.4 ± 29 mIU/L respectively. They had a relatively low level of ACTH (range: 14:72 pg/mL, mean: 39.4 ± 20 pg/mL) during hypoglycemia. All infants had GH concentration > 20 mIU/L at the time of hypoglycemia. All infants underwent the ACTH test. Their basal serum cortisol levels did not differ compared to cortisol levels during hypoglycemia, and all had a normal peak cortisol response (> 500 nmol/L) in response to i.v. ACTH stimulation test.

Conclusion: Infants with HH have low cortisol response to spontaneous hypoglycemia with normal response to exogenous standard-dose ACTH. Checking the hypothalamic-pituitary axis (HPA) axis later in infancy using low dose ACTH may be useful to diagnose persistent HPA abnormalities in these infants. All HH infants had an appropriate elevation of GH during hypoglycemia.

P2-13

Utilisation Of The I-CAH Registry As A Tool For Facilitating Health Quality Improvement Strategies- Results Of An International Survey Of Specialist Centres

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Background: Recent studies using data from the International Congenital Adrenal Hyperplasia (CAH) Registry (www.i-cah.org) (1), have provided valuable insight into the determinants of reported acute adrenal insufficiency (AI) related adverse events, demonstrating that the I-CAH Registry can be used as a tool to create clinical benchmarks in CAH care.

Methods: Care quality reports were created for 32 centres who participated in the previous I-CAH study (1), providing information on the quality of data in the Registry and the quality of CAH care, as reflected by sick day episodes and adrenal crises. An online survey was circulated to centre leads to obtain feedback regarding the content and structure of the reports.

Results: Of the 32 centres, 27 (84%) in 18 countries responded to the survey. 22 (82%) agreed that the I-CAH care quality report would lead to an improvement in their centre's record of entering data in the I-CAH Registry, with 12 (45%) strongly agreeing and 10 (37%) somewhat agreeing; 5 (19%) centres neither agreed nor disagreed and none disagreed. Overall, 19 (70%) agreed that

the report would help to improve the care of children with CAH at their centre, with 11 (41%) strongly agreeing; 6 (22%) neither agreed nor disagreed and 2 (7%) disagreed. 26 (96%) agreed that the report was useful to determine how their centre compares to other centres with regards to entering data into the Registry, with 16 (59%) and 10 (37%) strongly agreeing and somewhat agreeing, respectively; 1 (4%) neither agreed nor disagreed. Respondents were asked whether the report was useful to determine how their centre compares to other centres in looking after children with CAH, 21 (77%) agreed that the report was useful in this respect, 13 (48%) strongly agreed; 4 (15%) neither agreed nor disagreed and 2 (7%) somewhat disagreed. 19 (70%) stated that the amount of information in the report was satisfactory, 5 (19%) and 3 (11%) stated that there was too much or too little information, respectively.

Conclusions: The real world data within the I-CAH registry are a valuable resource for studying core clinical outcomes that can be used as benchmarks for improving clinical care. Further work needs to be undertaken to determine whether the exercise of producing regular care quality reports for centres is associated with an improvement in these benchmarks.

Reference

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P2-14

Clinical and hormonal evolution of aldosterone synthase deficiency: Is complete remission possible?

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Background: Aldosterone synthase deficiency (ASD) caused by mutations in the *CYP11B2* gene is characterized by isolated mineralocorticoid deficiency. Data is scarce regarding clinical and biochemical outcomes of the disease in the follow-up.

Objective: Assessment of the growth and steroid profiles of patients with ASD at the time of diagnosis and after termination of treatment.

Design and Method: Children with clinical diagnosis of ASD were included in a multicenter study. Growth and treatment characteristics were recorded. Plasma adrenal steroids were measured using liquid chromatography-mass spectrometry. Genetic diagnosis was confirmed by *CYP11B2* gene sequencing and *in silico* analyses.

Results: Sixteen patients from 12 families were included (8 females; median age at presentation: 3.1 months, range: 0.4–8.1). The most common symptom was poor weight gain (56.3%). Median age of onset of fludrocortisone treatment was 3.6 months (0.9–8.3). Catch-up growth was achieved at median 2 months (0.5–14.5) after treatment. Fludrocortisone could be stopped in five patients at a median age of 6.0 years (2.2–7.6). Plasma steroid profiles revealed reduced aldosterone synthase activity both at diagnosis and after termination of treatment compared to age-matched controls. We identified six novel (p.Y195H, c.1200+1G>A, p.F130L, p.E198del, c.1122-18G>A, p.I339_E343del) and four previously described *CYP11B2* variants. The most common variant was p.T185I (40%).

Conclusions: Fludrocortisone treatment is associated with a rapid catch-up growth and control of electrolyte imbalances in ASD. Decreased mineralocorticoid requirement over time can be explained by the development of physiological adaptation mechanisms rather than improved aldosterone synthase activity. As complete biochemical remission cannot be achieved, a long-term surveillance of these patients is required.

P2-15

Clinical and metabolic characteristics of hyperandrogenic girls with non-classic congenital adrenal hyperplasia and polycystic ovary syndrome

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Background: Non-classic congenital adrenal hyperplasia (NCCAH) and polycystic ovary syndrome (PCOS) present with similar hyperandrogenic symptoms in adolescent girls and may be associated with the development of cardiometabolic disorders.

Aim: The purpose of the study was to evaluate the prevalence and the association between the clinical and biochemical parameters of hyperandrogenism and metabolic disorders in girls with NCCAH and PCOS at the time of initial diagnosis.

Methods: A total of 114 girls (mean age 14.7±2.8 years), newly diagnosed with NCCAH (n=59) or PCOS (n=55) between 2016–2020, were included in the study. Anthropometry, full physical examination and ultrasound of the ovaries were performed; hormonal (total testosterone, 17OHPregesterone, DHEAS, androstendione, LH, FSH) and metabolic parameters (serum lipids, glucose, insulin, CRP) were assessed. The overweight/obesity prevalence was defined according to IOTF age- and gender-specific BMI cut-offs. Ethical clearance was provided by the Ethical commission at Medical university of Varna.

Results: The clinical symptoms of hyperandrogenism were significantly more common in NCCAH girls. Hirsutism was present in 84.7% of the NCCAH girls and 52.7% of the PCOS patients, $p<0.0001$. Acne and alopecia were found in 33.9% and 18.6% of the NCCAH girls, respectively, compared to 9.1% ($p=0.001$) and 3.6% ($p=0.012$) of the PCOS participants. Menstrual disorders were significantly more common in PCOS girls (94.5% vs. 60%, $p=0.02$). The overall prevalence of overweight/obesity among the participants was 41.2%, being twice higher among PCOS (56.4%) than in the NCCAH patients (27.1%), $p=0.001$. Girls with PCOS had significantly higher body weight, height and BMI compared to NCCAH girls ($p<0.005$ for all). The mean basal level of 17OHPregesteron in NCCAH and PCOS girls was 2.1 ± 1.8 and 0.7 ± 1.4 ng/ml, respectively, $p<0.0001$. Testosterone (1.5 ± 0.8 vs. 1.2 ± 0.7 nmol/l), androstendione (15.96 ± 5.9 vs. 12.02 ± 6.7 nmol/l) and LH (11.3 ± 11.3 vs. 5.8 ± 4.1 IU/l) were significantly higher in PCOS girls ($p<0.05$). No differences between the groups were found in DHEAS and FSH levels. Testosterone level correlated significantly with the presence of menstrual disturbances ($r=0.642$, $p=0.001$). Polycystic ovarian morphology was observed in 32.5% of all participants, with a significantly higher prevalence among PCOS patients (56.4% vs. 10.2%, $p<0.0001$). No significant differences were found in the parameters of lipid and glucose metabolism between the groups. Patients with PCOS had higher CRP values ($p=0.025$).

Conclusion: The current results suggest that hirsutism and acne are the main clinical symptoms in NCCAH girls at diagnosis, while PCOS patients present more often with menstrual disorders and obesity.

P2-16

Rapid clearance of hydrocortisone as a cause of poor control of CAH detected by 24-hour profiling of hydrocortisone concentrations

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Introduction: Hydrocortisone (HC) has a short half-life and individualization of treatment is required for optimal treatment of CAH, balancing between under- and overtreatment. Twenty four hour profiling of HC concentrations has shown large interindividual variation in clearance of HC and therefore has been used to

individualize treatment. We present a severely virialized girl with CAH, in whom high doses of steroids failed to suppress androgen production thought to be due to malabsorption. Investigations showed fast clearance of HC, and 24 hour profiling allowed for dose adjustment and improved disease control.

Clinical case: A 7.5-year old girl with 21-hydroxylase deficiency and Prader Stage V virilization and enlarged adrenal glands was referred for assessment for continuous subcutaneous HC pump treatment. Poor control of CAH was thought due to malabsorption due to complex bowel problems. Despite 8-hourly HC doses totaling 116mg/m²/d, her pre-dose saliva 17-hydroxyprogesterone (17-OHP) concentrations were very high. A HC clearance study using 15 mg HC IV, showed that HC was cleared quickly (5245 to 741 nmol/L in 150 min, t_{1/2} 57 minutes compared to usual 80 minutes) and that the 17-OHP could be suppressed. A 24-hour cortisol profile on her usual HC doses showed that HC was absorbed as she achieved cortisol concentrations up to 1439nmol/L. However 17OHP, androstenedione and ACTH concentrations were persistently high suggesting autonomous adrenal androgen production. In order to suppress that she was treated with oral dexamethasone and required 0.5 mg BD to suppress androgens and ACTH and normalize adrenal gland size. She was then switched back to her equivalent HC doses, and 24-hour cortisol profiles were used to allow gradual reduction of HC doses. Her 17OHP and androgens remained suppressed but once the dose was reduced to 32mg/m²/d in 3 divided doses, the 17-OHP increased whilst cortisol concentrations dropped quickly, in line with fast clearance. Under close follow up with 24-hour profiles, appropriate cortisol concentrations with appropriate suppression of androgen and 17OHP production was achieved once increasing frequency of HC doses to 5 times daily with a total dose of 34 mg/m²/day. Fludrocortisone was required at a dose of 260mcg/m²/day.

Conclusion: This case of poorly controlled CAH, where in depth investigations revealed rapid clearance of hydrocortisone and autonomous adrenal androgen production, is an example of where 24-hour hydrocortisone profiling and frequent dosing of hydrocortisone can help to improve control of CAH.

P2-17

A prospective study of children 0-8 years with congenital adrenal hyperplasia and adrenal insufficiency on treatment with hydrocortisone granules monitored by 17-OHP saliva sampling

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Context: Children with congenital adrenal hyperplasia (CAH) and adrenal insufficiency (AI) require hydrocortisone replacement from birth. Continuous monitoring of therapy during

growth is necessary. Until now, children were dependent on off label use with divided hydrocortisone tablets or pharmacy compounded capsules. A licensed paediatric formulation that allows accurate dosing down to 0.5mg is now available.

Objective: A prospective safety and efficacy study of 0-8 year old children with CAH and AI treated with hydrocortisone granules and monitored through 17-OHP saliva profiles.

Methods: Seventeen children with CAH (9 male) and 1 with hypopituitarism (male) were evaluated in 3 cohorts according to age at study entry in the previous study: cohort 1 (2-<6 years, n=9), cohort 2 (1 month-2 years, n=6) and cohort 3 (<28 days, n=3). Study visits were scheduled monthly for 3 visits and 3-monthly thereafter including physical examination, measurement of weight, length, blood pressure. Patients with CAH were asked to conduct a daily 17-OHP-saliva profile every three months.

Results: Study medication was given three times daily every eight hours; median duration of treatment (range) was 795 (1-872) days with 150 follow-up visits. Hydrocortisone dose was adjusted at 40/150 visits. In CAH patients this was based on 17-OHP monitoring (32 using salivary measurements, 8 based on blood sampling). Saliva sampling started at about 6 months of age. Mean daily hydrocortisone dose (mg/m²±SD) at study entry for cohorts 1, 2 and 3 was 11.06±3.01, 10.42±1.41 and 17.52±10.38 and at end of study was 10.47±2.67, 10.37±1.62 and 10.18±2.47. Hydrocortisone doses used at different time points varied from 0.5mg to 10mg and the dose distribution varied from the beginning to the end of the study within age groups. Youngest children (cohort 3) started with an equal dose distribution over the day (33-33-33%) while older children had a greater proportion in the morning and at night-time (40-20-40%). Height and weight showed no trends for accelerated or reduced growth. No adrenal crisis was observed despite 193 treatment-emergent adverse events, which were mainly common childhood illnesses. Nine severe adverse events were reported. None of the adverse events had a suspected causal relationship to study medication.

Interpretation: This first prospective study of glucocorticoid treatment in children with AI demonstrates that an individualized therapy with accurate dosing and monitoring from birth results in hydrocortisone doses at the lower end of the recommended dose range, normal growth, and no increase in adrenal crises.

P2-18

Cushing's disease treatment results correlation with pituitary MRI in children

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Objective: Transsphenoidal surgery (TSS) is a treatment of choice for Cushing's disease (CD), whose effectiveness range is from 70 to 90%. Recurrence rate after successful treatment is about 25%. Preoperative predictors of remission and recurrence are still unexplored what leads to further investigations.

Aim: Analysis of remission and recurrence rates of CD after radical treatment according to preoperative MRI.

Design: We conducted a retrospective analysis of 91 pediatric patients with CD who underwent treatment between 1992 and 2020.

Methods: Patients were divided into 3 groups according to preoperative MRI results: 1 group – patients with no visible adenoma [n=37], 2 group – patient with microadenoma (<10 mm) [n=41], and 3 group of patients with macroadenoma (>10 mm) [n=13]. 63 of 91 patients (69%) underwent TSS, and 28 patients – radiosurgery (31%). Efficacy of treatment was confirmed if the morning cortisol or 24-hour urinary-free cortisol (24-h UFC) values below normal range for the assay used. Recurrence of CD was defined as a manifestation of clinical symptoms consistent with CD with elevated 24-h UFC and lack of cortisol suppression during low-dose dexamethasone suppression test after confirmed remission of CD.

Results: 19 of 37 patients from the 1 group underwent TSS (51%), remission rate was 63% [12/19]; 18 patients underwent radiosurgery (49%), remission rate was 83% [15/18]. In the 2 group 32 of 41 patients underwent TSS (78%), remission rate of 72% was achieved [23/32]; 9 patients underwent radiosurgery (22%), remission rate was 78% [7/9]. In the 3 group 12 of 13 patients underwent TSS (92%), remission rate was 83% [10/12]; 1 patient underwent radiosurgery (8%), remission was achieved. If 1st line of treatment was unsuccessful [23/91], another therapeutic option (radiosurgery after TSS and vice-versa) or the same therapy repeatedly was performed [21/23], remission was achieved in 81% of patients [17/21], 6 patients were lost to follow-up. Recurrence rate after 1st successful treatment was 12% [8/68]: 1 of 27 patients from 1 group [4%], 4 of 30 patients from 2 group [13%], 3 of 11 from 3 group [27%]. Recurrence rate after few treatment options was 18% [3/17]: 1 of 5 patients from 1 group [20%] and 2 of 10 patients from 2 group [20%]. There were no significant differences in recurrence rates after successful treatment between groups (P=0.054) (χ^2 analysis).

Conclusions: Our study didn't show any differences in remission and recurrence rate after successful treatment according to preoperative MRI.

P2-19

Genetic analysis of paediatric primary adrenal insufficiency of unknown aetiology over 25 years

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Introduction: Primary adrenal insufficiency (PAI) is a potentially life-threatening condition that requires appropriate diagnosis and treatment. The most common cause of PAI is congenital adrenal hyperplasia (CAH), but other well-established aetiologies include metabolic and autoimmune disorders, and physical damage. Mutations in more than 30 genes have now been associated with PAI, with considerable biochemical and phenotypic overlap. It is therefore important to adopt a comprehensive genetic

analysis to help reach a diagnosis. Here, we report the molecular basis underlying PAI in children and young people over a 25 year-period, combining published and unpublished data from our research centres.

Methods: The main cohort consisted of 155 children with PAI of unknown aetiology from the UK studied at three research centres from 1993 until 2018. Children with CAH, metabolic and autoimmune causes of PAI were excluded. Genetic analysis was performed using Sanger sequencing and a candidate gene approach (1993 onwards) or next generation sequencing (NGS), using both targeted panels and whole exome sequencing (WES) (2013-2018). An additional sub-group of 51 patients were included where a genetic diagnosis of X-linked adrenal hypoplasia congenita (AHC) due to pathogenic variants in *NR0B1* (DAX-1) had been established through clinical genetic testing services.

Results: Using these approaches, a genetic diagnosis was identified in 103/155 (66.5%) individuals. Pathogenic variants were identified in 11 different genes: *MC2R* (ACTH receptor) (30/155, 19.4%), *NR0B1* (DAX-1) (7.7%), *CYP11A1* (7.7%), *AAAS* (7.1%), *NNT* (6.5%), *MRAP* (4.5%), *TXNRD2* (4.5%), *STAR* (3.9%), *SAMD9* (3.2%), *CDKN1C* (1.3%) and *NR5A1/SF-1* (0.6%). The adrenal insufficiency resolved in five children where no genetic cause was found. Taken together with the research cohort, X-linked AHC represented the largest group where a diagnosis was made (*NR0B1*, research n=12; clinical n=51). An excess of boys was observed, even when individuals with X-linked AHC were excluded from analysis. This difference in sex ratio was even more marked in the “undiagnosed” group of patients.

Conclusions: PAI in children and young people often has a genetic basis. Although age at presentation, treatment, ancestral background and birthweight can provide diagnostic clues, genetic testing was required to establish the definitive cause. NGS approaches improve the diagnostic yield when many potential candidate genes are involved. Defining the specific aetiology can have important implications for affected individuals and their families for the management of this lifelong condition, such as for monitoring associated features, counselling about recurrence risk in families, and sometimes for predicting disease course and modifying treatment.

P2-20

Panhypopituitarism after treatment procedures in pituitary-hypothalamic area – a single center experience

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Background: The most common conditions requiring surgery or radiation therapy of the sella and suprasellar area in childhood are craniopharyngiomas and pituitary adenomas. Therapeutic procedures involving pituitary gland often lead to multiple hormonal deficiencies, and experienced multidisciplinary team following guidelines and applying systematic approach could improve outcomes.

Aim: To evaluate hormonal replacement therapy among children and adolescents with post procedural hypopituitarism.

Methods and Materials: We conducted a retrospective observational study at a tertiary pediatric endocrine university center encompassing a period of 10 years (01 January 2010 to 31 December 2019). All post procedural hypopituitary patients followed for more than 1 full year were included in the study.

Results: A total of 9 patients (44% girls) with postoperative hypopituitarism consistent with the inclusion criteria were identified - 6 of them had craniopharyngiomas, 1 had meningioma, 1 - teratoma and 1 - germinoma. Mean age at diagnosis was 9.7 ± 2.7 years (6.5 - 14). In 7 (78%) subjects total extirpation of the tumor was achieved, and in 2 subtotal excision was achieved. Only one patient was operated at our setting, 3 were operated at other centers in the country and the rest 5 patients were operated abroad. In the postoperative period, 89% of the patients developed central hypothyroidism, 89% developed diabetes insipidus, 67% had ACTH deficiency and eventually, 22% developed hypogonadotropic hypogonadism. All hormonal deficiencies were adequately replaced. Follow-up showed that all patients demonstrated growth hormone (GH) deficiency, and required treatment that started at the mean age of 12.4 ± 2.4 years. More than half (55.5%) initiated recombinant human GH (rhGH) replacement therapy at least 2 years after tumor resection. The mean time until the start of rhGH was 3.0 ± 2.0 years after the operation, much shorter for patient initially diagnosed by us (1.6 ± 0.6 years) than for patients diagnosed and followed elsewhere before start of the rhGH therapy (3.8 ± 2.2 years). No recurrence of the tumor was observed after initiation of the rhGH therapy.

Conclusion: In half of the presented patients, treatment with rhGH was delayed compared to the recommended initial timeline of 1 postoperative year. In order not to delay rhGH replacement therapy, patients with sellar and suprasellar lesions and tumors should be referred to Expert centers for rare endocrine conditions as early as possible.

P2-21

The reliability of Salivary Cortisol compared to Serum Cortisol for diagnosing adrenal insufficiency in the gold standard ACTH stimulation test in children

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Introduction: The gold standard for the diagnosis of adrenal insufficiency (AI) is the ACTH stimulation test. According to the guidelines approved by the European Endocrine Society, the ACTH stimulation test should be performed with the administration of the standard dose of i.v. Synacthen® 250 µg for adults and children aged ≥ 2 years (infants should receive 15 µg/kg, children ≤ 2 years 125 µg). In many clinical settings a Synacthen® dose of 1 µg is currently used as an alternative to the standard dose ACTH stimulation test, because several studies have shown that both high dose ACTH test (HDT) and low dose ACTH test (LDT) have similar diagnostic accuracy. In last years, salivary cortisol has been proposed as an alternative to serum cortisol because it is less invasive and reflects free cortisol better than serum cortisol. We aimed to evaluate the reliability of salivary cortisol compared to serum cortisol for diagnosing AI in children that underwent HDT and LDT and to evaluate the sensitivity and specificity of salivary cortisol.

Methods: Data were collected retrospectively in the reference period 2015-2020. All patients were younger than 18 years of age. Salivary and serum cortisol values derived by 80 ACTH stimulation tests were obtained. For the HDT salivary and serum samples were collected at the baseline and after 30 and 60 minutes from ACTH i.v. administration, while for the LDT samples were collected at baseline and after 10, 20, 30, 40 and 60 minutes after the stimulation. A serum cortisol level >420 nmol/l ruled out AI.

Results: 24 HDT were obtained. The correlation coefficients between serum and salivary cortisol were 0.80 at t0, 0.48 at t30 and 0.75 at t60. All patients were adrenal sufficient. The number of LDT was 56: in 41% the peak of serum cortisol was indicative of insufficient adrenal function. The correlation coefficients between serum and salivary cortisol were 0.59 at t0 and 0.33 at the peak. For a cut-off of salivary cortisol <15 nmol/l, we calculated a sensitivity of 73.9% and a specificity of 69.6%.

Conclusions: Our data do not support salivary cortisol as a valid alternative to serum cortisol during LDT. In regard to the HDT, data about the correlation between salivary and serum cortisol are more encouraging but further studies are needed.

P2-22

Prevalence of adrenal insufficiency (AI) requiring treatment with hydrocortisone in children tested with the LDSST

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Synacthen tests are used widely in paediatric practice for diagnosis of AI. The standard dose test may be more specific and low dose test (LDSST), more sensitive. The LDSST requires dilution of commercially available Synacthen, which may result in unreliable dosing and over diagnosis of AI.

Aim: To determine the prevalence of AI requiring treatment with hydrocortisone (a) daily (peak cortisol <350nmol/L) (b) on sick days only (peak cortisol 350-499nmol/L), in children tested with the LDSST, according to the indication for testing.

Methods: Retrospective analysis of LDSSTs (Synacthen 500ng/1.73m², sampling 0',15,25',35') performed between 2008 and 2020. Only the first test was included if a child had >1 test.

Results: Data from 494 (296 M) children, age 9.5 (±5.2) were analysed.

Table 1. Cortisol concentrations in patients undergoing the LDSST, and indication for testing.

Indication for test (N)	Age (years)	Baseline cortisol (nmol/L)	Peak cortisol (nmol/L)	Peak cortisol 350-449nmol/L (%)	Peak cortisol <350nmol/L(%)
All (494)	9.3±7.5	223±123	513±166	85(17)	67(14)
ICS (106)	10.4±3.6	187±84	429±119	27(24)	22(21)
Other iatrogenic (40)	9.7±5.8	197±91	410±150	8(20)	12(30)
Structural brain abnormality (136)	9.2±4.9	245±125	556±161	15(11)	13(10)
Fatigue (37)	11.7±4.5	236±117	583±85	1(3)	0
Poor cortisol response to GH stim test (29)	9.9±4.5	236±86	649±88	3(10)	0
GHD (30)	9.4±4.5	241±85	639±137	3(15)	1(4)
Infants (35)	0.3±0.3	183±188	465±249	9(26)	13(37)
Autoimmune (19)	14.2±2.0	306±202	566±186	3(26)	0
Miscellaneous (66)	10.1±5.4	227±128	546±178	9(14)	7(9)

ICS: inhaled corticosteroids; GHD: growth hormone deficiency

Mean peak cortisol differed significantly between groups, adjusting for age, gender and including baseline cortisol as a predictor (F-test $p < 0.0001$). Peak cortisol was lowest in other iatrogenic (previous anti-inflammatory glucocorticoids), structural brain abnormalities and infants, whilst highest in fatigue, GHD and those with autoimmune disease.

Discussion: Thresholds for the prescription of hydrocortisone daily or on sick days only are derived from children tested following adrenal crisis during ICS therapy. Using these thresholds, 14% were prescribed daily hydrocortisone. The significance of cortisol peaks 350-449nmol/L is uncertain. Treatment on sick days only in children with a result in this range, together with education for the symptoms of AI, should reduce the risk of overtreatment.

P2-23

Serum cortisol and cortisone, and urinary cortisol, cortisone, and tetrahydro-metabolites concentrations in school-aged children born very preterm adequate for gestational age

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Introduction: Cortisol homeostasis dysregulation has been associated to essential hypertension in adults. Higher levels of cortisol have been described in preterm-born individuals, who have also a higher risk of hypertension at younger ages.

Several enzymes modulate peripheral cortisol metabolism. The 11 β -hydroxysteroid dehydrogenase (11 β -HSD) type 2 metabolizes cortisol into cortisone, preventing mineralocorticoid receptors' activation by cortisol. The inverse process is mediated by 11 β -HSD type 1. The A-ring reductases inactivate cortisol and cortisone to tetrahydro-metabolites, tetrahydrocortisol (THF) and tetrahydrocortisone (THE). Defects in 11 β -HSD2 produce cortisol-dependent mineralocorticoid excess, which is expressed with increased urinary cortisol/cortisone (F/E) ratio. Furthermore, 11 β -HSD1 overexpression has been associated with hypertension and metabolic disorders. The urinary THF/THE ratio reflects 11 β -HSD1 function.

Objective: To compare the serum concentrations of cortisol and cortisone, and urinary concentrations of cortisol (F), cortisone (E), THF and THE between very preterm (VPT) born and at term-born school-aged children, all adequate for gestational age (AGA).

Methods: In this cross-sectional study, 69 very preterm (< 32 gestational weeks) and 42 full-term (> 37 gestational weeks) school-aged children (4.9 to 8.9 years old) were included. Urine and serum samples were collected in early morning after an overnight fasting period. All the metabolites were measured by mass spectrometry.

Results: Serum cortisol and cortisone had similar profiles in both groups. However, urinary cortisone had a higher concentration in preterm children (p -value=0.01), but they maintain similar F/E ratio. In this way, the concentration of THE are higher in born VPT, as well.

Conclusion: In this sample, school-aged children born VPT AGA had similar profiles of serum cortisol. However, at renal level, the VPT children showed higher concentrations of cortisone and THE, inactive metabolites, that could be caused by a disbalance between 11 β -HSD1 and 11 β -HSD2 function, with a predominance of 11 β -HSD2. This disbalance could reflect an initial protective mechanism in preterm born children to prevent blood hypertension in the first years of life.

	Very-preterm (n=69)	Full term (n=42)	p-value
Serum			
Cortisol (ug/dL)	6.88 (5.09-9.33)	7.83 (5.20-9.98)	0.53
Cortisone (ug/dL)	2.22 (1.88-2.68)	2.45 (1.99-2.95)	0.35
F/E ratio	3.16 (2.52-3.58)	2.91 (2.44-3.72)	0.64
Urine			
F (ng/mL)	15.08 (8.29-22.71)	12.44 (8.01-18.02)	0.21
E (ng/mL)	45.68 (31.41-60.42)	33.7 (22.92-46.39)	0.01
F/E ratio	0.34 (0.26-0.42)	0.36 (0.31-0.43)	0.40
THF (ng/mL)	11.05 (7.3-17.82)	9.58 (6.48-15.31)	0.26
THE (ng/mL)	12.08 (8.74-25.42)	10.35 (6.12-15.86)	0.03
THF/THE ratio	0.81 (0.62-1.06)	1.01 (0.76-1.20)	0.02

Results are expressed in median and IQR

P2-24

The incidence and presentation of congenital adrenal hyperplasia in an unscreened population

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Background: Newborn screening for congenital adrenal hyperplasia (CAH) has been shown to reduce time to diagnosis, and thus morbidity and mortality. Internationally, newborn screening for CAH continues to expand and screening techniques have improved, with the implementation of second-tier testing and use of gestational age stratification. The aim of this study was to examine the incidence and spectrum of early clinical presentations of CAH in an unscreened population, in order to determine the case for newborn screening.

Methods: A national retrospective observational study was undertaken to identify all children diagnosed with CAH in the Republic of Ireland, between January 2005 and December 2019. Reporting clinicians completed anonymised clinical questionnaires.

Results: There were 103 cases of CAH reported and 69 cases met the study inclusion criteria. The estimated annualised incidence of CAH in the Republic of Ireland was 1:14,754 or 0.07 cases per 1000 live births. Forty-seven children presented clinically in the first six months of life, but only 17 of these had a confirmed diagnosis by day 10. Of these early presentations, there were 28 infants with salt-wasting, 15 females presented with virilised genitalia and four infants were detected due to a family history of CAH. Female infants presented at a median age of 0 days [IQR 0-1] and males at 14 days [IQR 9-21]. Seventy-eight percent of salt-wasting presentations occurred after day 10. Delays in clinical presentation, biochemical diagnosis and treatment initiation were identified.

Conclusions: The incidence of CAH is higher in Ireland than in other unscreened populations. In the absence of screening, clinicians should be aware of the possibility of CAH and appropriate investigations should be urgently requested. Life-threatening salt-wasting is the most frequent clinical presentation and many cases could be detected prior to decompensation if newborn screening were introduced. Consideration should be given to adding CAH to the Irish National Newborn Screening Programme, in line with best practice.

P2-25

Genotypic Sex and Severity of the Disease Determine the Time of Clinical Presentation in Steroid 17 α -Hydroxylase/17,20-Lyase Deficiency

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Context: Steroid 17 α -hydroxylase/17,20-lyase deficiency (17OHD) is characterized by decreased sex steroids and cortisol, and excessive mineralocorticoid action. The clinical symptoms of hypocortisolemia are subtle.

Aim: The clinical, biochemical, and molecular characteristics of patients with 17OHD were evaluated to determine the factors influencing the time of diagnosis and the management.

Patients and Methods: Clinical data, steroid profiles by liquid chromatography-tandem mass spectrometry, and Sanger sequencing of the *CYP17A1* gene was evaluated in 12 patients with 17OHD diagnosed between 2004 and 2020.

Results: Median age of diagnosis was 13.9 (range: 0.04-29.5) years. Ten of 12 patients had 46,XY karyotype. Except for one boy with partial 17OHD, all patients had female external genitalia hence raised as females. The clinical presentation of 17OHD was earlier (median age: 7 years) in patients, who presented with severe hypertension, atypical genitalia, or positive family history (n = 6, 50%) than those without (median age: 15.3 years; p = 0.0005). The latter group presented with amenorrhea (n = 6, 50%). Steroid profile of patients uniformly showed a typical pattern of 17OHD regardless of the age at diagnosis. Serum gonadotropin concentrations were elevated in patients >12 years (n = 7), normal in pre-adolescents (n = 4), and low in a patient, who had a digenic inheritance of homozygous *CYP17A1* and *KISS1R* mutations.

Conclusions: Early clinical presentation and diagnosis in 17OHD are associated with symptomatic hypertension in both 46,XX and 46,XY patients or inadequate virilization of external genitalia in 46,XY partial 17OHD. In the absence of these, the clinical presentation is at late pubertal ages at which time amenorrhea and elevated gonadotropins are the hints for diagnosis.

P2-26

Testicular adrenal rest tumour in children with classical congenital adrenal hyperplasia: A case series

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Introduction: Testicular adrenal rest tumour (TART) is a complication in males with congenital adrenal hyperplasia (CAH). However, the prevalence, risk factors and treatment in children are not clear.

Objective: 1) To identify the incidence of TART and risk factors in patients with classical CAH in our centre 2) To study the clinical characteristics, hormonal profile, treatment interventions and outcome of patients with TART.

Methods: Testicular ultrasound were performed in 16 patients with poorly controlled CAH (mean age 9.87 ± 3.11 , range 4.67-16yrs). Clinical characteristics, hormonal profiles and treatment were compared between patients with and without TART.

Results: TART lesions were detected by ultrasound in 6 patients (37.5%). The lesions were bilateral in all patients, mean diameter of 0.3cm, hypoechoic in nature and scarce in vascularity. Interestingly, testicular microlithiasis was found coincidentally

in one patient. There was no significant difference in height SDS and BMI SDS in patients with and without TART. TARTs were detected in 60% of patients who had attained final height. Only 1 patient had palpable nodules. The 17-hydroxyprogesterone level was higher in CAH patients with TART ($322.22 \pm 238.87\text{nmol/L}$) than in patients without TART ($149.61 \pm 201.20\text{nmol/L}$). Poor compliance was identified in 5 patients. 5 patients developed peripheral precocious puberty and two patients evolved into central precocious puberty. All patients were on hydrocortisone and fludrocortisone replacement. All had intensified hydrocortisone regimen after detection of TART (mean dose $17.3\text{mg/m}^2/\text{day}$) for 2-4 weeks, however only two had resolution of TART on repeated ultrasound.

Conclusions: Ultrasound of testes should be routinely performed in childhood, especially in those with poor disease control and at peri-pubertal age. Larger studies should be conducted to explore the risk factors and therapeutic modalities in TART.

P2-27

High doses op'-DDD cause metrorragia in young girls

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Gynecomastia is a well-known effect of treatment with op'-DDD in male adults. Metrorragia in young girls is a less known effect because only a few children receive this drug, mostly for bad prognosis adrenocortical carcinoma. Moreover, it has been reported that op'DDD causes precocious puberty, but cases are not well documented.

We report 2 cases of young girls receiving high-dose op'-DDD who presented recurrent metrorragia.

Case 1: An 18 month old girl was diagnosed with virilizing adrenal mass. Surgical excision was complete but histology confirmed a bad prognosis adrenocortical carcinoma. It was decided to start an adjuvant chemotherapy with op'-DDD. She received 8g/m^2 per day. 4 months after starting this drug, she presented gynecomastia and metrorragia. Ultrasound showed a uterine size of 55 mm,

Table 1. Comparison of clinical characteristics of patients with and without TART

	With TART (n=6)	Without TART (n=10)	p value
Age, years*	9.61	10.03	0.806
Weight SDS*	1.29	0.29	0.150
Height SDS*	0.76	-0.24	0.213
BMI SDS*	1.18	0.82	0.471
Bone age advancement*	4.89	1.28	0.037
17OHP*	322.22	149.61	0.143
Hydrocortisone*	15.10	14.14	0.371

*the values were expressed as mean

Table 2. Clinical characteristics of patients with TART

Patient	Age of CAH diagnosis, years	Age of TART diagnosis, years	17OHP (nmol/L)	Hydrocortisone dose ($\text{mg/m}^2/\text{day}$)	Resolution of TART
1	0.09	4.67	>60.6	18.0	Yes
2	0.3	6.00	8.8	14.5	Yes
3	0.09	13.08	141.6	18.0	No
4	0.09	13.83	572.0	18.4	No
5	3.50	8.33	246.2	17.9	No
6	0.09	11.75	614.9	16.9	No

with swelling corpus, endometrial thickness 4 mm and prepubertal ovaries. Estradiol was low. Op'-DDD level was high 26 mg/l. The dosage was lessened to 6 and then 4g/m2. Gynecomastia raised progressively and intermittent metrorragia every 3 to 6 months persisted. At the age of 3.5 years old, treatment was stopped, a last event of metrorragia was observed 1 month after stopping op'-DDD. Then, gynecomastia and uterine size decreased until a prepubertal uterine size (34 mm) 2 years after stopping treatment. Puberty started at 9.5 years old and first menses occurred at 11.5 years.

Case 2: An 18 month old girl was diagnosed with virilizing adrenocortical carcinoma. Microscopically incomplete surgical excision was done and an adjuvant op'-DDD therapy was started, dosage 8 g/m2. 4 months after starting therapy, gynecomastia develops progressively and a first episode of metrorragia occurred at 15 months of therapy. Uterine size was 50 mm with swelling corpus, endometrial thickness and prepubertal ovaries. Androgens and Estradiol levels were low (2.2 pg/ml) and she was still in remission of the adrenocortical carcinoma. At that time, Op'-DDD level was high 23.5 mg/l. Unfortunately, she developed a few month later a choroid plexus carcinoma and died rapidly.

Conclusion: These cases show that gynecomastia and metrorragia can occur during high dosage op'-DDD treatment even in very young girls and are reversible when therapy is interrupted. Even if gonadotropins levels were not measured, the clinical course of the first case is more in favor of an estrogen-like effect of this drug than central precocious puberty or estrogen secretion from the adrenocortical carcinoma.

P2-28

An Adolescent Case With Adrenoleukodystrophy Diagnosed After Detection Of Leydig Cell Dysfunction

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Introduction: X-linked adrenoleukodystrophy (X-ALD) is an inherited peroxisomal disease characterized by beta oxidation

disorder that causes the accumulation of very long chain fatty acids (VLCFA) in all tissues. It presents with clinical signs due to accumulation of VLCFA in brain white matter, testes, adrenal cortex and skin fibroblasts. Here, we will present a case applied to the outpatient clinic due to not going through puberty period and who was diagnosed with X-ALD by detecting Leydig cell dysfunction.

Case Presentation: A 16-years and 4-months-old male patient applied to the outpatient clinic due to not entering puberty and the lack of deepening in his voice. On physical examination, his height (173.3 cm; SDS: -0.06), body weight (53 kg; SDS: -1.55), body mass index (16.7 kg/m²; SDS: -1.9), testicular volume (25/25 ml), and stretched penile length (9.5 cm) were measured. His pubic hair growth was in stage-II. Remarkable laboratory test results were as follows: FSH: 3.34 mIU/mL, LH: 16.12 mIU/mL (0.5-8), total testosterone: 31 ng/dL (1.07 nmol/L) was detected. In laboratory tests on the inconsistency of the testosterone level with the testicular volume and the retardation of the pubic hair stage, ACTH was found 1014 pg/mL (223.3 pmol/L), cortisol: 3.5 µg/dL (96.5 nmol/L), DHEA-SO4: 10 µg/dL (0.27 µmol/L) and 1,4-Δandrostenedione: 0.12 ng/ml (0.41 nmol/L). A diagnosis of primary adrenal insufficiency and Leydig cell dysfunction was made. In the VLCFA panel, C24: 118.07 µmol/L (37.14-79.4), C26: 4.25 µmol/L (0.6-1.3), C24/C22: 1.97 (0.689-1.008), C26/C22: 0.07 (0.011-0.026) were higher. In his neurological examination, there was only slight inability in heel walking. In brain magnetic resonance imaging, hyperintense signal changes in the bilateral thalamus, posterior leg of the internal capsule, posterior pons, bilateral parieto-occipital white matter and corpus callosum splenium were observed in consistent with X-ALD. LOES score reported as 4. Hydrocortisone and Lorenzo's oil treatments were initiated. The combined heterozygous mutation of the ABCD1 gene c.652C>A (p.P218T) (p.Pro218Thr)/c.698C>T (p.A233V) (p.Ala233Val) was detected. Clinical disease phenotyping in X-ALD and, if necessary, bone marrow transplantation were planned according to the clinical course.

Conclusion: The case, who applied to the outpatient clinic with pubertal delay and was diagnosed as Leydig cell dysfunction with relative retardation in pubic hair growth, incompatibility in testicular volumes and total testosterone levels, and elevated LH, and primary adrenal insufficiency and then diagnosed with X-ALD is presented for its rare clinical presentation.

P2-29

Fludrocortisone is the salvage treatment in cases with calcineurin inhibitor related hyperkalemia

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Calcineurin inhibitors (CNIs) are widely used in pediatric transplantation for prevention of graft rejection, prophylaxis and treatment of graft versus host disease. Though hyperkalemia is a common adverse effect (10-45%), alterations in renin-angiotensin-aldosterone system in CNI-induced hyperkalemia are not well elucidated. Consequently, CNIs vital to transplantation are usually

switched. Here, we describe two cases with CNI-induced hyperkalemia due to hyporeninemic hypoaldosteronism (HH), successfully treated with fludrocortisone.

15-month-old boy was diagnosed with acute myeloid leukemia and BFM-2013 protocol was started. When he was 22 months old, allogeneic bone marrow transplantation was performed, cyclosporine (CsA) (3 mg/kg/day) was initiated on day -1, as preparative regimen. On day +22, hyperkalemia (5.9 mEq/L) and hyponatremia (133 mEq/L) were observed. He was normotensive, was not receiving intravenous fluid or potassium and hemolysis was ruled out. Serum chloride, blood urea nitrogen and creatinine were 103 mEq/L, 23.2 mg/dl, 0.5 mg/dl, respectively. Urinary sodium and potassium were 50.6 mEq/L and 6.3 mEq/L. Concomitant renin was 1.3 pg/ml (1.3-13.8), aldosterone was 71 pg/ml (35-300). Glucocorticoid deficiency (cortisol: 28 mcg/dl) or metabolic acidosis were not detected. Hyperkalemia was attributed to CsA related HH. Fludrocortisone 0.05 mg/day was started, and serum potassium decreased from 5.9 mEq/L to 3.8 mEq/L. CsA was continued for 6 months, following cessation, fludrocortisone was tapered and ceased, electrolyte imbalance was not observed.

3-year-old girl who underwent cadaver donor renal transplantation because of agenesis of the left kidney and cystic right kidney due to HNF1 beta mutation was started with CsA. Due to hypertrichosis, CsA was switched to tacrolimus. When she was 5 years old, hyperkalemia (7.37 mmol/L) and hyponatremia (128 mEq/L) were detected. Serum creatinine increased from 0.41 to 0.67 mg/dl, urinary sodium was 52.8 mEq/L and potassium was 13.89 mEq/L, serum renin and aldosterone were 1.18 pg/mL (1.3-13.8) and 47 pg/mL (35-300), respectively. Tacrolimus related HH was diagnosed and 0.05 mg fludrocortisone was initiated, serum potassium, sodium, and creatine were normalized within three days. The patient has been receiving fludrocortisone without dose adjustment for three years without electrolyte imbalance.

HH is established as the underlying mechanism of CNI-induced hyperkalemia. If hyperkalemia is detected in cases using CNIs, renin and aldosterone should be measured. Fludrocortisone is a safe and effective treatment for CNI-induced hyperkalemia. It also provides maintaining CNIs fundamental to pediatric transplantation.

P2-30

Development of a novel weight-based steroid emergency plan for patients with Duchenne Muscular Dystrophy

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Background: Long-term glucocorticoid therapy with Prednisolone or Deflazacort has improved outcomes in patients with Duchenne Muscular Dystrophy (DMD), however recommended dosages suppress the hypothalamic-pituitary-adrenal axis, leading to adrenal insufficiency. All boys prescribed glucocorticoid

therapy should be assumed to have adrenal suppression, and therefore at risk of adrenal crisis during illness or stress (eg. surgery, bisphosphonate infusions). The updated DMD Care Considerations consensus document (2018) recommends implementation of emergency plans. Despite this, no unified national or international guidance for illness management for this cohort exists. Previously emergency sick day plans were not consistently in place within our own specialist centre, and on national survey of 6 other Trusts, it was clear that advice and education for sick day steroid regimens was variable.

Aim: We sought to develop a weight-based steroid emergency regimen for DMD patients, many of whom are non-ambulant, and in whom accurate measurements for body surface area can be challenging.

Methods: A novel weight-based regimen of stress doses of oral hydrocortisone given 6 hourly was devised. This was to be implemented when needed, in addition to the glucocorticoid regimen the patient was taking for disease (prednisolone/deflazacort, daily/pulsed therapy).

Results: Approval from the Drugs and Therapeutics committee was obtained for a weight-based stress dose regimen of hydrocortisone, which was implemented in this cohort from April 2020. Additionally, training and education was provided to increase awareness of adrenal insufficiency among patients and families. All DMD patients with prescribed steroid therapy have written documentation of an emergency steroid plan to be followed during acute illness. All families and boys are educated about stress dosing plans, recognising signs/symptoms of adrenal crisis, and have been trained to give IM Hydrocortisone injections. Adrenal 'Flags' have been added to our electronic patient records alerting staff that these patients are at risk of adrenal crisis.

Conclusion: We are currently reviewing the results of our practice change. Anecdotally families report faster recovery times from illness since using stress-doses of hydrocortisone alongside their usual glucocorticoid. Previous regimens utilising a patient's usual disease-modifying glucocorticoid may not have taken into account the pharmacokinetics of these drugs; Deflazacort for example has a rapid plasma elimination half-life of 1-2 hours. The development of a unified, consistent approach to illness management, alongside structured education for DMD patients and families, are initial actions towards improving clinical outcomes. Further guidance at a national and international level is needed.

P2-31

Investigation of usage and acceptance of hydrocortisone granules in capsules for opening in children with adrenal insufficiency

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Context: Off-label and unlicensed use is widespread in medical therapy of children. Since 2007 there is an EU regulation, which includes the need for a pediatric investigation plan (PIP) in the drug approval process. In 2018, hydrocortisone granules

in capsules for opening (Alkindi®) became the first medicine to be approved for the treatment of adrenal insufficiency in children from birth.

Methods: An anonymised online survey (SurveyMonkey) was created to collect information on the underlying diagnosis, frequency and compliance with glucocorticoid therapy, use of glucocorticoids (stress dosing) during illness, and acceptance of or satisfaction with the hydrocortisone granules in capsules for opening. Participants were recruited by informing them about the survey during their visits in the outpatient clinic and with the help of self-help organisations.

Results: The following are preliminary results of the ongoing survey of parents of children aged 0-18 years. In 92% of those who have participated so far, children are treated by a paediatric endocrinologist. The children of most participants were suffering from CAH (67%). All children were treated with hydrocortisone as glucocorticoid therapy. In case of stress dosing, the usual medication was increased (90%), a prednisolone suppository was additionally administered (50%), licensed hydrocortisone tablets are used (40%) or an emergency injection of hydrocortisone is given (10%). In summary, 92% of the participants were satisfied with the new hydrocortisone preparation. For parents, the simplicity of handling (100%), the accuracy of dosing (70%) and an existing marketing authorisation (60%), but less the taste (30%) are important in the treatment of their children.

Conclusion: The hydrocortisone granules in capsules for opening show a good acceptance among parents. For relatives, important qualities of drug therapy in childhood are simplicity of handling especially for the medication of young children.

P2-32

Congenital Adrenal Hyperplasia caused by homozygous pathogenic variant in the HSD3B2 gene

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Introduction: Congenital Adrenal Hyperplasia (CAH) is an autosomal recessive disorder caused by impairment of one of the enzymes involved in the steroidogenesis pathway. 3 β hydroxysteroid dehydrogenase type 2 deficiency (3 β HSD2 deficiency) is a rare form of CAH (<0.5%) due to pathogenic variants in the HSD3B2 gene encoding for the enzyme Type 2 3 β -hydroxysteroid dehydrogenase Δ^4 - Δ^5 isomerase (3 β HSD2).

Case Presentation: A 15-day old female neonate was referred from a local hospital to the Pediatric Department of "G. Gennimatas" Hospital of Thessaloniki due to dehydration with hyponatremia and hyperkalemia, and hypertrophy of clitoris and labia majora. The patient was the first child of consanguineous parents

originated from Afghanistan, now living in Greece. The biochemical and hormonal profile of the proband was consistent with CAH (17OHP: 69.5ng/ml, Cortisol: 3.9 μ g/dl, ACTH: 621pg/ml, Potassium: 7.1mmol/L, Sodium: 123mmol/L, Testosterone: 309ng/dl, DHEAS: >1500 μ g/dl, Androstenedione: 18.9ng/ml, Plasma Renin Activity: 40.4ng/ml/h and Aldosterone: 289 pg/ml). She was immediately commenced on hydrocortisone (15mg/m²/day) and fludrocortisone (200mg/day) with a good response. Molecular analysis was obtained.

Methods: PCR and bidirectional sequencing for the CYP21A2, CYP11B1 and HSD3B2 genes was carried out sequentially in the Laboratory of Molecular Endocrinology, First Department of Paediatrics, Medical School, National and Kapodistrian University of Athens, "Agia Sophia" Children's Hospital. MLPA analysis was also performed for the identification of Copy Number Variations (CNVs) in the CYP21A2 gene (P050-C1 CAH).

Results: Molecular investigation of the CYP21A2 gene revealed that the index patient carried the Q318X pathogenic variant on a duplicated CYP21A2 gene in heterozygosity. Analysis of the parents showed that they were also carriers of the p.Q318X pathogenic variant on a duplicated CYP21A2 gene in heterozygosity. No pathogenic variants were detected in the CYP11B1 gene on the index patient. Analysis of the HSD3B2 gene revealed a homozygous 2bp deletion at codon 273 (p.[Lys273fs];[Lys273fs]). The parents were found to harbor the p.Lys273fs in heterozygosity.

Discussion: We herein present a patient with a homozygous deletion in the HSD3B2 gene. This variant has already been reported in homozygosity in 3 male patients with severe salt wasting CAH (2 of them originated from Afghanistan and 1 from Pakistan). To our knowledge, this is the first female patient presented with the homozygous p.Lys273fs deletion in the HSD3B2 gene. Another female patient has been reported with the p.Lys273fs variant in compound heterozygosity with p.Thr318fs variant, presenting pigmentation and mildly enlarged clitoris at birth. Molecular investigation is important in order to confirm the clinical diagnosis and provide proper treatment and genetic counseling to the family.

P2-33

Congenital Adrenal Hyperplasia with a CYP21A2 deletion overlapping Tenascin-X gene

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Introduction: Congenital Adrenal Hyperplasia (CAH) is a group of genetic diseases characterized by impaired cortisol synthesis. 95% of CAH cases result from mutation in the CYP21A2

gene encoding 21-hydroxylase. *TNX-B* gene partially overlaps *CYP21A2* and encodes a matrix protein called Tenascin-X (TNX). Complete tenascin deficiency causes Enlers-Danlos syndrome (EDS). A variant called CAH-X, has recently been described, resulting from *CYP21A2* deletions extending into the *TNXB* on at least one allele. This haploinsufficiency of TNX may be associated with a mild hypermobility form of EDS, as well as other connective tissue comorbidities such as herniae, cardiac defects and chronic arthralgia. We report four patients heterozygous for a CAH-X allele that do not present clinical manifestations of the Ehlers-Danlos syndrome.

Case Reports: Case 1: 18-year-old boy followed since classic salt wasting CAH presented in the newborn period. Molecular genetic testing confirmed the CAH diagnosis and identified (in heterozygosity) a *CYP21A2* deletion overlapping the *TNXB* gene, giving rise to a *TNXA/TNXB* chimera. Neither clinical features of hypermobility or cardiac alterations were documented in this boy. At the age of 12 he was diagnosed with a testicular adrenal rest tumour. Case 2: 14-year-old boy followed since the age of 7, when he was referred for evaluation due to precocious adrenarche. Endocrinologic parameters were compatible with non-classical CAH and genetic testing revealed a *CYP21A2* variant and a complete *CYP21A2* deletion on the other allele covering the last exons of *TNXB*. At physical exam he has a Beighton Score (BS) of 1 and history of joint disability. Cardiac defects were excluded. Case 3: 12 year-old brother of Case 2, who was studied after index case diagnosis. Genetic testing revealed the same deletion; he is currently asymptomatic, without joint hypermobility, and with normal cardiologic evaluation. Case 4: 15 years old girl referred to endocrine paediatric department for secondary amenorrhea, without hirsutism or acne; elevated basal and post-stimulation 17-hydroxyprogesterone triggered genetic testing. A *CYP21A2* deletion in one allele also affecting *TNXB* was identified. She has no clinical features of connective tissue disorders, and cardiac defects were also excluded.

Conclusion: These 4 CAH cases with a monoallelic *CYP21A2* deletion overlapping the Tenascin-X gene, highlight the importance of additional clinical evaluations related with the recently described CAH-X Syndrome. CAH patients, carriers of these *TNXA/TNXB* chimeras, should be evaluated for clinical manifestations related to connective tissue hypermobility, cardiac abnormalities and other EDS features allowing a better clinical management.

P2-34

Maternal primary adrenal cortex insufficiency during pregnancy: Spotlight on the Fetus and the Neonate. A systematic review and meta-analysis

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Background/Aim: Maternal primary adrenal insufficiency, has been infrequently described during pregnancy, due to its rarity. Based on the existing literature, maternal hormone deficiency influences pregnancy and has an impact on mother and fetus/neonate, with only a few studies emphasizing on the respective outcomes. The aim of this systematic review and meta-analysis was to evaluate the impact of maternal corticosteroid deficiency during pregnancy on the fetus and the neonate and identify the possible outcomes on this inefficiently studied population.

Materials and Methods: A systematic search was performed in PubMed/Medline, the Cochrane/CENTRAL and the Google Scholar online databases to identify RCTs, cohort studies, case series and case report studies presenting fetal and neonatal outcomes in pregnancies with active maternal primary adrenal insufficiency. After selection, 22 studies were included in the qualitative analysis and 7 studies to the quantitative analysis. Data on the prevalence of miscarriage, preterm birth, the occurrence of small for gestational age (SGA) neonates, as well as the neonatal birth weight were examined.

Results: Maternal primary adrenal insufficiency, presented either as Addison's disease or as Congenital Adrenal Hyperplasia, was associated with high miscarriage rates among PAI patients (22%, 95%CI: 16% to 29%, I²:67%). A miscarriage rate of 18% (95%CI: 10% to 31%, I²:82%) and 27% (95%CI: 18% to 40%, I²:73%) was present among AD and CAH patients, respectively. Prematurity (13%, 95%CI: 11% to 15%, I²:55%) and SGA neonates (9%, 95%CI: 5% to 16%) occurred among PAI patients, especially when PAI was undiagnosed and untreated. Fetal birth weight was favorable in the majority of the studies (3.238gr, 95%CI: 3.047gr to 3.430gr, I²:73%). Miscarriage rates in the meta-analyses were higher than those reported in the systematically reviewed studies.

Conclusion: Maternal adrenocortical insufficiency has a higher prevalence of adverse effects on fetal development and pregnancy duration in undiagnosed and untreated women, compared with healthy women or women under treatment. Additional studies on the impact of maternal hormone deficiency on the fetus in a wider range of pregnancies are required to establish the optimal therapy during pregnancy and elucidate underlying mechanisms.

P2-35

Assessment of blood pressure and carotid intima media thickness (CIMT) in children with primary adrenal insufficiency

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Background: Increased risk of cardiovascular disease and increased subclinical atherosclerosis have been reported in children with primary adrenal insufficiency (AI), including those with congenital adrenal hyperplasia (CAH), when compared to healthy children. Carotid intima media thickness (CIMT) can be used as an early marker of cardiovascular risk. The severity of adverse metabolic profile has been related to the total hydrocortisone dose and duration of treatment.

Aim: To assess the prevalence of increased CIMT, an early marker of cardiovascular risk, in children with primary AI.

Methods: Children with primary AI treated with hydrocortisone had CIMT measurements performed using ultrasonography. Measurements were taken approximately 0.5mm distal from the carotid bulb on their right carotid artery. Average measurements were taken from three images. Two sitting blood pressure measurements were taken from the left arm and an average was ascertained.

Results: Measurements were performed on 17 children (9 male), aged 9.9 ± 4.1 years. Diagnoses were Addison's (n = 3) and CAH (n = 14, of whom 9 had salt wasting CAH). 2 children, aged 5 and 7 years, could not tolerate the procedure.

Table 1. Demographics and clinical characteristics

	Mean $\pm$ SD
Height SDS	0.81 $\pm$ 1.34
BMI SDS	0.13 $\pm$ 1.21
Length of time since diagnosis (years)	6.06 $\pm$ 4.05
Hydrocortisone dose (mg/m ² /day)	10.8 $\pm$ 3.93
Systolic blood pressure centile (percentile)	75.6 $\pm$ 34.2
Diastolic blood pressure centile (percentile)	59.0 $\pm$ 25.3

*SDS = standard deviation score

Median CIMT measured 0.41mm (range 0.40-0.48). Two children had a systolic blood pressure of >95th centile. One child had a diastolic blood pressure >95th centile. Children with blood pressure readings >95th centile were on hydrocortisone doses of 5.6-10.8 mg/m²/day and fludrocortisone doses between 0-175 micrograms/day. Linear regression analysis, adjusted for age, length of time since diagnosis/start of hydrocortisone treatment and dose of hydrocortisone taken did not show an association with CIMT values.

Conclusion: These preliminary data show CIMT measurements that are within the normal range, in this cohort of children with primary AI. Contrary to historical data, early subclinical atherosclerotic changes have not been identified. This may reflect good clinical practice. Hydrocortisone doses are reviewed and adjusted regularly, guided by both clinical and biochemical parameters.

P2-36

Challenging in diagnosis and treatment of Cushing Disease in a 12 years old boy

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Background: Cushing's disease (CD) is caused by an ACTH-secreting pituitary corticotroph adenoma and it is the commonest cause of Cushing's syndrome (CS) in pediatric age.

CD is very rare disease almost in pediatric age and the most of pediatric endocrinologists have limited experience in the diagnosis and treatment of children with CD.

Microadenomas are the most of ACTH-secreting pituitary tumors in the pediatric age and the majority of these fails to detect on MRI because they have a hypointense signal on this examination and they show a normal appearance in about half of the patients. Therefore, results should be interpreted together with bilateral inferior petrosal sinus sampling (BIPSS) for ACTH.

Case: A 12 years old boy was presented with headache, rapid weight gain during 3 years, stunted height, increase hair growth and a typical Cushingoid appearance. His investigations showed the following values: cortisol 26.8 mcg/dL, ACTH 95.3 pg/mL (08⁰⁰ a.m.); cortisol 30.6 mcg/dL, ACTH 116.2 pg/mL (04⁰⁰ p.m.); salivary cortisol 10.55 ng/mL and 25.9 ng/mL (1100 p.m. in two consecutive days); free cortisol level in 24-h urine 556 mcg/24-h; cortisol prior to high-dose dexamethasone suppression test (HDDST) was 13.8 mcg/dL and 12.7 mcg/dL after it and DHEA-s 894 mcg/dL. FDG-PET Scan was performed but no ectopic ACTH-dependent focus was detected. An intervention to collect samples from inferior petrosal sinus (BIPSS) was performed under general anesthesia. Findings were consistent with left sided ACTH-secreting focus (ACTH 139 pg/mL in the right petrosal sinus and >2000 pg/mL in the left petrosal sinus after CRH). The patient underwent gamma knife therapy and after that he started using low dose of ketoconazole for medical adrenalectomy to inhibit steroidogenesis.

Keywords: Cushing's disease, Cushing's syndrome, Pediatrics, bilateral inferior petrosal sinus sampling, gamma knife.

P2-37

Congenital Adrenal Hyperplasia caused by compound heterozygosity of two novel CYP11B1 gene variants

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Introduction: Congenital Adrenal Hyperplasia (CAH) is an autosomal recessive disorder caused by pathogenic variants in seven genes involved in the cortisol and aldosterone biosynthetic pathway. The second most common cause of CAH, 11 β -hydroxylase

deficiency (11 β OHD), is attributed to pathogenic variants in the *CYP11B* gene encoding for the enzyme 11 β -hydroxylase (11 β OH).

Case presentation: A thirteen-year-old girl was referred to the pediatric endocrinologist due to syncopal episode. She was the third child of a non-consanguineous family. She presented premature adrenarche at the age of 6 years and menarche at the age of 12 years. On physical examination, she presented height of 154.5 cm, weight of 50 kg, acne, hirsutism, clitoromegaly and normal blood pressure. Laboratory investigations revealed increased androgen levels and poor response of cortisol to ACTH stimulation test. From the family history, the mother was diagnosed with CAH at the age of 10 years and was under treatment with methylprednisolone. Previous molecular investigation of the *CYP21A2* gene was negative. Due to the increased androstenedione levels in the index patient, the suspicion of 11 β OH was raised. She was then investigated for 11-deoxycortisol and 11-deoxycorticosterone levels that were found to be significantly raised at 98.1 nmol/L (NV: 1.4–5 nmol/L) and 1808 pg/ml (NV: 40–200 pg/ml), respectively.

Methods: PCR and bidirectional sequencing of the 9 exons and flanking intronic sequences of the *CYP11B* gene was carried out. Novel variants were evaluated employing 7 bioinformatics software tools and classified according to the ACMG guidelines for the interpretation of Sequence Variants. The frequency of novel variants was searched in the Genome Aggregation Database.

Results: *CYP11B* gene sequencing analysis revealed that our patient and her mother harbored two novel variants; the p.K370Q (c.1108A>C) in exon 6 and the p.G379S (c.1135G>A) in exon 7. The father was found to be heterozygote for the p.K370Q variant (p.[K370Q];[=]). Segregation analysis of the two siblings indicated that the patient and her mother were compound heterozygotes for the previously mentioned variants (p.[K370Q];[G379S]). Variant p.K370Q was predicted as pathogenic by the seven bioinformatics tools employed and classified as *Variant of Uncertain Significance* (VUS) according to ACMG criteria. Variant p.G379S was predicted as pathogenic by 3/7 tools and classified as likely pathogenic according to ACMG criteria. None of the variants were present in gnomAD database.

Conclusion: We present a case of 11 β OHD caused by two novel pathogenic variants of the *CYP11B* gene, in the index patient and her mother, emphasizing the importance of molecular investigation in order to confirm clinical diagnosis and allow proper genetic counseling of the family.

Case Presentation: A 10-year and 10-month-old female was admitted to the Pediatric Endocrinology Clinic for evaluation of suspected adrenal insufficiency. The girl reported longstanding complaints of fatigue, loss of appetite, recurrent gastric symptoms and salt craving. Medical history was significant for hospitalization at the age of 4 years and 11 months, when she presented with vomiting and dehydration and was found *underweight* (BMI SDS: -5.71), with a biochemical profile indicative of adrenal insufficiency (sodium 131 mEq/L, potassium 5.8 mEq/L, serum glucose 56 mg/dl, urinary sodium excretion 50 mmol/l). She was managed with intravenous hydration and *readmission at the* Pediatric Endocrinology Clinic was planned upon discharge; however, the family failed to attend the scheduled appointment. During the last months, extreme exhaustion and daily consumption of large amounts of salt prompted a second referral by the pediatrician. On examination, the girl was severely underweight (BMI SDS: -4.26), with normal female external genitalia, absent axillary and pubic hair and breast Tanner stage II-III. Generalized hyperpigmentation was noted, without mucosal candidiasis. Weight was 25 kg (1st percentile), stature 146 cm (67th percentile) and blood pressure 93/66 mm Hg. Investigations showed normal glucose and electrolytes (sodium 135 mEq/L, potassium 4.4 mEq/L, calcium 9.4 mg/dl, phosphorus 5.0 mg/dl), low morning level of cortisol (0.7 μ g/dl), and extremely elevated ACTH (5690, reference: 7–64 pg/ml). Plasma Renin Activity was elevated at 24.48 (0.5–4.7 ng/mL/h) and aldosterone inappropriately normal at 11.8 ng/dl (3.0–28). Cortisol was unresponsive to standard ACTH stimulation with peak level at 0.75 mcg/dL. She was started on stress doses of hydrocortisone with dramatic improvement in clinical status and then transitioned to oral hydrocortisone and fludrocortisone. Adrenal cortex autoantibodies are positive. The girl was also diagnosed with autoimmune thyroid disease and celiac disease, while no signs of hypoparathyroidism were detected. Thus, her diagnosis is Autoimmune Polyglandular Syndrome type 2, characterized by Addison's disease and either autoimmune thyroid disease or type 1 diabetes mellitus.

Conclusions: Clinical and biochemical profile of the patient, at the age of 4 years and 11 months, elucidates that the diagnosis was present for over 6 years. This case report highlights that symptoms of adrenal insufficiency are often underestimated by patients and possibly physicians, leading to delayed diagnosis.

P2-38

Addison's disease: Delay in diagnosis in a girl with longstanding symptoms

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Background: Autoimmune destruction of the adrenal cortex is the cause of primary adrenal insufficiency in 45% to 55% of cases in children.

P2-39

Clinical spectrum of congenital adrenal hyperplasia due to 3 beta hydroxysteroid dehydrogenase deficiency; A case series

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Background: In adrenal gland 3 β -HSD₂ catalyses the conversion of Δ^5 to Δ^4 steroids (i.e., pregnenolone to progesterone, 17 α -hydroxypregnenolone to 17-OHP and DHEA to androstenedione). Defect in this enzyme can affect glucocorticoid, mineralocorticoids and sex steroid synthesis but the clinical and biochemical

profile can be very complicating and confusing due to conversion of intermediate steroids to more active steroids by 3β -HSD₁ in peripheral tissues. Children typically present with ambiguous genitalia. Boys (46xy) tend to have severe hypospadias and small phallus with variable degree of salt loss. Girls (xx) can present ranging from mild clitoromegaly to completely normal female genitalia. Mild variety can present with premature adrenarche, hirsutism.

In our case series we will present genetically confirmed (HSD3 β) mutations with very variable and confusing presentations with multiple deaths in families due to late diagnosis.

Case Summaries: We identified 6 patients (4 male) from 3 families of CAH due to 3β HSD₂ deficiency variant of c.818_819del p.(Lys273Argfs*7) born to consanguineous parents with history of sibling death in 2 families. Family 1 had 5 sibling death (2 female and 3 male) and family 2 had 1 sibling death (male).

All presented within neonatal life (7 – 45 day of life) with failure to thrive and vomiting. Female patients were having normal genitalia at presentation, while 3/4 male presented with mild genital ambiguity (under-virilization) and 1/4 with normal male genitalia.

Initial workup of all revealed significant hyponatremia, hyperkalemia and raised renin. 17-OH progesterone was initially raised in 5 cases. DHEASO₄ (normal) and cortisol (low) was done only in 2 cases due to non-affordability.

After initial stabilization with hydration and stress dose of hydrocortisone, all were started on maintenance dose of hydrocortisone (15mg/m²/day) and fludrocortisone (0.1 mg daily) along with sick day education.

Conclusion: CAH patients due to 3β HSD₂ deficiency can present with normal male or female genitalia. We need to have a strong suspicion of it in region where there is increase consanguinity and no screening tests, to avoid preventable deaths due to this variant.

P2-40

Retrospective Evaluation of Cases Diagnosed with Classical Congenital Adrenal Hyperplasia Due to 21 Hydroxylase Deficiency

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Introduction: Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder. Diagnosis, monitoring of treatment, adjustment of drug doses are important for height, puberty and psychologic status of patients and their families.

Materials and Methods: Patients with classical CAH due to 21-hydroxylase deficiency who were followed regularly in pediatric endocrinology clinic between 1994 and 2019 were included in this study. Informations of admission, follow-up, control and laboratory findings were obtained from electronic file data of patients.

Results: Half of the patients were female. 30% of the virilized female patients' families were informed wrongly about their babies' gender. The mean age of diagnosis was 55.8±76.8 days (5 days -10 months) in patients with SW-CAH and 3.56±2.36 years (50 days -6 years and 7 months) in patients with SV-CAH. Vomiting, inability

to gain weight, suspicious genitalia were the most common complaints at admission. Half of the cases had consanguinity between their parents, 65% had a family member with CAH and 38% of cases were siblings. Clinical status was variable among siblings. 42% of patients were diagnosed with hyponatremia at neonatal period. 75% of cases were SW and 25% of cases were SV. 9 patients were diagnosed by standart dose ACTH test. 44% of patients had a good metabolic control. 44% of patients needed corrective surgery due to ambiguous genitalia. Two 46XX patients were raised as male. 23% of patients had treatment for puberty precocious with a mean duration of 3±1.7 (1-5) years and had a mean height gain of 10.5±6.6 (3-24) cm. 8 patients treated for puberty precocious reached final height. Final height-SDS values of these patients were -2.07±1.47 [(-3.95-(+0.34))]. Although hydrocortisone doses, body mass index-SDS and target height-SDS values of SW and SV were similar, final height SDS values of SW were less than SV (p=0.029). 7 patients had obesity, 8 patients had hypertension, 4 patients had insulin resistance, 3 patients had dyslipidemia, 6 patients had short stature, 6 patients had adrenal rest tumor, 5 patients had enuresis, 2 patients had massive acne, 2 patients had gynecomastia, 1 patient had amenore, 1 patient had epilepsy due to hypoglycemic convulsion, 2 patients had ovarian cyst, 1 patient had major depression, 1 patient had psychosis (schizophrenia), 1 patient had anorexia nervosa, 1 patient had autism and 1 patient had mild mental retardation. IVS2 homozygous mutation was most frequent genetic defect.

Conclusion: Close follow-up and psychological support is required for monitoring of chronic diseases like CAH.

P2-41

Corticotropin-independent Cushing's Syndrome in toddlerhood: a challenging diagnosis and treatment

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Background: Endogenous Cushing's Syndrome (CS) is a rare disease in children, and corticotropin-independent forms are even scarcer. In childhood it carries a significant burden, resulting from both prolonged hypercortisolism long-term effects and treatment-associated morbidity.

Case Report: A 23-month-old girl presented with irritability, central obesity with rapid weight gain and arrested linear growth, cushingoid facies with facial hair and acne, cervical acanthosis nigricans, and severe hypertension. Laboratory evaluation highlighted corticotropin-independent CS: hypercortisolemia (42 µg/dL at 5 am; RR 2,5-23,0 µg/dL), unmeasurably low ACTH (<5 pg/mL), elevated 24h hypercortisoluria (462,6 µg, RR 28,5-213,7 µg), loss of cortisol circadian rhythm and negative overnight dexamethasone suppression test. MRI revealed normal adrenal glands, without enlargement or focal lesions. After 1 week of metyrapone (15 mg/kg/dose q6h) adrenal suppression, along with Lugol's iodine solution (32,5 mg/day) thyroid inhibition, scintigraphy with ¹³¹I-NP-59 (activity 19,7 MBq) was performed. A two-times

higher bilateral adrenal radiopharmaceutical uptake was observed at 3rd, 5th, and 7th days, on a sequential thoracoabdominal-pelvic imaging protocol. As the sign was slightly more pronounced on the right side, a right adrenalectomy was then performed. Macroscopic exam revealed a normally dimensioned adrenal gland (3,6 x 2,5 x 0,5cm) with homogenous yellowish appearance and six 0,5-1,2cm nodular lesions. The histological exam showed nodular adrenal hyperplasia without malignant features. A genetic study by mendeliome sequencing was inconclusive, and more tests are being performed to unravel the etiology.

Two weeks after surgery, blood pressure improved to values right below 90th percentile and antihypertensive therapy withdrawal could be started. In three weeks' time, there was a positive evolution with a decrease in serum cortisol (15,6 µg/dL) and an increase in ACTH (53,40 pg/mL), as well as an evident regression of cushingoid facies, acne, hypertrichosis, and acanthosis nigricans.

Discussion: Some forms of adrenal cortisol hyperproduction may not be readily apparent on routine imaging techniques, posing additional difficulties in the diagnosis. In these cases, scintigraphy studies are a diagnostic paramount. On the other hand, whenever possible unilateral adrenalectomy may be a safe and effective therapeutical option, preventing (or at least postponing) hormone replacement therapy.

P2-42

A case of adrenal insufficiency during the course of multisystem inflammatory syndrome in children (MIS-C)

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Introduction: Multisystem inflammatory syndrome in children (MIS-C) is associated with Covid-19. MIS-C was first reported in April 2020 with similar symptoms to Kawasaki disease and has several treatment options, one of which is glucocorticoids. Autopsy studies in Covid-19 patients have shown degenerative adrenal changes. It has been reported that rarely Covid-19 may affect adrenal function and cause both primary and secondary adrenal insufficiency. Here we present an 11-year-old boy with MIS-C and developed adrenal insufficiency.

Case: An 11-year-old boy was referred with a five-day history of fever, vomiting and rash. He had Covid-19 one month previously and had recovered within two days. At presentation hypotension (80/50 mmHg), tachypnea, tachycardia and rashes that faded under pressure were evident.

C-reactive protein and erythrocyte sedimentation rate were elevated (378 mg/L and 82 mm/h, respectively). Serum glucose was 85 mg/dL, sodium was 124 mmol/L, potassium 3.19 mmol/L, while other biochemistry was normal. Covid-19 IgM was 1.83 (<10), IgG was 6.1 (<1.4). He was evaluated by rheumatology and infectious diseases and was diagnosed with MIS-C. Adrenal function was not

assessed at admission; normotension was achieved with fluid and inotropic treatments. He was started on 60 mg/day methylprednisolone after a dose of intravenous immunoglobulin. On the second day of treatment, he developed hyperglycemia, defined as stress hyperglycemia. The glucocorticoid regimen was changed on the third day of treatment to 500 mg methylprednisolone daily. After receiving 500 mg/day methylprednisolone for three days, the dose was reduced to 60 mg/day by the sixth day of treatment. On the eighth day of treatment, while on 40 mg of methylprednisolone/day, glucose and sodium decreased (from 140 to 129 mmol/L), and potassium increased (from 4.3 to 5.2 mmol/L). Serum adrenocorticotrophic hormone was 18 pg/mL (0-45), cortisol 1.34 µg/dL (6-22), aldosterone 4.9 ng/dL (3.7-31) and plasma renin activity 0.02 ng/mL/h (0.06-4.69) which indicated relative adrenal insufficiency. Adrenocorticotropin stimulation test was not performed because of glucocorticoid therapy. Methylprednisolone was discontinued and hydrocortisone was started at 300 mg/m²/day. Serum sodium and potassium normalised within two days (138 and 3.6 mmol/L, respectively) and hydrocortisone dose was gradually reduced to 7.5 mg/m²/day. After three months of hydrocortisone treatment, the hypothalamus-pituitary-adrenal axis function was assessed as normal and hydrocortisone was discontinued.

Conclusion: Clinicians should be aware that there may be clinically significant impairment of adrenocortical response in Covid-19 infection. Hypothalamus-pituitary-adrenal axis should be evaluated, especially in Covid-19 patients with unexplained hypotension and hyponatremia.

P2-43

Aetiology and different clinical conditions of primary adrenal insufficiency in a region of North Africa

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Introduction: Adrenal insufficiency is relatively rare in childhood and adolescence. Signs and symptoms may be non specific; therefore, the diagnosis may not be suspected early in the course. It may be categorized as primary or secondary and congenital or acquired.

Many etiologies have been reported worldwide of which CAH was the commonest etiology in children.

Objective and Hypotheses: To determine the clinical features and evolution of childhood primary adrenal insufficiency in our centre.

Methods: Longitudinal retrospective study of patients diagnosed with primary adrenal insufficiency (PAI) from January 2005 to December 2019. Clinical features at presentation as well as the possible etiology were described, investigations and management.

Result: Between 2005 and 2019, 50 patients (36 girls, 14 boys) were followed for a mean (range) duration of 7.5 [1-14] years. Mean age at diagnosis and start of treatment was 16.3[0.4-60] months. Consanguinity was present in 28(56%) of cases, and there were 7 familial cases (14%). Of 22 cases presented CAH (44 %), 14 (64 %)

had virilized genitalia (females), 4 boys were diagnosed after salt wasting crisis, 4 cases had presented signs of androgen excess. Of the 28 cases presented other etiologies, symptoms at presentation included hyperpigmentation, fatigability, abdominal pain, diarrhea vomiting and shock. Delay in diagnosis was observed in 13 cases (46 %). Aetiology was unknown in 9 cases who need a genetic investigation, 8 cases were Allgrove syndrome, 5 cases ACTH resistance including one in neonatal period, ALD in 1 case, autoimmune polyglandular syndrome type 1 in one case, Fraser syndrome in 1 case, and others (3 cases). Mean ACTH at diagnosis was 1746 ± 1731 pg/ml. ACTH test have been realized in 8 cases to confirm a diagnosis. 17 OHP was high in the 26 cases with CAH, MRI of brain was necessary in one case, and abdomen ultrasonography in 16 cases. Antibodies investigation is not available in our country.

Conclusion: Adrenal disorders can be difficult to diagnose and are associated with considerable morbidity and mortality if undiagnosed. The clinical and biochemical features at presentation and the natural history of the condition vary depending on which adrenal steroids are affected, as well as the underlying pathological condition. Although a specific diagnosis can be reached in many children and young people with PAI, sometimes the cause remains unknown. Our experience underlines the need to establish links with centres which are able to carry out the necessary genetic analyses in our patients.

P2-44

Clinical and evolutionary aspects of Allgrove Syndrome, Algerian experience

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Introduction: Allgrove syndrome is a rare autosomal recessive disorder involving alacrymia, achalasia, Addison's disease (3A) and neurological disorders (4A), it results from mutations in the AAAS gene located on chromosome 12q13 which codes for a protein known as ALADIN (ALacrymia Achalasia aDrenal Insufficiency Neurologic disorder).

Alacrymia is diagnosed by Schirmer's test, achalasia by esophageal manometry while adrenal insufficiency is confirmed by the determination of cortisol and ACTH.

Goal: To describe the clinical and evolutionary aspects of patients who present with Allgrove syndrome in our department.

Results: Age at diagnosis is 5 ± 1.4 years, diagnostic time is 3 ± 0.6 years, Tte sex ratio is 3/1; consanguinity in only 1 case. All the patients had alacrymia.

The age of the first symptoms is 2 ± 0.8 years marked by hypoglycemia with convulsions in 2 cases, vomiting in one patient and dehydration in another. Melanoderma and difficulty in ingesting solids are found in all patients, and neurological disorders in one.

All patients had low cortisol with high ACTH, alacrymia confirmed by Schirmer's test and achalasia confirmed by esogastro-duodenal endoscopy and oesogastroduodenal transit.

The 3A syndrome is retained in 2 cases, the 2A syndrome in 1 case and a 4A syndrome in one case.

All the patients were put on glucocorticoids, artificial tears; on average, 5 dilation sessions were performed [2-11].

Evolution: We have an average follow-up of 4 years (6 months - 8 years).

Improvement in adrenal insufficiency was achieved in all patients.

Successful dilations were obtained in 2 cases, the other 2 underwent a successful Heller cardiomyotomy.

Comments: Alacrymia is the most constant symptom, it has been found in all of our patients, but which unfortunately has been trivialized by parents and has gone unnoticed by doctors, the same for melanoderma. In our series, one patient had a heavy, strongly suggestive family history (the brother presented with alacrymia and achalasia and sister presented with alacrymia), which unfortunately were completely ignored, resulting in delayed diagnosis.

Adrenal insufficiency was certainly improved in all our patients, but the diagnosis was made only at the stage of decompensation with the need for management at the level of the intensive care unit for one patient.

Conclusion: Allgrove syndrome is a rare disease, early diagnosis and treatment improves the prognosis. The education of parents and patients must take place at each consultation, the only guarantee of a good progression of the disease.

P2-45

A Rare Coexistence of two autosomal recessive conditions: Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency (CYP21A2 mutation) with Beta Thalassemia Major

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Background and Aim: Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is an autosomal recessive condition characterized by inadequate production of cortisol and aldosterone and accumulation of androgens. Beta thalassemia is an autosomal recessive condition caused by defective beta-globin resulting in accumulation of unbound alpha globin chains leading to ineffective erythropoiesis.

We are reporting an unusual case of CAH due to 21-hydroxylase deficiency with co-existing beta thalassemia major.

Case Summary: We are reporting a young boy, born to consanguineous parents, with history of beta thalassemia major in one sibling. He was presented at 20th day of life with failure to thrive, vomiting and loose motions and was found to be dehydrated with normal male like genitalia (bilateral testis palpable in scrotum). Initial investigation revealed severe hyponatremia (128 meq/l), hyperkalemia (8.8 meq/l), metabolic acidosis with raised 17-OH

progesterone (> 320 nmol/l), all suggestive toward salt looser CAH. Later genetical analysis confirmed CAH (21-hydroxylase deficiency) due to homozygous pathogenic CYP21A2 variant c.955C>T p.(Gln319*). After initial stabilization with rehydration and IV hydrocortisone he was started on long term oral hydrocortisone (20mg/m2/day) and fludrocortisone (0.1mg/day).

At 11 months of age, he presented again with marked pallor and hepatosplenomegaly. Full blood count showed Hb of 5.6 g/dl with reticulocytes count of 2.8 % and peripheral smear showing anisocytosis and poikilocytosis. Hb electrophoresis showed HBA (14.6%), HBA2 (4.9%) and HBF (80.5%) suggestive of beta thalassemia major. He was started on folic acid supplementation and frequent transfusions with plan to monitor ferritin level.

Conclusion: Congenital adrenal hyperplasia due to CYP21A2 mutation and Beta thalassemia are two different autosomal recessive condition. We are reporting rare co-existence of two autosomal recessive condition in one patient. This high penetration of two different autosomal recessive condition could be due to increase prevalence of consanguineous marriages in our country, Pakistan.

P2-46

X-linked Adrenoleukodystrophy in south of Tunisia

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Introduction: Adrenoleukodystrophy (ALD) is a rare X-linked disease caused by a mutation of the peroxisomal ABCD1 gene.

It is a progressive condition with a variable clinical spectrum that includes primary adrenal insufficiency, axonal demyelination and the accumulation of high levels of very long chain fatty acids (VLCFA) in the plasma and tissues.

Methods: It's a retrospective study of all cases of X-linked ALD who were diagnosed in the pediatrics department of the university hospital of Sfax between 2004 and 2020.

Specific data related to epidemiology, phenotype and diagnosis of patients with X-linked adrenoleukodystrophy were collected and analysed.

Results: Six cases of ALD were included. The mean age at first symptoms of ALD was 4 years 3 months old. Parental consanguinity was noted in one case and a family history of ALD was reported for 4 children.

For four patients, X-linked ALD started as primary adrenal insufficiency, manifesting with skin hyperpigmentation and vomiting. For two patients, neurological signs were the first symptoms of the disease. All children developed adrenal insufficiency during the course of the disease.

Brain magnetic resonance imaging (MRI) showed signs of leukodystrophy in 2 cases.

The plasma very long chain fatty acids (VLCFA) level were significantly increased for five children. Genetic testing identified the mutation of ABCD1 gene in 4 cases.

Conclusion: X-linked ALD should be screened for boys with adrenal insufficiency. This disorder is confirmed by serum VLCFA levels and/or genetic testing.

Confirmation of the diagnosis of X-ALD by analysis of mutations in ABCD1 is particularly recommended to identify heterozygous women and for antenatal diagnosis of ALD.

P2-47

Clinical, biological and genetic aspects of congenital adrenal hyperplasia in children at the Central Army Hospital in Algiers

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Context: Congenital adrenal hyperplasia (CAH) is a rare genetic defect. Its prevalence is estimated at one case per 3,000 births in Algeria and one case per 15,000 births worldwide. The most common form is due to 21-hydroxylase deficiency associated with mutations in the 21-hydroxylase gene, which is located at chromosome 6p21. Molecular defects of CYP21A2 systematically decrease the activity of this enzyme and result in expression of varying severity and phenotypes. Unfortunately, the search for the genetic anomaly of CAH is not carried out in Algeria.

Goal: Describe the clinical, biological and genetic characteristics of a population of children followed for CAH in the Endocrinology department of the army central hospital in Algiers between 2007 and 2021.

Methods: The study included 26 patients (13 boys and 13 girls) aged 2 to 31 years, followed for CAH. Clinical data from the neonatal period and at the first consultation have been described. The results of the initial biological assessment have been specified (17OHP, Cortisol, ACTH). The genetic study was done in 18 patients with a complete characterization of CYP21A2 mutations.

Results: The diagnosis of CAH was made at birth in 11 of our patients, and during the first 2 months in 8 patients. Four children at the age of 4. The other 3 patients between 11 and 14 years old.

Four out of 13 girls have Prader 4 male virilisation,

Girl exhibited Prader 5 full male virilization

Seventeen of the 28 patients presented the classic form with loss of salt.

The most frequent genetic defect was the IVS2-13A / C>G mutation which is found in 9/18 children (50%), 7/9 of the patients presented with a classic form with loss of salt.

The p.I172N mutation was found in 4 children (22%) in the heterozygous state, and all presented a simple virilizing form.

A rare mutation p.Q41Afs * 39 was found in one case: a girl who presented a biological profile of an 11 beta hydroxylase.

Conclusion: The frequency of the underlying mutations in our patients, with the classical form of CAH, varied but were quite similar to those reported in the Mediterranean region. Therefore, identifying CYP21A2 abnormalities in Algerian patients and

comparing them with incidence and severity in different populations will create a valuable diagnostic tool for genetic counseling.

Key Words: CAH, virilization, CYP21A2, 21-hydroxylase deficiency, salt wasting.

P2-48

Coexistence of Adrenal Insufficiency and Hypergonadotropic Hypogonadism: P450scC Deficiency

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Introduction: Steroid hormone biosynthesis is initiated by the cholesterol side-chain cleavage enzyme (P450scC), which converts cholesterol to pregnenolone, the precursor of all steroid hormones. This enzyme is encoded by the CYP11A1 gene and is responsible for glucocorticoid, mineralocorticoid and sex steroid synthesis in the adrenal glands, gonads and placenta. Early or late onset adrenal insufficiency, 46, XY sex development disorder, and hypergonadotropic hypogonadism may develop in patients with CYP11A1 mutation. Herein, a case presenting with adrenal insufficiency and found to have a CYP11A1 mutation will be presented.

Case Report: A three and a half year old male patient was admitted to an external center with vomiting and change in consciousness. Upon detection of sodium 126 mEq / L and potassium 6.4 mEq / L in his examinations, he was referred to us with a pre-diagnosis of adrenal insufficiency. In the physical examination; height: 101.8 cm (0.34 SDS), weight: 16 kg (0.06 SDS), BMI: 15.4 kg/m² (SDS: 0.24), BP: 90/60 mmHg, testicular volume 2 ml/2 ml, stretched penile length 4 cm, hyperpigmentation was present on the skin, gums, axilla, and genital area. He was born at term, weighing 3400 g, with C/S. Parents were first degree cousins. In his examinations; Glucose: 89 mg/dl, Cortisol: 2.9 µg/dl, ACTH: > 1250 pg/ml, Renin: 2.78 ng/ml / h, Aldosterone: 20 pg/ml, 17-Hydroxyprogesterone: 0.08 ng/ml, DHEA-SO₄: 17.1 µg/dl, peak cortisol response to ACTH stimulation test was 2.2 µg/dl. In abdominal ultrasonography; bilateral adrenal glands were normal. Hydrocortisone and fludrocortisone treatments were initiated. Genetic analysis revealed a mutation in the CYP11A1 gene. At the last control of the patient at the age of 14; testicular volumes were determined as 25 ml, FSH: 8.4 mIU/ml, LH: 11.1 mIU/ml, Total testosterone: 62.5 ng/dl. The patient is being followed up for hypergonadotropic hypogonadism.

Conclusion: P450scC deficiency is a new, rare disease that can present with acute adrenal insufficiency at any time from infancy to early childhood. Since gonadal steroid synthesis may also be affected, patients should be carefully monitored in terms of gender development disorder and gonadal insufficiency.

P2-49

Assessment of Patients With Congenital Adrenal Hyperplasia in Armenia

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The congenital adrenal hyperplasias (CAH) comprise a family of autosomal recessive disorders that disrupt adrenal steroidogenesis.

Aim: To investigate the clinical features of the patients with CAH.

Methods: The current study was conducted on 106 Armenian patients with CAH.

Results: Distribution between regions: 45.3% were from Yerevan, 13.2%-Syunik region, 11.3%-Lori region. The diagnosis was assigned until 3 months among 39.6%, from 3 months to 1 year-2.8%, from 1 to 3 years 5.7% and later than 3 years among 51.9% (for this group mean age was 14.03 years). Nonclassic forms of CAH were diagnosed in 42.9% of patients, classic salt-wasting forms have 39.0% and Simple virilizing forms were registered among 18.1%. The history of assisted conception has only 4 cases (3.8%). Original sex wasn't assigned among 4.7%, the male was 50.9%, female 44.3%. Current gender- 42.5% are males, 57.5%-females. Nobody among females changed the gender. 5 not assigned cases currently have female gender and 9 males changed their gender into a female. Among all cases clinical and biochemical features were certain. Family history of disorders of sex development has 18 cases (17%).

P2-50

First case in Lebanon of homozygous mutation in CYP 11B2 leading to isolated aldosterone deficiency

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Isolated hypoaldosteronism is a rare cause of salt wasting in infancy and may be life-threatening, especially in the newborn. Isolated aldosterone deficiency results from loss of activity of aldosterone synthase encoded by CYP 11B2 gene.

We reported the case of a newborn, who presented at the age of 4 weeks with severe dehydration, vomiting and hypotonia. Blood investigations showed severe hyponatremia, hyperkalemia and metabolic acidosis. The familial history revealed a first degree consanguinity, with many patients who were treated with fludrocortisone during the first few years in their infancy.

Hormonal assessment confirmed severe deficiency in Aldosterone with high level of Renine, normal Cortisol, ACTH and Androgens level. The patient was treated by fludrocortisone and sodium.

The Genetic analysis of CYP 11B2 revealed homozygous mutation ((grch 37) g.143996461C>A or NM_000498.3: c.595+1 G>T

intron 3) which confirm the diagnosis of isolated deficiency in Aldosterone.

In conclusion, some cases of salt wasting in neonatal period can be due not to congenital adrenal hyperplasia but to isolated aldosterone synthase deficiency. The treatment has to be adjusted to limit the overprescription of hydrocortisone and the genetic testing can be very helpful. We report the first case of a Lebanese newborn with isolated aldosterone deficiency with a probable common founder mutation.

P2-51

A Rare Cause of Hyponatremia in a Child with Hirschsprung Disease Operated with an Ileostomy

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Background and Objectives: Pseudohypoaldosteronism (PHA) is a rare condition characterized by hyponatremia, hyperkalemia, metabolic acidosis and high plasma aldosterone level. Pseudohypoaldosteronism secondary to gastrointestinal losses is rare in the pediatric population. We present a case with secondary pseudohypoaldosteronism due to excessive gastrointestinal losses through ileostomy.

Methods: A 1.5 year-old-male child, who was diagnosed with Hirschsprung disease at the age of 2 months with ileostomy creation, presented 2 weeks postoperatively with picture of hypovolemic shock. There was history of gastrointestinal fluid losses through ileostomy of 5 days duration. Laboratory tests showed picture of pseudohypoaldosteronism. Hormonal work up was sent and patient was started on hydrocortisone and intravenous fluid, in addition to management of hyperkalemia.

Results: Hormonal work up showed picture of pseudohypoaldosteronism. Hydrocortisone was tapered and discontinued. Excessive losses of fluids and sodium, leads to activation of renin-angiotensin system. Subsequently, aldosterone can no longer cause potassium excretion in presence of excess sodium loss; leading to hyperkalemia. At the age of 14 months, Duhamel pull-through operation was done with closure of ileostomy, with maintenance of normal sodium and aldosterone levels.

Conclusion: Pseudohypoaldosteronism should be included in the differential diagnosis when evaluating hyponatremia especially in those with excessive fluid losses. Due to the rarity of this condition, there is a high possibility of delayed diagnosis; which would lead to increased morbidity and mortality.

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P2-52

Adrenal insufficiency masquerading as biliary atresia in an infant

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Background: *Adrenal insufficiency* is a rare cause of *neonatal cholestasis*, which is reversible with prompt glucocorticoid administration.

Case Presentation: A 2-month old baby boy was referred to the paediatric endocrine department for evaluation of intermittent hypoglycaemia associated with metabolic acidosis, hyponatraemia and hyperkalaemia. The infant was second born to second-degree consanguineous parents whose firstborn had died in the neonatal period with a history of hypoglycaemia and septic shock. The baby was born at term with a birth weight of 2.19 kg and was transferred to a tertiary care centre for further management of projectile vomiting associated with acid-base imbalance and hypoglycaemia.

The infant was under evaluation for prolonged cholestatic jaundice and was considered for Kasai procedure while considering the reduced benefit of surgical correction at this point. Other medical problems included congenital cytomegalovirus (CMV) infection, dilated left ventricle and myocarditis for which he was on ganciclovir and anti-heart failure regimen.

On examination, the infant was pigmented, mildly jaundiced without associated pallor or hepatomegaly and had normal external genitalia with pigmented scrotal sacs.

Results: Biochemistry revealed direct hyperbilirubinaemia with mildly raised liver enzymes and a normal coagulation profile. Ultrasound abdomen did not reveal a gall bladder and the 99-Tcnetium HIDA scintigraphy revealed findings compatible with biliary atresia. A standard dose synacthen test produced cortisol levels of 9.5 nmol/L, 4.5 nmol/L and 3.3 nmol/L at 0 minutes, 30 minutes and 60 minutes respectively, and a normal 60-minute 17-hydroxyprogesterone level (3.87 nmol/L). Plasma renin concentration was elevated (> 1000 mU/L). The thyroid function test was mildly deranged (TSH 10mIU/L) with a normal thyroid ultrasound.

Following the commencement of hydrocortisone, direct hyperbilirubinaemia improved but liver enzymes worsened for which liver failure regimen was commenced. Repeat abdominal ultrasound and 99-Tcnetium HIDA scintigraphy 6 weeks later revealed a normal gall bladder and a normal hepatobiliary study.

Conclusion: A clinical diagnosis of congenital adrenal hypoplasia was made and genetic confirmation was not feasible. Adrenal insufficiency can present with severe neonatal hepatitis and mimic biliary atresia, and should always be excluded in a neonate with prolonged cholestatic jaundice and can prevent unnecessary complex surgery.

P2-53

Mutation of NROB1 and Double mutants in cis of CYP21A2 gene in a Chinese boy with primary adrenal insufficiency

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Background: X-linked Adrenal Hypoplasia Congenita (AHC) is a very rare hereditary cause of pediatric primary adrenal insufficiency (PAI). Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21OHD) is most common hereditary cause of pediatric PAI with autosomal recessive inheritance.

Objective: To present a Chinese boy with PAI with the pathogenic mutation of NROB1 and Double mutants in cis of CYP21A2 gene.

Methods: Mutational analysis of CYP21A2 by Sanger sequencing and MLPA, target sequencing for PAI gene by NGS.

Patient and Results: The one-month-old boy was the third child (birth weight, 2.9 kg, full term) of non-consanguineous healthy parents of Chinese Han ethnicity, who presented with salt losing adrenal insufficiency early in two days of life in local hospital. On physical examination, marked skin pigmentation was noted, with normal looking male genitalia. Hormonal evaluation revealed ACTH > 440.4 pmol/L, cortisol 100.0 nmol/L, P 0.3 ng/ml, 17(OH)P 2.89 ng/ml, Androstenedione > 35 nmol/L, Na 113.1 mmol/L, Cl 79.8 mmol/L, K 5.98 mmol/L. CAH 21OHD was suspected and CYP21A2 gene mutation analysis was performed by Sanger sequencing and MLPA. Treatment was started with oral hydrocortisone (10-15 mg/m²/day), 9 α -fluorocortisol (0.1 mg/day), and salt supplementation (NaCl 1 g/day). 1 month later, CYP21A2 gene analysis showed two pathogenic mutations c.844G>T & c.920-921insT, and the patient was diagnosed with CAH 21OHD in local hospital. The boy started growing properly.

At 6-month-old, serum androstenedione was less than 1.5 nmol/L. At one-year old, he came to us and was admitted to our hospital for precise diagnosis, with oral hydrocortisone (9.2 mg/m²/day) and 9 α -fluorocortisol (0.1 mg/day). Plasma ACTH > 440.4 pmol/L, cortisol < 0.08 μ g/dL, P < 0.1 ng/ml, 17(OH)P 0.08 ng/ml, Androstenedione < 1.5 nmol/L, DHEAs 0.08 μ mol/L, T < 0.13 ng/ml, Na 138.0 mmol/L, Glu 4.9 mmol/L, K 4.8 mmol/L, normal plasma renin (55 pg/ml). The adrenal glands were normal on abdominal ultrasound. Parental mutational analysis of CYP21A2 showed the same two mutations in the father, nor in the mother, indicating the patient carried double mutants of CYP21A2 in cis, which cannot explain the patient's clinical symptoms. Target sequencing for PAI gene was requested and a heterozygous maternal pathogenic mutation of c.610G>T [p.(Glu204*)] was found to NROB1 exon 1. X-linked AHC was determined.

Conclusions: We identified a mutation of NROB1 in a Chinese boy with PAI carrying double mutants in cis of CYP21A2 gene. Slightly elevated 17OHP and high level of Androstenedione in the early stage may be contributed to the double mutants in cis of CYP21A2 gene.

P2-54

Clinical and hormonal features of the manifestation of various forms of congenital adrenal hyperplasia in children in real clinical practice

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Introduction: Congenital adrenal hyperplasia (CAH) is a disease characterized by a defect in one of steroidogenic enzymes or the gene encoding the transport proteins. Frequency of occurrence is 1:14000 newborns.

Objective: To determine the age, clinical manifestations, the incidence and the effectiveness of treatment various forms CAH in children.

Materials: Medical History of 35 patients aged from 1 to 16 years diagnosed with CAH in 2003-2018 have been analyzed in the Republican Center for Pediatric Endocrinology.

Findings: Among the 35 patients participating in the study (57% boys, girls 43%) 71.4% is with salt wasting form (SWF), 25.75% with virilising form (VF), 2.85% with non-classical form (NF). In the SWF group boys (64%) predominate over girls (36%), in contrast to the VF group (55.5% girls, 45.5% boys). The mean weight SDS at birth is -0.08 ± 1.17 , the mean height SDS is 0.012 ± 1.6 . Age of diagnosis SWF is 17.4 ± 16.3 days, VF is 4.03 ± 4.6 years. The most frequent signs of manifestation in SWF were regurgitation (28.6%), body weight loss (22.8%), vomiting (8.6%), dry skin (8.6%), hypotension, exicosis (5.7 %); in VF - premature pubarche (14.3%). At the time of diagnosis, 17-hydroxyprogesterone (17OHP) was higher than normal range in all groups: SWF - $840, 34 \pm 298.6$ nmol/l, VF - $386, 1 \pm 80.9$ nmol/l, NF - 35.2 nmol/l; increase morning values of adrenocorticotrophic hormone (74, 06 ± 2.05 pg/ml). It was revealed that before treatment there were changes in electrolytes (K, Na) only in group with SWF (6.71 ± 1.6 mmol/L and $125, 6 \pm 10.98$ mmol/L respectively). Blood glucose and pH in children with SWF were 3.2 ± 1.14 mmol/L and $7, 34 \pm 0.067$ co-responsibly. All children received hydrocortisone replacement therapy at a starting dose of $63, 7 \pm 28.1$ mg/m² in SWF group; $21, 84 \pm 21.5$ mg/m² in VF group; 21 mg/m² in NF group. Patients with SWF additionally took fludrocortisone at a starting dose of $787, 3 \pm 130.8$ mg/m². 14 children from the total sample have reached puberty age. Height SDS is -0.4 ± 1.3 , weight SDS $1, 13 \pm 1.33$, BMI $24, 2 \pm 3.6$ kg/m², 17OHP - $13, 56 \pm 13.47$ nmol/l.

Conclusion: Late diagnosis of the disease in patients was revealed regardless of the form of CAH. Metabolic acidosis, hyponatremia and hyperkalemia, high level of 17-OHP are registered in the SWF group at the time of manifestation. There was noted compensation of metabolic parameters, achievement of target growth indices, when children receive adequate replacement hormonal therapy.

P2-55**Twin infants with salt-wasting: double the trouble**

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Introduction: Failure to thrive (FTT) is a common entity encountered by pediatricians. It can be caused by inadequate energy intake or "organic causes" such as inborn errors of metabolism or disorders of the endocrine system. One cause that is rarely seen is a deficiency of aldosterone.

Case Presentation: A set of 3-month-old monozygotic male twins presented with failure to thrive and dehydration. Initially, they were evaluated for gastrointestinal/anatomical causes that were ruled out. They were also found to have persistent hyponatremia and hyperkalemia despite rehydration. Cortisol, corticotropin and 17-hydroxyprogesterone levels were normal. Aldosterone levels were undetectable in both twins, and plasma renin was normal. Gene sequencing of CYP11B2, the gene coding for the enzyme aldosterone synthase (AS), is currently pending. The patients were started on fludrocortisone 0.1 mg twice daily with sodium supplementation, which resulted in rapid improvement of electrolyte imbalances and growth.

Discussion: Hyponatremia and hyperkalemia in the setting of failure to thrive should elicit consideration of primary adrenal insufficiency, which in infancy is most commonly due to congenital adrenal hyperplasia (CAH). However, aldosterone deficiency and insensitivity may mimic the symptoms of CAH and should be considered as well. AS is only expressed in the zona glomerulosa of the adrenal cortex and is regulated by the renin-angiotensin system. The enzyme catalyzes the final three reactions of mineralocorticoid synthesis, which ultimately converts deoxycorticosterone to aldosterone.

Conclusion: We present a unique case of monozygous twins with aldosterone deficiency. While the differential of FTT in infants can be broad, the importance of identifying and treating rare causes of FTT can ultimately be lifesaving. We aim to highlight that although aldosterone deficiency is rare, it can mimic the electrolyte abnormalities of CAH. Genetic testing should also be pursued for the confirmation of biochemical diagnosis and genetic counseling.

P2-56**Effect of treatment of double precocious puberty in a 9-year-old girl- case report**

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Non- classic form of congenital adrenal hyperplasia due to 21-hydroxylase deficiency is the most common disorder, which is

associated with the use of hydrocortisone. Clinically patients present the GnRH-independent precocious puberty with rapid growth and advanced bone age. Inappropriate inhibition of androgen secretion can induce precocious central puberty.

We present the case of 9-year-old girl, who was treated of the congenital adrenal hyperplasia due to 21- hydroxylase deficiency.

When the girl was 5 years old, she was diagnosed because of precocious puberty. The height and weight were over 97 percentile, bone age – 11 years, advanced puberty by Tanner stages: Th1, Pub 3, Ax 1, enlarged clitoritis. In laboratory tests the patient had normal cortisol level in serum and elevated adrenal androgens. Congenital adrenal hyperplasia was confirmed in steroid profile in urine. The hydrocortisone had been administered orally in dosages of 8-12mg/m²/day in three divided doses. The side effect of that therapy was hypertension. The result of using hydrocortisone was slow down progression of bone age. When the girl was 7,5 years old, because of progress precocious puberty, the test with GnRH was performed. Central precocious puberty was treated with triptorelin to achieve gonadotropin inhibition. Due to insufficient improvement after treatment with hydrocortisone the using therapy with dexamethasone (0,5 mg daily orally) caused decreased level of androgens, slowed growth during first year of treatment and normalization steroid profile in urine.

Results: 1). The preferred glucocorticoid for chronic treatment of the congenital adrenal hyperplasia due to 21- hydroxylase deficiency is hydrocortisone. 2). Sometimes, precocious puberty should be treated centrally in children. 3). Proper treatment of precocious puberty prevents final short stature.

P2-57**Classical Congenital adrenal hyperplasia: about 7 cases**

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Introduction: Congenital adrenal hyperplasia (CAH) is a group of autosomal recessively inherited disorders of various enzymes participating in the adrenal steroidogenesis. 21-hydroxylase deficiency (21-OHD) is the most common type of CAH (90–95%). Less frequent types of CAH are 11 β -hydroxylase deficiency (up to 8% of cases), 17 α -hydroxylase deficiency, 3 β -hydroxysteroid dehydrogenase deficiency, P450 oxidoreductase deficiency and StAR deficiencies. Patients with these enzyme deficiencies can have various alterations in glucocorticoid, mineralocorticoid, and sex steroid production, which in some cases require hormone replacement therapy.

Materials and Methods: This is a retrospective descriptive study of 10 patients with congenital adrenal hyperplasia, who are followed-up in the Department of Endocrinology-Diabetology-Nutrition of Mohammed VI University Hospital Center of Oujda in eastern Morocco.

Results: In our study 7 patients had classical congenital adrenal hyperplasia; four of these female patients were born with atypical genitalia, three male patients had neonatal salt wasting. Five of

these patients had 21-hydroxylase deficiency and 2 patients had 11 β -hydroxylase deficiency. Female patients with atypical genitalia benefited from genital surgery. All of our patients are treated with hormone replacement therapy.

Conclusion: The salt-wasting congenital adrenal hyperplasia (SW) is the most severe type of CAH and accounts for 75% of all cases of classical CAH. While female infants with classic CAH typically have ambiguous genitalia at birth due to intrauterine exposure to high androgen concentrations.

Bone, Growth Plate and Mineral Metabolism

P2-58

Denosumab therapy for giant cell granuloma in a paediatric patient: using quantification of Tc99m-MDP uptake on SPECT imaging to guide treatment

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Background: Giant cell granulomas (GCG) are uncommon bony lesions that most commonly affect the maxilla and mandible; whilst generally benign they can be disfiguring to the face. Historically, GCGs have been treated with steroids or bisphosphonates to try and avoid surgical resection. Over recent years denosumab, a human monoclonal antibody which acts against the receptor activator of nuclear factor kappa B ligand, has been shown to be effective in treating GCGs, although there are risks in using the drug in growing children. We present a case of a child treated with denosumab using quantification of Tc99m-MDP uptake on SPECT imaging to guide treatment.

Case Presentation: An 11-year-old female presented with an oral lesion. CT scan and biopsy confirmed a diagnosis of GCG of the maxilla. Initial treatment with weekly steroid injections resulted in a short period of stability before growth progression returned. MRI/SPECT imaging showed an expansile, lytic left maxillary lesion with increased Tc99m-MDP uptake, measuring 36mm x 41mm x 42mm. Zoledronic acid was commenced, after which a small reduction in lesion size was noted, although MRI/SPECT imaging after a year of treatment showed no change with increased sclerosis and increased Tc99m-MDP uptake.

Denosumab was commenced at 60mg every 4 weeks (increased to 120mg after 11 months) by subcutaneous injection with calcium and vitamin D supplementation. The patient had close monitoring of biochemistry and bone turnover markers, bone densitometry, plain radiographs and dental reviews. After 14 months of denosumab, the patient had suppressed bone formation markers, MRI scan showed lesion size was unchanged but with increased

sclerosis. However, semi-quantitative analysis showed a reduction in the ratio of Tc99m-MDP uptake in the lesion, compared to normal bone, from 4.9 to 1.4.

The lesion has clinically reduced after 19 months of denosumab with only mild facial asymmetry. Denosumab weaning has begun with the aim of stopping treatment in the next 6 months. Regular imaging with semi-quantitative analysis of uptake will continue to guide future treatment.

Conclusion: This case report adds further support for the use of denosumab in the treatment of GCG in paediatric patients. Imaging using SPECT with semi-quantitative analysis of Tc99m-MDP uptake allowed for valuable assessment of denosumab effect which was difficult to appreciate on standard MRI/SPECT images.

P2-59

Vertebral compression and shape in children with osteogenesis imperfecta on regular Zoledronic acid infusions

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Introduction: Osteogenesis Imperfecta (OI) is a group of rare hereditary collagen disorders. Vertebral compression fractures and vertebral deformities are well-known complications of OI.

Intravenous zoledronic acid is widely used to improve the bone mineral density in children with OI.

This study aimed at assessment of the changes in vertebral compression and shape in children who received regular zoledronic acid infusions.

Methods: This was a prospective study that ran over approximately 5 years recruiting infants, children and adolescents with OI attending the Paediatrics Endocrinology Clinic of Ain Shams University (PECASU). It included 23 patients with OI who completed the required follow up.

All participants had full history taken and detailed examination including anthropometric measurements and laboratory assessment.

Clinical follow up and zoledronic acid infusions were done at 3 monthly intervals for those < 3 years and at 6 monthly intervals for older children. All patients were prescribed the recommended daily doses of calcium and vitamin D.

Lateral X-rays of the thoracic and lumbar spine were done for each patient at initial enrolment then each year till they reached the minimum X-ray score then no further X-rays were done. The Score of Spine Morphology (SSM) by Koerber et al., 2012 was used to assess the effect of Zoledronic acid infusions on thoracolumbar spine morphology. The SSM relied on three criteria: vertebral compression, thoracolumbar kyphosis and deformity type to formulate a severity classification which was then used to develop a severity score.

Results: The mean age of the included patients was 5.3 ± 0.9 years, their length/height SDS was -3.42 ± 0.61 and their BMI SDS was -0.82 ± 0.46 at inclusion in the study.

The severity score showed significant improvement across the follow up period ($p=0.001$). The maximum and average point values for spine compression showed significant improvements with treatment ($p=0.026$ and $p=0.008$ respectively). However, the angle of kyphosis on lateral thoracolumbar spine X-ray showed no significant difference (0.067). The maximum and average point values for spine deformity showed non significant results ($p=0.252$ and $p=0.054$ respectively).

Conclusion: Regular Zoledronic acid infusions in children with OI improved the severity score of spine morphology without significant adverse effects or electrolyte disturbances. Zoledronic acid infusions were associated with a significant reduction in vertebral compression with less remarkable effects on vertebral shapes and the angle of kyphosis.

P2-60

Osteosclerotic Metaphyseal Dysplasia: A novel homozygous LRRK1 mutation in two siblings

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Background: Osteosclerotic metaphyseal dysplasia (OSMD, OMIM 615198) is an extremely rare autosomal recessive disorder, within the family of sclerosing bone dysplasias. It is a distinctive type of osteopetrosis characterised by a unique pattern of osteosclerosis predominantly involving the metaphyseal margins of the long tubular bones. OSMD is characterised by skeletal deformity and multiple fractures and associated clinically with developmental delay, hypotonia, seizures and osteonecrosis of the jaw.

To date, only eight families with ten affected individuals have been reported. Three homozygous sequence variants in the leucine-rich repeat kinase 1 (LRRK1) gene have been identified to cause OSMD in four of the above individuals. We present two male siblings with OSMD with a novel LRRK1 mutation.

Cases: The index case was referred aged 9 months when diffuse sclerosis of the ribs and vertebral bodies, suggestive of osteopetrosis, was incidentally identified on a chest radiograph done for suspected lower respiratory tract infection. Parents were consanguineous (first cousins). Clinical assessment revealed developmental delay, significant genu valgus deformity and nystagmus. Further evaluation showed bilateral optic nerve hypoplasia with severe visual impairment and an abnormal bone texture indicative of osteopetrosis.

His older sibling (aged 7 years) had similar clinical course with recurrent respiratory infections in infancy, nystagmus with bilateral visual impairment and significant valgus deformity but no apparent developmental delay or hypotonia. He suffered from chronic osteomyelitis of the left mandible that required debridement, debulking and long-term antibiotics. Dense bones were

confirmed at the time of operation. A skeletal survey revealed widespread diffuse sclerosis with Erlenmeyer flask deformity of the femurs, similar to previous reports. Unlike previous reports suggesting sparing of the skull, our patient had scaphocephaly with evidence of osteosclerosis on CT scan. Neither sibling had significant skeletal fractures or cytopenia.

Genetic testing for the common autosomal recessive and dominant pathogenic variants of osteopetrosis was negative. Whole Exome Sequencing (WES) followed by Sanger sequencing, identified a homozygous LRRK1 c.2506C>T p.(Gln836Ter) nonsense variant which is predicted to result in premature truncation of LRRK1 transcript.

Discussion: Our cases confirm and expand the spectrum of clinical and radiological features of OSMD reported in the literature. Increasing reports of LRRK1 mutation in this phenotype raises the question of whether LRRK1 gene should be included in targeted osteopetrosis panels. Bone histology in previous cases has shown this to be an osteoclast rich form of osteopetrosis and therefore bone marrow transplantation may be an appropriate treatment modality.

P2-61

Experience of 6-months of burosumab therapy in five siblings with X-linked hypophosphataemic rickets in the State of Kuwait

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Background: X-linked hypophosphataemic rickets (XLH) is a genetic disorder, characterized by hypophosphatemia and caused by a mutation in the phosphate regulating endopeptidase homolog, X-linked (PHEX) gene which leads to overexpression of fibroblast growth factor 23 (FGF23).^{1,2} Conventional therapy, supplementation with oral phosphate and vitamin D analogs, does not treat the underlying cause of the disorder and is associated with poor treatment adherence, high rate of failure and long-term side effects.³ Burosumab, a human monoclonal antiFGF23 antibody, has been shown to alleviate symptoms of XLH by addressing the underlying pathophysiology of the disease.⁴ This study aimed to assess the effect of 6-months of burosumab treatment in XLH patients from a Kuwaiti family.

Methods: This prospective observational study collected clinical and biochemical parameters (fasting serum phosphate [mmol/L], tubular maximum reabsorption of phosphate to glomerular filtration rate [TmP/GFR; mmol/L], serum calcium [mmol/L], alkaline phosphatase [ALP; IU/L] and active vitamin D [nmol/L]) for 5 XLH patients at baseline (prior to burosumab treatment) and every 4 weeks during the first 6-months of treatment. X-rays were also performed at baseline and at 6-months. Burosumab was initiated at a starting dose of 0.8 mg/kg for the three pediatric patients and 1 mg/kg for the two adult patients, following a washout period of one week after cessation of conventional therapy.

Results: All patients were female, aged 2-5 years at diagnosis and 7-20 years at burosumab initiation. All patients experienced increased serum phosphate (mean change versus baseline +0.23

mmol/L) following 6-months of burosumab treatment, with three patients achieving levels within the normal range. All patients also had reduced ALP (mean -81.40 IU/L) and increased TmP/GFR (mean +0.06 mmol/L) following 6-months of burosumab treatment. X-rays showed improvements in rickets. Patients also reported improvements in their quality of life - having more active mobility and experiencing less bone pain as well as being free of daily medications. No adverse events were reported with burosumab treatment.

Conclusions: Six-months of burosumab treatment led to improvements in clinical and biochemical parameters in these five XLH siblings from the State of Kuwait.

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P2-62

Severe Hypophosphatemic Rickets due to Tumor-Induced Osteomalasia

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Introduction: Hypophosphatemic rickets is usually due to genetic causes but in rare cases it can develop secondary to MAS, Fanconi syndrome, or oncogenic causes. Oncogenic osteomalacia, also called Tumor-Induced Osteomalacia (TIO), is a rare acquired paraneoplastic syndrome that develops as a result of excessive phosphate loss from renal tubules by FGF23 released from tumour tissue. In addition to the clinical features of rickets, gait disturbances, growth retardation, and skeletal deformities may develop.

Case: A 16-year-old male boy who had been completely healthy until 13 years of age underwent surgery for leg pain and limping that began 3 years ago and was found to have a cyst in the proximal right tibia. He developed severe deformities due to recurrent fractures after surgery and applied to us for further examination. He had painful deformities, tachypnea, and tachycardia on physical examination. The results of the laboratory tests are summarized in Table 1. Due to severe hypophosphatemia, oral phosphorus (up to 55 mg/kg/d), calcitriol (up to 60 ng/kg/d) and calcidiol (1200 U/day) were started. MRI of the right knee was taken to determine the possible location of the tumour and GA-68-DOTATATE-PET was performed due to the suspicious appearance of the mass and metastasis. An 8.5x7.5 cm heterogeneous mass with minimal involvement in PET was detected in the right knee. In biopsy, a phosphaturic mesenchymal tumour with osteoblastoma-like appearance was detected. Surgical resection was planned.

Conclusion: TIO is a rare paraneoplastic syndrome that presents clinical symptoms after overexpression of FGF-23 in benign mesenchymal tumours. TIO is usually diagnosed late and difficult

to localize because of their slow progression and small size. Extensive resection of the tumour is very important for both the chances of cure and prevention of recurrence. It should be included in the differential diagnosis of acquired hypophosphatemia. This case presented due to its severity and large mass.

Table 1. Laboratory tests of the patient at registration

	11.01.2021
Ca (mg/dL)	8.7
P (mg/dL)	0.6
ALP (U/L)	615
PTH (pg/mL)	119.1
25(OH) vit D (ng/mL)	13.3
1-25(OH) vit D (ng/L)	36
TRP (%)	86
TmP/GFR (mg/dL)	0.51
Intact FGF23 (pg/mL)	1329 (<52)

P2-63

Diagnostic Challenges of Vitamin D-Dependent Rickets Type 1A (VDDR1A) caused by CYP27B1 mutation in Resource Limited Countries: A Case Series from Three families

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Background and Aim: Vitamin D-dependent rickets type 1 A (VDDR1A) is an autosomal recessive condition caused by mutation in *CYP27B1*, which encodes 1 α -hydroxylase enzyme that catalyzes the conversion of 25-hydroxyvitamin D (25OHD) to 1,25-dihydroxyvitamin D (1,25 (OH)₂D).

We are reporting 4 cases of VDDR1A due to *CYP27B1* mutation initially misdiagnosed as vitamin D deficient and hypophosphatemic rickets.

Case Summaries: We identified 4 cases (all male) from 3 different families of VDDR1A due to homozygous *CYP27B1* mutation (c.1319_1325dup p.(Phe443Profs*24)) over 1 year. All were born to consanguineous parents with one case had a history of 4 siblings' death.

Initial presentation was bony deformities and failure to thrive in late infancy (9- 12 months). Three had additional complaints of abdominal distension with repeated diarrheas and one had a history of fracture after minor trauma. All were initially misdiagnosed as vitamin D deficient rickets and hypophosphatemic rickets

(treated with cholecalciferol and joule's solution) and referred to tertiary care at mean age of 2.8 (1.5-3.9) year because of failure to respond to treatment.

At presentation mean height was at -4.10 (-2.10 to -4.88) SD and BMI was at -0.18 (1.96 to -1.84) SD. All cases had signs of frank rickets and three had abdominal distension with hepatomegaly. Bone profile revealed low-normal calcium (7.9-8.9 mg/dl), low phosphate (1.5-2.2 mg/dl), normal magnesium (2-2.5mg/dl), raised Alkaline phosphatase (868 – 3723 IU/l), normal to raised 25-OHD level (39.8-122 ng/ml) and raised PTH (80.9- 771 pg/ml). Fractional excretion of phosphate was > 15% (17%-23%) and tubular reabsorption of phosphate was <85% (76-84%). 1,25 (OH)₂ D were not done due to non-availability. Skeletal survey showed florid rickets with marked osteopenia.

After genetic confirmation of VDDR1A due to *CYP27B*, joule solution was stopped, and alfacalcidol was started at the dose of 150 ng/kg/day along with calcium supplementation. Two months post-treatment follow up showed they are catching up with mean height velocity 7.7 (4.06-12.3) cm/year, normalization of calcium and phosphorus, decreasing trend of alkaline phosphatase and PTH, normal urine calcium to creatinine ratio and x-ray showing interval improvement with zone of healing.

Conclusion: VDDR1A is often missed and presented late in resource limited countries due to lack of availability of 1,25 (OH)₂ D level and genetic testing. It is easily treatable condition with excellent outcome if diagnosed timely and managed promptly.

P2-64

Lack of Cinacalcet response in Neonatal Severe Hyperparathyroidism (NSHPT) due to homozygous CASR mutation

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Background: Neonatal severe hyperparathyroidism (NSHPT) is a rare disorder caused by inactivating calcium-sensing receptor (CASR) mutation characterized by striking hyperparathyroidism leading to severe hypercalcemia. Heterozygous loss of function in CASR gives rise to a benign variant called familial hypocalciuric hypercalcemia which needs no treatment.

We are reporting 3 cases of NSHPT due to inactivating homozygous CASR mutation not responding to cinacalcet.

Results: We identified 3 cases (2 females) from three families of neonatal severe hyperparathyroidism (NSHPT) due to inactivating

CASR mutation. Two were carrying homozygous mutation in CASR gene (parents' carrier) while in one patient's genetic analysis could not be done (later both parents found carrier). Case 1 had a novel CASR variant at c.295G>C p.(Asp99His), case 2 had CASR variant at c.2069G>A p.(Arg690His) and case 3 had CASR variant at c.206G>A p.(Arg69His).

All cases were born to consanguineous parents with history of unexplained sibling death in case 1 and still birth in case 2. Case 1 and 3 were born IUGR and presented in neonatal age group with complains of lethargy, reluctance to feed, failure to thrive and polyuria, while case 2 presented at 4 months of age with nephrocalcinosis.

Initial bone profile in all cases revealed marked hypercalcemia (20.4-23.1 mg/dl), low phosphate (1.2-2.2 mg/dl), normal magnesium (2.3-2.4 mg/dl), raised alkaline phosphatase (>400 IU/L), strikingly high PTH (642-1077 pg/ml), low normal 25OH vitamin D level (16.7-20.9 ng/ml), high urine calcium to creatinine ratio (>0.20) and skeletal survey showed reduced bone density.

After initial stabilization with hyperhydration and Pamidronate, trial of cinacalcet was given. Cinacalcet was started with dose of 1mg/kg/day and was gradually increased to 3mg/kg/day. None of our case responded to cinacalcet and needed repeated pamidronate infusion to optimize calcium level. Parathyroidectomy was planned in all. Cases 1 and 2 underwent successful parathyroidectomy (3 and half parathyroid removed and half implanted in sternocleidomastoid) with smooth Post-operative recovery and bone profile showing normal calcium, phosphate and PTH. Case 3 had a sad demise before surgery due to hospital acquired infection.

Conclusion: NSHPT is a rare disorder due to CASR gene mutation that is often underdiagnosed due to lacking genetic facilities in resource limiting countries. We are reporting 3 cases of CASR mutation (1 novel mutation) which did not respond to cinacalcet and two of them ended up in parathyroidectomy. We believe efficacy of cinacalcet in NSHPT due to CASR needs further randomized control trial.

P2-65

Is conventional treatment still the first choice in pediatric patients with PHEX mutations in an era of monoclonal FGF-23 antibody?

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Objective: Hereditary hypophosphatemic rickets is a rare renal phosphate wasting disorder causing burden on pediatric patients despite conventional treatment of phosphate and calcitriol. The aim of this study is to analyze genetic and clinical variability of children with X-linked hypophosphatemic rickets (XLHR), focusing on short term, long term and pubertal impact of conventional treatment.

Design: Retrospective cohort study

Methods: Mutation analysis of *PHEX* was performed in 16 patients from 12 unrelated families with HR via Sanger sequencing

first than multiplex ligand-dependent probe amplification. If a molecular defect was detected, first-degree relatives were analyzed. 13 patients (81%) and five first-degree relatives with XLHR were analyzed to determine the correlation between phenotype with genotype or gender. In addition, clinical characteristics and response to conventional treatment were determined retrospectively.

Results: Nine different *PHEX* mutations were identified, four were novel. Four led to disrupted splice-site, three were point mutations, and two were single exon deletions.

In XLHR, despite conventional treatment, median adult height was lower than median height on admission (-3.8 and -2.3 SDS; respectively), metabolic and radiographic recovery were not achieved, adherence was low (30%). Although mean adult height was better in compliant patients than noncompliant ones (-2.6 vs -3.7 SDS; respectively), they were shorter than their peers. A correlation between phenotype and genotype or gender could not be shown. Median phosphate decreased significantly throughout puberty ($p=0.014$). Median pubertal height (-4.4 SDS) was lower than that of prepubertal height (-3.6 SDS) and pubertal growth spurt was not observed. In the long term, nephrocalcinosis (60%) and hyperparathyroidism (40%) were observed, correction osteotomy (33%) was required.

Conclusion: Metabolic, clinical and radiographic recovery were not achieved owing to limited benefits of conventional treatment. In addition, response to treatment worsened during puberty. Thus, introduction of monoclonal FGF-23 antibody as first-line treatment may be an alternative after infancy. However, long-term adverse effects are yet to be seen.

P2-66

Vosoritide Clinical Study Data Demonstrates CXM is a Superior Biomarker of Endochondral Bone Growth

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Vosoritide is a C-type Natriuretic Peptide (CNP) analogue therapy for treatment of achondroplasia. Vosoritide acts on growth plate chondrocytes through the Natriuretic Peptide Receptor-B to stimulate increased endochondral bone growth, leading to increased growth velocity in treated subjects. In Phase II clinical studies, subject blood and urine samples were analyzed to monitor putative bone growth biomarkers including cross-linked C-terminal telopeptides of collagen II (CTXII), Bone-Specific Alkaline Phosphatase (BSAP), N-terminal pro-peptide of collagen I (PINP), and an N-terminal fragment of Collagen X (CXM). While all of the biomarkers analyzed were variable, CXM demonstrated dose-dependent increases, BSAP appeared to increase

slightly over time on treatment for all dose levels, and there was no apparent trend or dose dependent response for CTxII or PINP. Based on these results, BSAP and CXM were incorporated into the placebo-controlled Phase III vosoritide clinical study 111-301 and pre-treatment natural history study 111-901. The Phase III study data confirmed that CXM was increased in subjects that received vosoritide, but not placebo, while differences in BSAP between vosoritide and placebo groups were small. Overall, the data from vosoritide clinical studies suggest that CXM is superior to CTxII, PINP, and BSAP for monitoring changes in endochondral bone growth.

P2-67

X-linked hypophosphatemic rickets caused by a large deletion in *PHEX* gene in a Brazilian family

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Background: X-linked hypophosphatemic rickets (XLHR; OMIM 307800) is an X-linked dominant disorder caused by mutations in the phosphate-regulating neutral endopeptidase homolog X-linked (*PHEX*) gene, which is located at Xp22.11.

Objective: To clarify the underlying mechanism of a Brazilian family with hypophosphatemic rickets whose clinical manifestations were very broad among members of different generations.

Design and Patients: The proband is an 8-year-old child. She and her 5-year-old brother show similar clinical features such as bowing of legs together with hypophosphatemia, but the brother developed also cranial synostosis and Arnold-Chiari malformation type I. Their mother has only mild features of the disease with no bone bowing, but presenting only mild short stature. Due to paucity of clinical manifestations in the mother, recessive hypophosphatemic rickets/osteomalacia (ARHR) was at first suspected.

Results: Sequencing of all coding exons and exon-intron junctions of *DMP1* and *FGF23* genes showed no mutation. Subsequent analysis revealed that there is a deletion of exons 10 and 11 in *PHEX* gene in the younger sib, later confirmed by studies with MLPA. His sister was found to be a heterozygote for the same deletion indicating that they are suffering, in fact, from XLH. The same deletion was detected in the mother.

Conclusion: Careful genetic analysis is mandatory for correct differential diagnosis of genetic hypophosphatemic rickets. Next generation sequencing (NGS) allowed the use of multi-gene panels as way to better analyze multiple genes at the same time. Nevertheless, large deletions in *PHEX* gene still need to be better characterized using techniques such as MLPA in combination with NGS.

Mutational analysis and genotype-phenotype correlation of the PHEX gene in Brazilian patients with X-linked hypophosphatemic rickets

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Background: X-Linked hypophosphatemic rickets (XLH) is a disorder of phosphate homeostasis, characterized by renal phosphate wasting and hypophosphatemia, with normal to low 1,25-dihydroxy vitamin D3 serum levels. PHEX is the gene defective in XLH and different mutations and genomic rearrangements have been described in different families affected by this disease.

Objectives: To detect inactivating mutations in the PHEX gene in a cohort of patients referred to genetic investigation of XLH.

Materials and Methods: 18 patients (12 females, 6 males), representing seven families, presented with suspected XLH from biochemical and clinical evidence. They were all referred for mutational analysis of the PHEX gene.

Results: Analysis of PHEX revealed mutations in 13 hypophosphatemic rickets patients. In 7 patients, in whom no PHEX mutation had been previously detected in 22 exons, MLPA (Multiplex Ligation-dependent Probe Amplification) analysis was carried out and large deletions in PHEX gene was found in 5 patients from the same family. No correlation was found between the severity of disease and the type or location of the mutation, even the ones with large deletions. However, among patients with a family history of hypophosphatemic rickets, there was a trend toward more severe skeletal disease in patients with truncating mutations. Family members in more recent generations had a more severe phenotype in 4 families, nevertheless even patients from the same kindred harboring the same mutation could show different phenotypes. Postpubertal males had a more severe dental phenotype.

Conclusion: Molecular genetic analysis confirms the clinical diagnosis of XLH and should include sequence analysis as well as the search for large deletions, which is facilitated by MLPA technique. Although identifying mutations in PHEX may have limited prognostic value, genetic testing may be useful for the early identification and treatment of affected individuals, in particular with advent of specific therapies with phocus in FGF23 metabolic pathway. Furthermore, this study suggests that other genes and environmental factors affect the severity of hypophosphatemic rickets.

Evaluation of Admission Characteristics, Treatment and Follow-up Findings of Children with Primary Osteoporosis

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Introduction: Primary osteoporosis (POP) is a rare and important problem in childhood that can cause serious skeletal deformities and morbidity.

In this study, we aimed to reveal the spectrum of POP in childhood, and also to assess the effectiveness and safety of bisphosphonates in increasing BMD, reducing fractures, and improving quality of life.

Method: Patients with POP and who received at least one course of pamidronate (PA) or zoledronic acid (ZA) between 2000 and 2020 were included in the study. Patients were divided into two groups as OI and other POP patients. We retrospectively enrolled demographic, anthropometric, clinical, laboratory, and radiological findings. Bone densitometer parameters, activation scores, pain status, deformity status, number of fractures per year were evaluated in all patients at admission, and after the treatment.

Results: Of 31; 21 OI, and 3 spondyloocular syndromes, 2 Bruck Syndrome, 5 idiopathic juvenile osteoporosis were included. The mean age at diagnosis in our patients (F/M = 17/14) was 6.95 ± 4.53 [5.29 ± 3.97 for OI] years. Patients with OI were diagnosed at a younger age. They had similar height and BMD with the other POP group. Thirteen of these had a family history of OI. According to the expanded Sillence classification, 10 were type I, 5 were type III, 5 were type IV, and 1 was type VI OI.

All patients with POP had received bisphosphonate therapy. Of 21 had received PA treatment, while only 4 received ZA and 6 of them switched from PA to ZA. At the end of the treatment, the total BMD (g/cm^2) increased from 0.31 ± 0.11 to 0.53 ± 0.13 . Mean BMD Z score increased from -4.04 ± 2.08 to -0.95 ± 1.34 , and height adjusted Z score increased from -3.39 ± 1.30 to -0.95 ± 1.34 . There was no difference between the two groups in terms of improvement in BMD increase. The number of fractures per year decreased from 2.28 ± 2.67 to 0.29 ± 0.69 . The activation score increased from 2.81 ± 1.47 to 3.16 ± 1.48 . The pain decreased significantly. There was no difference in BMD increase treated with PA or ZA.

Conclusion: POP is a heterogeneous problem that most often arises as a result of OI.

Those with OI were diagnosed at an earlier age with severe deformity and fractures. Bisphosphonate treatment (PA or ZA) increased both BMD and improved quality of life in all with POP.

P2-70

Phenotype characterization of a PHEX intron mutation in an Italian family affected by X linked hypophosphatemic rickets

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Introduction: X-linked hypophosphatemia (XLH) is a rare hereditary condition caused by mutation in the gene encoding the phosphate-regulating endopeptidase homolog, X-linked (*PHEX*). It is characterized by altered phosphate homeostasis with persistent hypophosphatemia and hyperphosphaturia resulting in deficient skeletal mineralization, rickets, bone deformity, growth failure, dental problems, joint pain and impairment.

Case Presentation: We report a family affected by XLH, with two adults siblings (case II-2 and II-3) and two children, daughters of case II-2 (case III-1, a 4 years old girl, and III-2, a 18 months old girl), harbouring a rare *PHEX* intron mutation, c.1586+6T>C. This variant alters mRNA splicing causing partial exon skipping as previously demonstrated by in vitro study but clinical phenotype has not been described. All the patients exhibited features of severe short stature, genu valgum and waddling gait; children suffered from active rickets while adults have an history of vitamin D- unresponsive rickets and orthopaedic surgeries for progressive bone deformities associated to reduced joint excursion and severe bone pain impairing daily living activities. Laboratory investigation revealed low serum phosphorus according to reference values for age with increased renal wasting (Tubular Reabsorption of Posphate, TRP<90%), elevated blood alkaline phosphatase and normal calcium levels in all subjects. Burosumab therapy has been started in paediatric patients. In the first semester of treatment a linear growth improvement of 0.44 SDS and 0.4 SDS was registered for case III-1 and III-2, respectively. Growth velocity rate increased from -0.61 SDS to 0.17 for case III-2 and almost doubled for case III-1 (from -2.39 SDS to 1.42 SDS). Serum phosphate increased up to normal range in both patients with a clear upward trend in TRP values. Recently also adult patients started burosumab for compassionate use.

Discussion and Conclusion: Data inhere presented extend the phenotypic characterization of rare intronic mutations in the *PHEX* gene. This report suggests this splicing donor site alteration has complete penetrance and severe expressivity. Correct and precocious diagnosis is mandatory to start the appropriate treatment timely. We are confident that precocious therapy onset in infancy will positively address growth failure and major skeletal abnormalities in our pediatric patients as some preliminary data in prepubertal cohorts have suggested.

P2-71

Premature epiphyseal fusion induced by Palovarotene in a young girl with fibrodysplasia ossificans progressiva

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Retinoic acid receptor agonists can have dramatic negative effects on growth and even induce premature growth cessation and epiphyseal fusion (1, 2).

An 11 5/12-year-old, prepubertal girl with fibrodysplasia ossificans progressiva presented in our pediatric skeletal disorders clinic with the concern of early growth cessation. She had participated in a clinical trial of Palovarotene ("MOVE", NCT03312634), a retinoic acid receptor-gamma agonist, since the age of 9 10/12 years. At the visit, she had recently discontinued her participation in the study. During the 19 months since starting on Palovarotene, her height had only increased 1.9 cm to 136.4 cm. A skeletal survey detected fusion of several growth plates that normally remain open until the end of puberty including the growth plates of proximal humerus, distal ulna and distal radius. One year after stopping Palovarotene, she was in early puberty and her height had increased another 3.9 cm to 140.3 cm (-2.6 SDS). Measurements of height, sitting height, and arm span confirmed that growth of arms and legs had ceased, whereas growth of the spine continued.

This report supports previous findings indicating that high-dose retinoic acid receptor agonists can induce premature epiphyseal fusion even before puberty and may thus cause significant, disproportionate short stature if used in young children. The finding that growth of the spine, but not legs and arms, resumed after the treatment was discontinued suggests that long bones are more susceptible than vertebrae to retinoic acid-induced epiphyseal fusion.

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P2-72**ACAN gene skeletal dysplasia (short size syndrome, with or without advanced bone age and early onset osteoarthritis)**

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Aggrecan is a structural glycoprotein of the extracellular matrix of cartilage present in the articular cartilage, growth plate and cartilage of the intervertebral disc. Biallelic pathogenic variants are the cause of aggrecan type spondyloepiphyseal dysplasia (OMIM#612813) while the presence of heterozygous pathogenic variants determine Kimberley type spondyloepiphyseal dysplasia (OMIM#608361) and short stature associated or not with acceleration of bone maturation and early onset of osteoarthritis and familial osteochondritis dissecans (OMIM#165800). The clinical characteristics of 5 patients with heterozygous pathogenic variants in the ACAN gene are presented.

Patients:

Family 1 - Index Patient: 9,4 years old prepubertal girl with short stature (-2.2SD) disharmonious and bone age of 10 years. Father with disharmonious short stature (-2.7SD), maternal height (-1SD). A phenotype with retrognathia and low set ears stands out. Normal skeletal series. Exome sequencing identifies a heterozygous pathogenic variant in the ACAN gene (c.1097dup(p.(Glu367*)1),) confirmed by Sanger sequencing, not previously described.

Family 2 - Index Patient: 9,9 years old prepubertal boy with an idiopathic short stature family history. Presents disharmonious height (-2SD) and bone age 12.6 years. Also, non-severe genu varus and osteoarthritis in his right knee without other morphological alterations. Skeletal series: short cubes and curved rays and 4th metacarpal shortening. A 4.6 years old sister and 4.3 years old first cousin with harmonic short stature (-2.4SD and -3.0SD respectively). In both, the bone age is advanced. Normal phenotype. The skeletal series is normal in the sister, while in the first cousin there are widened distal femoral diaphysis. A pathogenic variant in ACAN (c.7276G>T;p.(Glu2426*)) is identified in the exome sequencing confirmed by Sanger sequencing in all of them, described in the literature.

Family 3 - Index Patient: 9.8 years old prepubertal girl with harmonic short stature (-2.6SD) and bone age of 10 years without assessable phenotypic characteristics. Harmonic short stature mother (-2.6SD) with repetitive knee osteochondritis. The paternal height is -1.1SD. Exome sequencing identifies a heterozygous pathogenic variant in the ACAN gene (c.11061_1062del p.(Phe354Cysfs*13)), confirmed by previously undescribed Sanger sequencing.

Conclusions: New patients and pathogenic variants of the ACAN gene have been identified with highly variable phenotypic and radiological characteristics, without the skeletal disproportion and the advance of bone maturation being constant. The ACAN gene study should be included in the study of patients with idiopathic short stature. More studies are required to establish the genotype-phenotype correlation in patients with genetic variants in the ACAN gene.

P2-73**PTEN downregulation in mouse osteoprogenitor cells impacts on bone stability and turnover**

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Background: Signaling through the phosphoinositid-3-kinase (PI3K) pathway modulates bone development and remodeling. We aimed to dissect the role of phosphatase and tensin homolog (Pten), a negative regulator of PI3K signaling, in osteoprogenitor cells.

Methods: Femura, tibiae and bone marrow stromal cells (BMSCs) from mice with Cre-inducible Pten knockdown in cells expressing the transcription factor Osterix (Pten cKO) and Cre negative control mice were compared. Bone phenotyping was performed by μ CT and 3-point bending test. Number of osteoclasts and osteoblasts was determined by tartrate resistant acid phosphatase (TRAP) immunohistochemistry, bone marrow fat was quantified by osmium staining. Proliferation of BMSCs was measured by counting Hoechst and Ki-67 stained cells, adipogenic and osteogenic differentiation was determined by Oil Red O lipid and alkaline phosphatase staining, respectively.

Results: We detected a higher trabecular bone volume/total volume (BV/TV) and higher bone mineral density (BMD) in Pten cKO of both sexes, while BV/TV and BMD was lower in cortical bone. Biomechanical analysis revealed a significantly higher maximum force (3.7fold, $p=0.0003$ for males) and elasticity of Pten cKO femura. There were less osteoclasts (0.7 fold) and more osteoblasts (2.0fold, $p=0.0006$) per bone surface in bones from male Pten cKO mice compared to controls. Serum markers for bone turnover (P1NP and CTX) were significantly increased both in Pten cKO male and female mice. The percentage of bone marrow fat was higher in male (1.4fold, $p = 0.007$), but not female Pten cKO mice compared to controls. An increase in proliferation for male (1.8fold), but not female BMSCs from Pten cKO compared to controls was detected. While there was no significant difference in adipogenic differentiation in vitro, osteogenic differentiation capacity was significantly enhanced in BMSCs from both male and female Pten cKO mice.

Conclusion: Pten downregulation in Osterix-expressing osteoprogenitor cells increases bone stability and elasticity and leads to increased proliferation and osteogenic differentiation.

Primary hyperparathyroidism due to a deletion of the CDC73 gene

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Introduction: Primary hyperparathyroidism (PHPT), often caused by a single adenoma (80%–85%) or hyperplasia or adenomas involving multiple glands, is the major cause of hypercalcemia. PHPT is common and occurs in individuals of all ages, but its prevalence is lower in young adults. Parathyroid tumors and PHPT can be caused by germline (hereditary PHPT) or somatic mutations of tumor suppressor genes (e.g., multiple endocrine neoplasia type 1 and CDC73) and proto-oncogenes. Approximately 5%–15% of PHPT cases occur in a familial setting, either in an isolated form (familial isolated hyperparathyroidism) or associated with other syndromal features (MEN1-2A, familial hypocalciuric hypercalcemia). In 15–20% of sporadic parathyroid carcinomas a mutation in the CDC73 gene (HRT2) is identified, which is why some authors, consider it a tumor suppressor gene.

Objective: To present a patient with a parathyroid adenoma carrying a deletion of the CDC73 gene in heterozygous state

Methods: We investigated the pathogenic mutations in the CDC73 gene and analyzed their relationship with the phenotype in the patient with PHPT and parathyroid adenoma using Multiplex-ligation dependent probe amplification (MLPA).

Results: A 17-year-old female presented with pathological fracture of the middle third of the humerus with polyuria, polydipsia, radiographs with generalized osteopenia and osteolytic lesions and nephrocalcinosis.

Laboratories with calcium of 17 mg / dl and ionic calcium of 4.24 mmol / l. PTH 1834pmol / l. Phosphorus 3.6 mg/ dl, alkaline phosphatase of 2037, bone densitometry -4 SD, scintigraphy with sestamibi showed oval mass in the left lower lobe probable left atypical parathyroid adenoma. Months later she became psychotic, 5 years later the tumor relapsed in the neck, showed cervical nodule reported as metastasis of parathyroid adenoma; with no evidence of parathyroid injury. With calcium 13mg / dl, PTH> 2000pmol / L. Genetic study reported a heterozygous deletion of the CDC73 gene. Genetic study reported a Heterozygous Deletion of the CDC73 gene, no family history of hyperthyroidism.

Conclusion: PHPT is the main cause of hypercalcemia. Although the most common disease is sporadic PHPT, due to a single adenoma, there are heritable forms in 10% of cases. Patients with parathyroid carcinoma should undergo a careful review of their family history and should be offered a genetic study of the CDC73 Gene.

Afebrile seizure in a toddler girl with alopecia: a case report

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Background: Calcium homeostasis is primarily regulated by vitamin D. In the absence of the active hormone or a functional receptor, bones are inadequately mineralized, leading to the development of rickets. Vitamin D-dependent rickets type 2 (VDDR2) is a rare autosomal recessive disorder caused by mutations in the vitamin D receptor (VDR) gene.

Case Report: A 12-months-old girl was transported to the local hospital ED with a three-minute 1st episode of seizures: unconsciousness, hypotonia, ocular reversion, cyanosis, and sialorrhoea. There was no history of trauma, accidental drug ingestion, fever, or other infectious signs. During the patient's stabilization, capillary blood gas showed severe hypocalcaemia (Ca++ 0,76mmol/L) without hypomagnesaemia. Intravenous (iv) calcium gluconate was administered. On further examination, she had total alopecia, closed anterior fontanelle, dentition according to her age, enlarged wrists, and bowed legs. Parents were nonconsanguineous. Pregnancy and delivery were unremarkable. She had alopecia since birth and was not yet able to walk, even with support. Additional blood evaluation showed severe hypocalcaemia, hypophosphataemia, hyperparathyroidism, increased alkaline phosphatase (ALP), and markedly elevated 1,25(OH)₂D. 25(OH)D was in the normal range. Full body skeleton X-ray showed diffuse bone demineralization, "rosary ribs", and metaphysis flaring, fraying, and cupping. Renal ultrasound was normal. VDDR2 was presumed and iv calcium gluconate was titrated up to a maximum of 1,15mmol/kg/day. After calcium stabilization, oral calcium carbonate was started (1g/day), with progressive increasing dosage (maximum 6g/day) and parallel reduction of calcium gluconate, which was suspended after 2 months. Calcitriol (maximum 21µg/day) was also started with significant improvement in calcaemia and gradual reduction in PTH and ALP. Genetic analysis found a homozygous mutation c.133A>G p.(Lys45Glu) in the VDR gene, confirming VDDR2. Nine months after discharge, and exclusively on oral therapy, calcium levels have been moderately stable (total calcium: 8,7 to 9,7mg/dl). PTH and ALP still have an oscillatory profile, but with a downward trend and near reference range levels.

Discussion: Genetic mutations cause about 13% of rickets cases. VDDR2 secondary to Lys45Glu mutation prevents VDR from activating gene transcription. High levels of 1,25(OH)₂D and alopecia are the distinct points of this disease. Alopecia is thought to be a sign of disease severity. Control of secondary hyperparathyroidism is the therapeutic goal, decreasing bone demineralization. Intravenous calcium treatment for several months, followed by high doses of oral calcium and calcitriol, seems to be an effective approach.

A rare cause of hypophosphatemic rickets; Non-lethal Raine syndrome

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Background: Raine syndrome (RS) also known as lethal osteosclerotic bone dysplasia, is a rare autosomal recessive bone disorder. Most of patients with RS die within the first days or weeks of life due to pulmonary hypoplasia. The causative gene FAM20C is located on chromosome 7p22.3. FAM20C is one of the genes that regulate phosphate production. Here, we present a case of RS with hypophosphatemic rickets and a new mutation in FAM20C gene.

Case Report: A seven-year-old girl who had recurrent tooth extractions was referred to our clinic for possible underlying bone disease. Her past history revealed that she had been operated for choanal atresia, cleft palate and atrial septal defect, and bowing of her legs after the age of one. According to his family history, our patient was the fifth child of consanguineous parents and her cousin had similar findings. Physical examination at admission revealed a short stature girl (height sds -2.07) with facial dysmorphism (hypertelorism, exophthalmos, high palate, flattened nasal root, and anteverted ears), odontodysplasia, craniosynostosis, and o-bain deformity. On laboratory; serum calcium level was 9.7mg/dL, phosphorus 2.7mg/dL, alkaline phosphatase 400U/L, parathormone 187ng/L, 25 (OH) D 24.2ng/mL. Tubular reabsorption of phosphate was 92%. There was a minimal metaphysical fraying on x-ray of the knees, no apparent osteosclerosis was seen in the radiographs. Brain MRI showed a Chiari malformation. Based on the clinical and laboratory findings, a diagnosis of hypophosphatemic rickets was made and oral phosphate and calcitriol treatments were started. Raine syndrome was considered due to her additional dysmorphic features, and then a new homozygous mutation was established in the FAM20C gene.

Conclusions: The clinical features of non-lethal forms of RS are extremely heterogeneous. The present case shows the phenotypic features of Raine syndrome who had a new mutation of FAM20C gene. RS should be considered especially in the differential diagnosis of patients with hypophosphatemia and odontodysplasia. Because of the small number of reported cases, little evidence of life expectancy and clinical outcome in non-lethal RS.

Effect of tamoxifen on linear growth of precocious female SD rats

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Background: Tamoxifen is a selective estrogen receptor modulator, administrated in girls with precocious puberty such as McCune-Albright syndrome.

Objective: To explore the effect of tamoxifen on the linear growth of precocious pubertal female rats.

Method: At 16-22 day of age, 16 precocious pubertal female rats (induced by 300 µg danazol s.c. at 5-day old), were randomized blocks (brood) to 2 groups(n=8). Group TAM received once weekly 20mg/kg tamoxifen s.c for 5 times, while Group Ctrl received solvent injections. Rats were killed 5 weeks later. Measurements of body weight and length (=nose-anus length) were taken every 3-4 days. Vaginal opening was observed from 4-week age. On the day of sacrifice, body weight, body length and left tibial length were measured, plasma were taken for determining E2 level, IGF-1 (IRMA) and IGFBP-3 (IRMA) concentrations; liver samples were taken for detecting GHRmRNA, IGF-1mRNA and IGFBP-3mRNA by real-time RT-PCR; right tibia were fixed, demineralized and processed for paraffin-embedding. Paraffin sections were HE stained for growth plate measurements. IGF-1 and IGF-1R level on growth plate were immunohistochemical localized and image analysed.

Results:

1. **Skeletal growth:** Tamoxifen decreases both of the body weight and body length without influencing the tibial length.
2. **Growth plate HE measurement:** Tamoxifen increases the width of PZ[(185.0±12.7µm)VS (172.5±61.0µm), P<0.05], decrease the width of HZ[(167.5±37.0µm) VS (188.3±33.7µm), P<0.05] and cell number[(7.2±1.0) VS (8.9±0.6),P<0.05] in HZ without changing total EGP width[358.1±45.0 VS (373.3±35.7µm),P<0.05].
3. **Plasma concentration determination:** Tamoxifen does not alter plasma E2 level, decreases plasma IGFBP-3 level (443.8±65.5 ng/ml versus 537.7±94.1 ng/ml, P<0.05). Tamoxifen does not alter hepatic GHRmRNA, IGF-1mRNA or IGFBP-3mRNA, and does not alter local IGF-1 and IGF-1R level on growth plate.

Conclusion: Tamoxifen inhibited growth, especially weight gain and fat accumulation. Besides, tamoxifen has dual effects of anti-estrogen and estrogen-like on the growth plate. So tamoxifen is inapplicable for central precocious puberty treatment. The safety of tamoxifen for peripheral precocious puberty needs to be reevaluated.

P2-78**Deleting STX16 exon 4 to understand the genetic mechanisms underlying pseudohypoparathyroidism-1B and GNAS imprinting**

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Autosomal dominant pseudohypoparathyroidism type-1b is characterized by renal parathyroid hormone resistance, with resultant hypocalcemia and hyperphosphatemia. This disorder is associated with an isolated loss of methylation at GNAS exon A/B and most patients carry maternal microdeletions in the neighboring STX16 gene. The shortest deletion overlap is a 1.2-kb region spanning STX16 exon 4 and thought to harbor a cis-acting element regulating GNAS A/B methylation. However, ablation of the orthologous mouse region does not recapitulate the patient findings and no functional data exists supporting the association between the STX16 gene and GNAS imprinting. The A/B methylation is established in the female germline and maintained throughout the development in somatic cells. We thus investigated the role of the 1.2-kb STX16 region in the maintenance of A/B methylation, employing HCT116 cells, a near-diploid human cell line derived from colorectal carcinoma. To delete this region, we used CRISPR/Cas9 and suitable guide-RNAs targeting upstream and downstream of exon 4. We first generated HCT116 cells stably expressing Cas9 and introduced the guide-RNAs into those cells by lentiviral delivery. After antibiotic enrichment of the transduced cells, the presence of a 2.1-kb deletion spanning STX16 exon 4 and flanking intronic regions was confirmed by PCR, followed by TA-cloning and Sanger sequencing of the products. Multiplex ligation-dependent probe amplification (MLPA) indicated a modest reduction in the STX16 exon 4 copy number, suggesting that the deletion was present only in a subset of cells. Methylation specific-MLPA analysis, which was performed in non-clonal cells, indicated normal methylation status at GNAS exon A/B, and this finding was confirmed by the combined bisulfite restriction analysis.

Thus, our initial findings suggest that the putative cis-acting element within STX16 does not regulate the maintenance of exon A/B methylation. To further confirm these results, we are in the process of selecting and analyzing clonal HCT116 cells homozygous or heterozygous for this deletion. In addition, we are introducing the same deletion into human ES cells, so that we can determine its impact on GNAS imprinting during early development.

P2-79**Clinical, molecular characterization and long-term follow-up of a patient with neonatal severe hyperparathyroidism**

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Introduction: Heterozygous inactivating mutations of the calcium-sensing receptor encoding gene (CASR) cause autosomal dominant familial hypocalciuric hypercalcemia (FHH), whereas mutations that inactivate both alleles cause neonatal severe hyperparathyroidism (NSHPT), a rare and potentially fatal disease. We present the clinical and genetic characterization of a Portuguese family with FHH/NSHPT as well as the long-term follow-up of the proband.

Case Report: A female 16-day-old newborn was admitted to neonatal intensive care due to progressive hypotonia, feeding refusal, and dehydration. Serum calcium and PTH levels were markedly increased. Radiological evaluation revealed osteopenia and several fractures. Total parathyroidectomy with reimplantation of ¼ of one gland was performed. She has been regularly followed-up since then. At 15-year-old she is clinically well, growing normally (height -0.53 Standard Deviation Score), has normal calcium levels and detectable parathormone values, under calcium and α-calcidol treatment. CASR gene sequencing revealed a germline homozygous nonsense mutation (c.679C>T p.Arg227Ter), which is predicted to encode a severely truncated receptor. The proband's parents and grandfathers were asymptomatic, heterozygous carriers of the same mutation.

Conclusions: NSHPT complexity requires a multidisciplinary approach to minimize morbidity. In the present case, total parathyroidectomy with reimplantation was needed to control hypercalcaemia. After a challenging admission to control calcium levels the proband is currently clinically well. Identification of a CASR mutation allowed family genetic counseling.

Effect of Soy and Whey on growth pattern in young male Sprague-Dawley rats

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Background and Aims: The most effective environmental factor that affect longitudinal growth is nutrition, but the exact composition and the relative benefits of specific dietary proteins in supporting linear growth is unknown. In the current study, we compared the effect of whey and soy proteins on linear growth and bone strength in young fast growing male rats. Both proteins contain all essential amino acids and are considered the best proteins in their categories according to the protein digestibility-corrected amino acids score. Soy ranks second after whey as a complete food protein and is the most popular plant proteins utilized in the production of newborn formulas and dietary supplements.

Methods: Young male Sprague Dawley rats, fed ad libitum with either Whey or Soy based diets (matched for calories, macro- and micro-nutrients), were followed for short (11d, 24d) or long (74d) term experiments. At sacrifice, humeri length and growth plate (GP) height were measured and blood was taken. Micro CT analysis was used to evaluate effect on bone structure and mineralization

Results: In the short-term experiments, we found that the soy fed group consumed more food, and were heavier, with longer humeri, while GP height was greater in the whey fed group. Interestingly, the effect on weight and humeri length was diminished at 74 days; however, the GP height of the whey fed group was still greater. Furthermore, the GP was better organized with more cells and more proliferative columns compared to the soy fed rats. Micro CT analysis showed that in short-term experiments, the diaphysis diameter of the humeri was greater in the soy fed rats. In the long-term study, the humeri of the whey fed rats had greater bone mineral density and cortical thickness.

Conclusions: The results suggest a differential growth rate, with the soy fed rats growing faster. Although both groups reached the same length at the age of 100 days, the increased GP height of the whey group, suggest a better growth potential. A longer follow up may indicate if the potential is translated to differences in length. Studying the interaction between skeletal growth and nutritional factors.

Early-onset osteoporosis due to LRP5

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Introduction: Primary osteoporosis are frequently linked to syndromic conditions such as osteogenesis imperfecta which also involves extra eskeletal tissues.

With the advancement of medicine, this group has been reduced, due the ability to specifying the causal pathogenic variants. Among these, the LRP5 (Low-density lipoprotein receptor-related protein 5) gene mutations are the most frequent cause.

LRP5 is a fundamental coreceptor in the wnt/betacatenin signaling pathway, which is the main metabolic pathway of osteoblasts, the mutations of this one, result in decreased bone formation and could be one of the main causes of primary osteoporosis.

Case Report:

Case N°1: A 12-year-old boy, previously healthy, evaluated for chronic knees and back pain. Not medical history of bone disease, no familiar history of osteoporosis. Physical exam with out blue esclera, no dismorphic features, not enamel tooth alterations or other extraeskeletal findings.

Laboratory: Serum Calcium 2.35 mmol/L, phosphemia 1.42 mmol/L, albumin 4.5 g/dl, FA: 172 U/L, PTH 5.3 pmol/L (normal value <6.89), 25OH vitamin D 16.7 mg/dl, TSH 1.98 IU/L, FT4 1.4 ng/dl, negative hypercalciuria, negative anti-transglutaminase antibodies and nugent test. Chest X-ray showed diffuse osteopenia, vertebral fracture in T6-T9.

Bone mineral densitometry of lumbar spine: 0.136 gr/cm³, Z score: -5.0.

Genetic study shows a variant of uncertain significance in LRP5 gene c.1021G> A; pGlu341Lys. When is classified in varsome, it could be reclassified as probably pathogenic if correspond a de novo variant.

Case N°2: 12-year-old boy, evaluated for a history of 1 year of lumbar pain, x-ray of spine showed a fracture in vertebral bodies from D 12 to L3.

No personal or family history of bone mineral disease, no history of bone fractures.

Physical Exam: No abnormal findings. Laboratory: Calcium: 2.15 mmol/L, phosphemia 1.23 mmol/L, albumin 4.0 g/dl, FA 246 U/L, PTH 2.6 ng/dl normal value <6.89), 25OH vitaminD 51 mg/dl, TSH 1.87 IU/L, T4 9.3 ng/dl, negative hypercalciuria, negative anti-transglutaminase antibodies. Lumbar spine volumetric bone density of 0.205 gr/cm³ and Z score -2.7 DS. Genetic study results in a variant of uncertain significance in LRP5, c.1696C> T; p.Arg566Cys. Again, reclassified in varsome, it could be pathogenic, if parentes do not have the mutation.

Discussion/Conclusion: LRP5 gene mutations have been reported as one of the main causes of primary osteoporosis. There are 2 phenotypes due to loss of protein function, early-onset osteoporosis autosomal dominant, and the osteoporosis-pseudoglioma syndrome autosomal recessive.

P2-82**Vitamin D - What is the Optimal Level in the Pediatric Population**

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Introduction: The optimal level of 25-OH-Vitamin D in children is not clear since most studies have been performed on adults. Creating normal levels is problematic since the recommended level of vitamin D is based on the effect of vitamin D on other parameters and not upon its level in the population.

Methods: This is a "big-data" study in which we analyzed Vitamin D tests from 49,935 children sampled in Clalit Health Services, Jerusalem district between 2009 and 2019. The number of samples with associated data were as follows: corrected calcium – 16,333, phosphate – 3174 and PTH – 449. We tested correlations between each parameter and vitamin D.

Results: There was a positive correlation between 25-OH-Vitamin D levels and three different parameters corrected calcium, phosphate and PTH. The level at which further increase in vitamin D did not cause further significant alteration in the corresponding parameter was for calcium and phosphate – at least 100 nmol/l (40 ng/ml), and for PTH there was a significant negative correlation up to 40 nmol/l but the trend continued up to 100 nmol/l.

Conclusion: It appears that the recommended level of 25-OH-D in children should be slightly higher than for adults, in the range of 100 nmol/l.

P2-83**Schimke immune-osseous dysplasia manifested by stunted growth and spinal epiphyseal dysplasia: a case report**

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Objective: To recognize Schimke immune-osseous dysplasia from a case of spinal epiphyseal dysplasia.

Method: Summarize the characteristics of one case of Schimke immune-osseous dysplasia, and increase awareness of this disease.

Result: The patient, male, with non-consanguineous parents, was born on May 8, 2012. He was hospitalized in our hospital in January 2020 due to his short stature for more than 7 years. At the age of 4, the number of café-au-lait spots in the body gradually increased and the patient was hospitalized in the local hospital. The gene testing result of the patient showed that Smarcal1 had compound heterozygous mutations: (1) exon 12, c.1930c > t, P.

(arg644trp), (from father) was a suspected heterozygous mutation; (2) exon 8, c.1444delc, P. (leu482fs), (from mother) was a heterozygous mutation. Past history: He was born prematurely at 33 gestational weeks with a birth weight of 1.3KG (< P3) and a body length of 39cm (< P3). Physical examination: body length 95.1cm (< 3SD), weight 19kg (< 3SD), BMI 21kg / m2 (+ 2.2SD), head circumference 49cm, upper part length of the body 48CM, finger distance 100.5cm. The nose bridge collapses. The neck is short. Disproportionate short stature with the short spine. Hyperpigmented macules predominantly on the trunk. The abdomen is slightly swollen with the abdominal circumference 61cm. Lab examination: Lymphocyte count decreased and CD4-positive cells decreased. 24-hour urine protein content was 2.29g. CHOL 6.98mmol/L, Alb29.4g/L. Thyroid function was normal. MRI + MRA of the brain were normal. Karyotype was 46, XY. The bone age is 6 years old (G & P method). Metacarpal bone is generally shorter.

The anterior and lateral films of the spine show that the upper front edges of the vertebral body are stunted, and the upper and lower edges are swollen. The epiphysis of both femoral diaphysis was irregular, the acetabulum fossa of pelvis became shallow, sclerotic and dysplastic.

Conclusion: Our child is a mild SIOD. He has been followed up ever since birth, and he has no kidney involvement and recurrent infections except for his uneven shortness. In the most recent examination (7 years and 8 months), a large amount of proteinuria was found, but albumin still had 29.4g / L. In addition to spinal metaphyseal dysplasia, hip dysplasia is associated with dislocation which is a little bit different from the cases that had reported.

P2-84**A rare cause of childhood hypercalcemia: Parathyroid adenoma**

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Introduction: Hyperparathyroidism is a disorder usually seen in adults and rarely in childhood.

Case: A 14 years and 7 months old girl complaining of constipation applied to pediatric gastroenterology department was consultant to pediatric endocrinology department due to increased plasma calcium levels. She was healthy previously and had no vitamin D usage. In her physical exam; body weight: 53.8kg (-0.12 SD), height: 153.5cm (-1.32 SD), BMI: 22.83kg/m2(0.74 SD), blood pressure:90/60mmHg and puberty was Tanner Stage-5. Other systemic exams were normal. In laboratory detection; plasma calcium:12.7mg/dL(8.8-10.6), phosphorus:3.0mg/dL(4.5-5.5), PTH:306pg/ml(15-68), alkaline phosphatase:168U/L(30-500),

spot urine Ca/creatinin:0.21 and 25-hydroksivitamin-D:4.9ng/ml(N>20). Hemogram, venous blood gas detection, plasma free thyroxin, Tyrotropin releasing hormone, BUN, creatinin, albumin and magnesium levels and QTc time in electrocardiogram were normal. Via these data she was diagnosed as primary hyperparathyroidism and initial intravenous hidration and furosemid treatment started. Plasma calcium levels did not decrease after initial treatment and she had pamidronat infusion with the dose of 0,8mg/kg/day, twice and plasma calcium levels decreased to normal levels in 48 hours time. X-Ray detections of hand-ankle and head, urinary ultrasonography was normal. Thyroid USG revealed an image next to posterior-inferior right thyroid lobe, with dimensions of 12x4.5 mm, smooth borders and central hyperechogen identification which suggests a parathyroid adenoma. Teknesyum-99m sestamibi (99mTc MIBI) scintigraphy revealed an extra thyroid, partially hypoechoic lesion in right thyroid inferior region next to posterior thyroid capsule with dimensions of 10x8x10 mm. The patient was operated with the diagnosis of parathyroid adenoma. Postoperative plasma Ca was 11 mg/dL, and PTH: 378 pg/ml. Pathological examination was normal parathyroid tissue and she underwent second surgery. After reoperation plasma Ca was 9.6 mg/dL, and PTH: 25 pg/ml. Pathological examination was concordant with parathyroid adenoma.

Conclusion: Although is very rare in childhood, parathyroid adenoma should be keep in mind in patients with hypercalcemia and no history of vitamin D usage. Early diagnose and treatment is important because late diagnosis may result irreversibl target organ damages.

P2-85

One gene, two diseases: osteogenesis imperfecta, or Bruck syndrome?

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Background: Osteogenesis imperfecta (OI) is a genetic disorder characterized by diffuse osteoporosis, recurrent fractures, and resulting deformities. Bruck syndrome (BS) is a rare autosomal recessive disease that manifests with many symptoms of OI. In addition to the deficiency of type I collagen in OI, congenital joint contractures also occur in BS. BS is caused by mutations of FKBP10 (BS type 1) and PLOD2 (BS type 2) genes encoding the chaperone-collagen complex. Here, we present a BS type 1 case with recurrent fractures and congenital joint contractures and discuss its genetic etiology.

Case: A 3-year-and-5-month-old male patient, who had been born by cesarean section with a weight of 3000 grams at term, had multiple bone fractures (3 femoral, 1 humeral, multiple costal)

from minor trauma. Due to congenital pes equinovarus, splint had been applied for six months, and then surgery had been performed. His parents were fourth-degree relatives.

At presentation, the patient had a height of 71 cm (-7.16 SDS) and a weight of 7 kg (-7.65 SDS). He had blue sclera, pectus excavatum, severe kyphoscoliosis, knee and elbow flexion contractures, and no dentinogenesis imperfecta or hearing loss. His calcium, phosphorus, alkaline phosphatase, 25-OH vitamin D, and parathyroid hormone serum levels were normal. A bone survey showed mild microcephaly, Wormian bones within the cranium, tubulation defect in all long bones, coxa vara in both femurs, bendings secondary to prior fracture at lower ends of the femur, bilateral rib fractures, sloped appearance of the clavicles, and severe osteoporosis in all skeletal structures. The patient's lumbar DEXA Z-score was -8, and genetic analysis revealed a homozygous deletion in exons 5-8 of the FKBP10 gene.

Conclusion: FKBP10 mutations can be detected in OI and BS type 1 and affect the endoplasmic reticulum chaperone complex, which is involved in post-translational modifications of type 1 procollagen. The physician should consider BS in cases presenting with findings resembling OI and congenital joint contractures. Genetic analysis and long-term follow-up of these cases are critical to elucidate the genotype-phenotype relationship.

P2-86

Spontaneous Reshaping of Vertebral Fractures in an Adolescent with Osteogenesis Imperfecta

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Introduction: Vertebral fractures (VFs) are a common and severe finding in secondary and primary osteoporosis. VFs in patients with osteogenesis imperfecta (OI) are an important factor of morbidity and mortality and their presence serves as supportive evidence to initiate bisphosphonate (BP) therapy. In children, VFs have the potential to reshape and regain their original configuration. Vertebral reshaping is regarded a desired effect of BP therapy in children with OI who have sufficient remaining growth potential. *Spontaneous* vertebral body reshaping (i.e., medication-unassisted) has been reported in patients with secondary osteoporosis. To our best knowledge, spontaneous reshaping has not been reported in children with OI.

Case Report: This 17-year-old female had been diagnosed with OI type I aged 5 years (*COL1A1* mutation) and had sustained more than 40 fractures. She had received regular physiotherapy but, due to parental reservations about medication, never received BP therapy or any other bone active medication.

At the time of the first consultation, the patient had not sustained any fractures since age 15y, no back pain or other body pain. She had grown and matured normally. She had blue sclera but no dentinogenesis imperfecta and no skeletal deformity apart from a slight right-convex scoliosis. A lateral spine X-ray demonstrated transparent bones, with a mild anterior reduction in the height of vertebral bodies T6 and T7. A bone density scan demonstrated

total BMD HAZ -2.1, subtotal BMC for Height -1.3, lumbar spine BMAD -1.1.

Of great interest were previous spine X-rays taken at age 6 years at an external institution, which showed four VF at thoracic spine with moderate to severe deformities (Grade 2-3, modified Genant Semi-Quantitative Classification). Therefore, the two lateral spine x-rays, taken 11 years apart, demonstrate that substantial spontaneous vertebral reshaping had occurred during puberty.

Discussion: To date, vertebral reshaping in children with OI has been largely attributed to the effect of BP therapy in children who have sufficient remaining growth potential. This unusual case demonstrates that spontaneous reshaping of VF can also occur in BP-naïve OI patients. We hypothesize that natural growth plate activity of vertebrae, pubertal hormones, physiotherapy and avoidance of trauma may have contributed to the spontaneous reshaping in this case. Undoubtedly however, the persistent low bone mass predisposes this patient to future fractures

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P2-87

A rare presentation of Dysplasia Epiphysealis Hemimelica combined with Familial Hypocalciuric Hypercalcemia – Is this association possible?

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Background: Familial Hypocalciuric Hypercalcemia (FHH) type 1 is a benign condition of hypercalcemia with autosomal dominant inheritance caused by pathogenic variants in the calcium-sensing receptor gene (*CASR*). *CaSR* plays a crucial role in the regulation of calcium balance. Inactivating mutations in *CASR* result in altered calcium-sensing and inappropriate parathyroid hormone (PTH) release concerning the calcium concentration. Dysplasia Epiphysealis Hemimelica (DEH) is another rare developmental bone disorder characterized by localized, asymmetric osteochondral overgrowth affecting single or multiple epiphyses, mainly the distal femur, proximal tibia, and talus. It is more often in boys with no evidence of a simple mendelian basis.

Case Report: We report a 9-year-old boy with dysplasia in his right ankle, associated with a leg length discrepancy observed since 1.9 years old. He had no history of consanguinity, previous surgery, and medication use. Laboratory tests showed slightly elevated calcemia (total and ionized calcium were 10.9 mg/dL and 1.46 mmol/L, respectively), a high normal magnesium (3.2 mg/dL), normal PTH (30.1 pg/mL), normal phosphate (5.1 mg/dL), and decreased 24-hour urinary calcium (10 mg/24h). Vitamin D was marginally low (18.5 ng/mL). Skeletal X-ray depicted asymmetric epiphyseal enlargement of the proximal right femur, thinner in the medial portion with dysplasia of the acetabular roof characterized by verticalization and sclerosis with irregular margins. Right knee radiography showed distinctive bone densities that involve lateral femoral condyle. Ankle and foot radiography

revealed asymmetrical mass-like osseous hypertrophy in the distal epiphyses of the fibula and tibia, and talus, associated with irregularities and sclerosis of talus margins. These skeletal findings resembled DEH. Patient was referred to a Geneticist who suggested a targeted sequencing panel which revealed a heterozygous variant of uncertain significance (VUS; Chr3:122.282.171A>AG) in the *CASR*. It promotes the replacement of the amino acid glutamate in position 558 by glycine and creates a premature stop codon for protein translation (p.Glu558Glyfs*7). Considering the NGS result associated with clinical findings, we diagnosed this patient with FHH type 1. Parents have not performed laboratory and mutational analyses yet.

Conclusion: The *CaSR* is expressed in chondrocytes, osteoblasts, osteoclast precursors, and osteoclasts. It may also play a role in the embryonic development of the skeleton, postnatal bone formation, and osteoblast differentiation. To the best of our knowledge, patients with FHH type 1 did not present skeletal dysplasia. Our findings open up the possibility for further investigation relating DEH and FHH type 1 and/or the *CaSR*.

P2-88

Two sibling cases with heterozygous calcium sensing receptor (*CaSR*) gene mutation

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Background: Heterozygous inactivating mutations in the calcium sensing receptor (*CaSR*) gene cause mild hypercalcemia, normal to slightly elevated parathormone (PTH) levels and may vary from an asymptomatic clinical picture to a mild course. This clinical picture is also called familial hypercalcemic hypocalcemia. In this study, it is aimed to present two sibling cases due to *CaSR* mutation with interesting features.

Case 1: 12 year 3-month-old female was consulted for mild hypercalcemia while she was being followed up with a diagnosis of recurrent pancreatitis. No cause for recurrent pancreatitis was found. Her weight was 47.05 kg (0.21 SDS), height was 156.6 cm (0.53 SDS), and she had puberty Tanner Stage V. The lower and upper limit values of the laboratory tests during the follow-up were as follows; calcium 10.1-12 mg/dL, phosphorus 2.7-4.5 mg/dL, PTH 75.5-113.9 pg/mL, 25OHD 14.8-25.3 ng/mL, urine calcium/creatinine the ratio 0.02-0.21. No mutation was found in the serine protease inhibitor *kazal* type 1 and cystic fibrosis transmembrane conductance regulator genes, both genes can play a role for recurrent pancreatitis. A c.1583T>A (p.1528N) (heterozygous) mutation was detected in the *CaSR* gene. Cinacalcet 30 mg/day, 2x0.5 tablet (20.8 mg/m²/day) was started, because mutation was

accepted as a pathogenic, and no pancreatitis attack was observed in the next 3.5-year follow-up.

Case 2: The patient, who was delivered via C/S at 25 weeks, 780 gram, was consulted at the age of 66 days due to low phosphorus when she was followed up in the intensive care unit. It was learned that she is sister of Case 1. The laboratory tests during the follow-up were as follows; calcium 9.9 mg/dl, phosphorus 1.48 mg/dl (3.7-4.3), PTH 1.2 pg/ml, 25OHD 35 ng/ml, ALP 1044 IU/L. Oral phosphorus solution was started in the neonatal period with the diagnosis of osteopenia of prematurity. However, while calcium values were normal, the same mutation was found in the *CaSR* gene, because her sister had this mutation. In the sixth month, the patient had calcium 12.2 mg/dl, phosphorus 4.6 mg/dl, PTH 143.2 pg/ml, 25OHD 21 µ/L, and then cinacalcet treatment was initiated.

Conclusions: It should be considered that *CaSR* mutations may cause recurrent pancreatitis, and the setting of hypercalcemia clinic may extend to the sixth month due to renal and tubular immaturity due to prematurity.

P2-89

Clinical Profile of Parathyroid Adenoma in Children and Adolescents: A single-center experience

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Introduction: Parathyroid adenoma (PRAD) is less common than in adulthood, but its morbidity is higher in children. The typical presentation is incidentally discovered as asymptomatic hypercalcemia. We aimed to evaluate the clinical characteristics of PRAD and our clinical experience since the early disease is often asymptomatic.

Method: From 2010-2020, all children diagnosed with PRAD at our institution were reviewed. We evaluated clinical, biochemical, radiological aspects, and follow-up characteristics.

Results: There were eight subjects (F/M=6/2) ranging in age from 10 to 17 years. Two were prepubertal. Only three were symptomatic. The symptoms were stomachache (n=3), myalgia (n=2), weakness (n=2), pancreatitis (n=1), constipation (n=1), nausea (n=1), anorexia (n=1). One had a family history of MEN-1 syndrome, and two were sisters with a family history of PRAD.

Laboratory findings on admission were as followings: the mean calcium (Ca) 12.59 ± 1.28 [11.2 - 15.3] mg/dl, the mean phosphorus (P) 3.57 ± 0.87 [2-4.6]mg/dl, the mean alkaline phosphatase (ALP) 222.38 ± 116.51 [83-399]IU/L, and the mean parathyroid hormone (PTH) 244.81 ± 173.61 [74.9-645.4]pg/ml (n=8). All subjects underwent neck ultrasonography (US), and long diameters of PRADs (n=7) were measured as 11 to 19mm. PRAD could not be demonstrated by the US in one patient. Tc-99m-Sestamibi scintigraphy revealed the presence of PRAD in only six. Arrhythmia, nephrolithiasis, and bone resorption were not observed in any of the subjects.

They underwent parathyroidectomy. One subject was on pamidronate, and one other subject was on alendronate before surgery. The mean Ca decreased to 8.78 ± 0.59 mg/dl [8.2 -9.2], and the

mean PTH decreased to 56.9 ± 71.86 [7.7-195.9]pg/ml at the first postoperative day. After a year of surgery, physical examinations of all were normal, laboratory findings were as followings: the mean Ca 9.71 ± 0.27 [9.4-10.2]mg/dl, the mean P 4.63 ± 0.73 [3.84-5.94] mg/dl, PTH 44.55 ± 8.38 [33.5-76.4]pg/ml. In our follow-up, two subjects needed reoperation.

Molecular analysis of six subjects could be done. Only one of three subjects with a family history had *MEN1* positive. *RET* sequence analysis of two, and *Casr*, *GNA11*, *AP2S1* sequence analysis of three were normal.

Conclusion: PRAD should be considered in children older than 10 years of age with hypercalcemia. It should be kept in mind that most of the cases are asymptomatic at diagnosis. Suspected cases should undergo both US and scintigraphy to detect PRAD. Patients should be carefully followed up for risk of familial HPT.

P2-90

Changing reality: rebirth of old diseases in new circumstances. Severe vitamin D deficiency presenting as hypocalcemic seizures in a healthy adolescent after prolonged COVID-19 lock-down

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Context: Nutritional vitamin D deficiency is rare in the high income countries; its manifestations are usually associated with the combination of accompanying risk factors, as malnutrition, chronic illness, dark skin or restricted exposure to sunlight due to cultural practices.

Objective: The aim of this case report is to increase the awareness to severe vitamin D deficiency as a result of extreme indoor isolation due to the COVID-19 pandemic.

Subject and Results: The patient is a 12.5 year healthy white-skinned teenager from a high social level family in a sunny developed country. During a family first outdoor weekend following nearly one year of indoor isolation he experienced breathing difficulties, myalgia, paresthesia, perioral and carpal spasms, which matches signs of hypocalcemic seizures.

Biochemical evaluation revealed undetectable level of 25-hydroxyvitamin D (sufficiency >30ng/ml), serum calcium level of 6.8 mg/dl (8.8-10.4), phosphorus level of 7.4mg/dl (3.0-5.9), alkaline phosphatase 850U/L (80-405), PTH level 94pg/ml (6.5-36.8), albumin 4.2g/dl (3.5-5.5). Renal function tests were normal. Vitamin D therapy was initiated by his primary care physician with 1000 units/day. One month later his calcium level increased to 8.8 mg/dl and 25-hydroxyvitamin D to 9.5ng/ml, while phosphorus level decreased to 6.7mg/dl, alkaline phosphatase to 738U/L and PTH to 74.1pg/ml.

Conclusions: This case illustrates severe vitamin D deficiency as another consequence of COVID-19 pandemic and prolonged indoor isolation even in sunny high income countries. It is imperative to encourage patients for daily sunlight exposure or to use vitamin D supplements.

P2-91

Two-year experience of burosumab therapy in pediatric XLH patients in Saudi Arabia

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Background: X-linked hypophosphatemia (XLH) is a rare, often debilitating genetic disorder caused by mutations in the phosphate-regulating gene with homologies to endopeptidases on the X-chromosome (PHEX) that is characterized by excess fibroblast growth factor 23 (FGF23), hypophosphatemia, skeletal deformities, and growth impairment.^{1,2} Conventional therapy with the combination of phosphate and active vitamin D is associated with poor treatment adherence, high rate of failure and long-term adverse events.^{2,3} Burosumab, a fully human IgG1 monoclonal antiFGF23 antibody, addresses the underlying physiopathology of XLH and demonstrates significant clinical improvement in children.^{1,4} This study evaluates the effect of burosumab treatment in Saudi pediatric XLH patients previously on conventional therapy.

Methods: This observational, retrospective study analyzed the data of 6 pediatric XLH patients (median age of 8.8 years) collected from 3 centers [National Guard Hospital (Riyadh), King Faisal Specialist Hospital (Riyadh) and National Guard Hospital (Jeddah)] from 2018-2020. Biochemical parameters including serum phosphate, alkaline phosphatase (ALP) and tubular maximum reabsorption of phosphate to glomerular filtration rate (TmP/GFR) were collected at diagnosis; every month until 3 months, and every 3 months until 24 months into burosumab treatment. Burosumab was administered at a starting dose of 0.8 mg/kg and the dosing was increased at 3 months to 1.14 mg/kg and 1.07 mg/kg in two patients and at 6 months to 1.03 mg/kg in one patient.

Results: All burosumab-treated patients had increased serum phosphate and reduced ALP levels in the first year of treatment. Burosumab also led to improved TmP/GFR levels at 12 months, in 5 patients for which data was available. Four patients reported continuous improvement in the serum phosphate levels in the second year of burosumab treatment. Two patients reported initial serum phosphate improvement but presented with reduced levels after 21 months due to treatment compliance issues with episodic discontinuations related to the COVID-19 pandemic. The improvement in ALP levels was consistent for all patients throughout the burosumab treatment duration. No clinically significant safety findings were observed with burosumab.

Conclusion: This two-year experience demonstrates that treatment with burosumab led to marked improvement in the biochemical parameters of pediatric XLH patients in Saudi Arabia.

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P2-92

Pseudohypoparathyroidism with hypokalemia and hypomagnesemia: association or separate entity?

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Introduction: Pseudohypoparathyroidism (PHP) is a group of heterogeneous disorders characterized by end organ resistance to parathyroid hormone (PTH) action. In 1942, Fuller Albright first described the phenotype of Albright Hereditary Osteodystrophy (AHO) associated with end organ hormone resistance (brachydactyly, rounded face, short stature, central obesity, subcutaneous ossifications, and variable degrees of mental retardation). Recently EuroPHP network proposed new classifications of PHP to minimize confusion and simplify this rare disease. Molecular defects affecting the PTH/PTH-related Peptide signalling disorders have been described.

Case Report: YG, currently 22 years old, presented at the age of 12 with hypocalcaemic seizures. Bone profile showed corrected calcium: 1.18 mmol/L, phosphate: 2.6 mmol/L and serum PTH: 181.3 pg/ml (15-65 pg/ml). The 25-hydroxy vitamin D level was 18.46ng/ml (20-32 ng/ml), which was easily corrected. She was started on oral calcium carbonate 750mg TDS and T. alfacalcidol 1mcg OD. Clinical examination revealed a short and thin girl, weight: 23.7kg (below 3rd percentile) and height: 129cm (below 3rd percentile). Normotensive, no goitre. No other features of Albright hereditary osteodystrophy. YG was born term with birth weight of 3.2kg. She was exclusively breastfed till 3 months old before the introduction of formula milk. Normal developmental milestone and an average student at school.

At 15 years old, she was noted to have asymptomatic hypokalaemia and hypomagnesemia needing replacement. Potassium: 2.8-3.2mmol/L, Magnesium: 0.6-0.7mmol/L. Urine potassium: 52mmol/L. No metabolic alkalosis/acidosis and no hypocalciuria. Renin: 54.2 mU/L (N:4.2-59.7), Aldosterone: 660.9 pmol/L (N: 102.5- 1196.6). Unfortunately, throughout the years, she developed small speck of cataract of right eye with normal visual acuity. Her annual ultrasound kidney, ureter and bladder did not detect any nephrocalcinosis. She attained menarche at 15 years old. She was diagnosed with epilepsy at the age of 18 and was commenced on lamotrigine and levetiracetam. There were multifocal brain parenchymal calcifications in her CECT brain and generalised atypical spike wave discharges consistent with structural (symptomatic) epilepsy seen in her EEG.

Discussion and Conclusion: YG, a young lady with pseudohypoparathyroidism associated with persistent hypokalaemia and hypomagnesemia not fulfilling either Bartter or Gitelman syndrome as the cause of her tubulopathy. Only 2 case reports

mentioned pseudohypoparathyroidism type 1b associated with Bartter like syndrome have been reported. YG is awaiting her genetic review for molecular diagnosis. Whether these abnormalities are associated with her PHP or a different entity is yet to be determined.

P2-93

Characterization of Patients with Achondroplasia in a pediatric clinic of Cali, Colombia

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Introduction: Achondroplasia is the most common of the skeletal dysplasias and short stature with severe anatomic disproportion. Bone endochondrial growth is affected. The entity was described by Depaul in 1851 and the name which comes from the Greek word chondros (cartilage) and plasis (formation) was given by Parrot. It is an autosomal dominant monogenic disease with complete penetrance. Incidence is 1/25000 to 1/40000 of live births. It is caused by a mutation of the gene of fibroblast growth factor (FGFR3) located on the short arm of chromosome 4. Diagnosis is clinical and patients present with asymmetrical short stature, poor development of the solid middle phase, flattening of the middle phase, flat nasal bridge, small thorax, thin ribs, elbow limitation, hypotonic trunk with macrocranium, flat chest, prominent abdomen, thoracolumbar kyphosis, lumbar hyperlordosis, articular hypermobility and bowing of the middle segment of the leg. Diagnosis of hypochondroplasia and thanatophoric dwarfism types I and II should be considered. Males reach 131±5.6 cm and women 124±5.9 cm. There are many complications and reduced life span requiring a multidisciplinary management.

Objective: To characterize patients with achondroplasia seen in the Pediatric Endocrinology Clinic of Club Noel of Cali, Colombia between June of 2015 and June of 2020, an observational descriptive type of number of cases.

Materials and Methods: Review of clinical charts during the established period.

Results: We found 8 patients with equal sex distribution. 75% of cases were diagnosed in utero and 87.5% were born full term (Range 29 to 40 weeks). Average weight at birth of 3.388 kg and height of 47 cm.

Clinical findings in percentage are shown: 100% of patients had: Macrocranium, Middle phase hypoplasia, Lumbar hyperlordosis. Disproportion of segments, Rhizomelia. Short stature. The 85% had Trident hand and Hydrocephalus to 25%. Hypothyroidism and hypoacusia were not present in any of the patients. In 37.5% lower limb surgery was required with bone elongation in 25%. Mutation of FGFR3 gene was confirmed in 4 patients. Mean final growth was 127 cm, 138 cm the male and 122 cm the female.

Analysis: The clinical expression showed 100% penetrance of the disease.

Patients with achondroplasia consult for asymmetrical short stature with bone and neurologic abnormalities requiring a multidisciplinary approach to improve the quality of life.

P2-94

A Rare Cause of Familial Hypomagnesemia: A Case with Trpm6 Mutation

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Introduction: Familial hypomagnesemia with secondary hypocalcemia is a rare autosomal recessive disease characterized by very low serum magnesium levels. It is caused by mutations in the gene encoding the transient receptor potential melastatin 6 (TRPM6). It typically occurs in the first months of life with symptoms of increased neuromuscular excitability such as convulsions, muscle spasms and tetany. Prolonged untreated hypomagnesemia may lead to developmental delay, intellectual disability, failure to thrive and severe cardiomyopathy. Herein, we present a case who exhibited hypocalcemic seizure due to hypomagnesemia and was found to have a mutation in the TRPM6 gene.

Case Report: The patient, who presented to us at the age of 3 months, was admitted to an external center at the age of 35 days due to contraction in the right arm and right leg. Magnesium and calcium treatment was started when the calcium level was 6.1 mg/dl and the magnesium level was 0.68 mg/dl in the examinations. In the physical examination of the patient at the age of 3 months; Height: 56 cm (-1.5 SDS), Weight: 6.2 kg (0.54 SDS), head circumference: 41 cm (0.81 SDS), BMI: 19.7 kg / m² (SDS: 2, 15), system examinations were normal. She was born at term, weighing 3400 g, with C/S. There was a first degree cousin marriage between the parents. In laboratory examinations; Calcium: 7.5 mg/dL, Magnesium: 0.22 mmol/L, 25-OH Vitamin D: 62.3 ng/mL, Parathormone (PTH): 14.5 pg / mL, Urine ca/kr ratio: 0.17. Urinary ultrasonography was normal. Calcium and magnesium treatments were started. In the genetic analysis, c.762T>A p. (Tyr 254 *) homozygous mutation was detected in the TRPM6 gene. The treatment of the patient was continued with oral magnesium. During the follow-up, there was no recurrence and neurological development was normal.

Conclusion: Although it is a rare disease, familial hypomagnesemia with secondary hypocalcemia should be considered in any pediatric patient presenting with persistent hypocalcemic seizures and severe hypomagnesemia. If diagnosed and treated early, patients can show normal physical and neurological development.

P2-95

Effect of cholecalciferol treatment on serum FGF-23, vitamin D-binding globulin and α -klotho levels in children with vitamin D deficiency

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Introduction and Aim: FGF-23 is a hormone that works by inhibiting phosphorus reabsorption in kidneys, and systematic regulation of phosphate homeostasis by FGF23 depends on the activity of the membrane protein Klotho. It affects the active vitamin level according to the bioactive free vitamin hypothesis, which binds DVBP to vitamin D and prolongs its half-life. In this study, it was aimed to investigate 1.25 (OH) Vitamin D, Vitamin D Binding Protein, FGF-23 and α -Klotho levels and how these parameters changed with the treatment of cholecalciferol in vitamin D deficiency.

Method: Patients with rickets were included in the study. Vitamin D, parathormone (PTH), calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), Fibroblast Growth Factor-23 (FGF-23), α -Klotho, vitamin D binding protein (DVBP) levels in blood samples were examined before and after the treatment. The study was supported by Ataturk University Scientific Research Projects Coordination Unit (BAP) with project number 7181.

Results: 16 children under the age of 2 were included in the study. The average age was 8.57 ± 6.16 months. Two patients (13%) applied to our clinic with the hypocalcemic seizure. While serum Ca ($p < 0.001$), P ($p < 0.001$), vitamin D ($p < 0.01$) levels significantly increased, serum FGF-23 ($p < 0.05$), PTH ($p < 0.01$) and ALP levels ($p < 0.01$) significantly decreased after cholecalciferol treatment. There was a positive correlation between serum FGF-23 and PTH levels ($p < 0.05$).

Conclusion: Serum Ca, P, ALP and PTH levels reached normal levels with cholecalciferol treatment. FGF-23, not α -Klotho and vitamin D binding protein, plays an important role in rickets pathophysiology.

P2-96

HDR Syndrome (Barakat Syndrome): Case Report

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Introduction: Barakat Syndrome (HDR Syndrome) components are hypoparathyroidism (H), sensorineural deafness (D) and renal disease (R) caused by an autosomal dominant inheritance, being mostly associated with deletions in chromosome 10p14 or mutations in GATA3 gene.

Case Report: An 11 years old female, was born to non-consanguineous parents. She came to an emergency department complaining of the occurrence of one attack of tonic convulsion with loss of consciousness. Physical examination on admission revealed positive spasm of the feet and hands, she wears hearing aids, Laboratory assessment revealed low total serum calcium (5.2 mg/dL, reference value (RV): 8.8 to 10.8mg/dL), low parathyroid hormone

(PTH) concentration (9.12pg/mL, RV: 9 to 52pg/mL), high serum phosphorus (10 mg/dL, RV: 4-7 mg/dL), Magnesium (2.1 mg/dL, RV 1.7 to 2.7), Alkaline phosphatase (385 U/L, RV 46-116). The abdominal ultrasound reported a simple cyst with a thin wall and clear content in mid zone diffuse increase in cortical echogenicity of the kidneys. The audiogram revealed bilateral severe sensorineural hearing impairment. MRI revealed absent basal ganglia's calcification. Treatment was initiated with calcitriol and calcium carbonate supplementation.

Conclusion: The combination of hypoparathyroidism congenital and sensorineural deafness and pointed to the diagnosis of HDR syndrome.

P2-97

Hungry Bone Syndrome associated to Rickets

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Introduction: Hereditary causes of rickets often take longer to be diagnosed because they are not very frequent. 1 α -hydroxylase alteration is the most frequent vitamin D-dependent rickets. A delay in the treatment associated to a late diagnosis generates an abrupt parathormone deficiency. When initiating treatment, these patients have a risk of hungry bone syndrome.

Case: 2-year-8-month-old male patient, with a history of psychomotor retardation, cellular immunodeficiency, short stature, epilepsy, and suspicion of skeletal dysplasia. Patient is hospitalized in Intensive Care Unit due to pneumonia. Tests results showed ionic calcium 1.43 mg/dL, phosphorus 2.5 mg/dL y magnesium 1.3 mg/dL, alkaline phosphatases 963 U/L, parathormone 225 pg/mL, 59.43 ng/mL, TRPi 70.48%, creatinine 0.15 mg/dL. X-rays present generalized osteopenia with widening and cupping of the metaphyseal regions and multiple long bones fractures. Vitamin D-dependent rickets is diagnosed and later confirmed with genetic study: CYP27B1 c.[196-2A>G]; [1226C<T]. When admitted, patient initiates treatment with calcitriol 0.25 ug every 12 hours with dose titration up to 5 ug every 12 hours, due to differential diagnosis of vitamin D receptor alteration, prior to genetic test result; increase of oral and intravenous calcium needs up to 500 mg/kg/day of elemental calcium, alongside magnesium and phosphorus. During the first 10 days, lowered parathormone and alkaline phosphatases were observed, with an increase up to 300 pg/mL and 1250 U/L respectively with normal levels on day 35. After two months of follow up, patient is supplemented with low doses of calcium and calcitriol 0.5 ug every 12 hours and evolves with progressive catch up in size, recovers developmental milestones progressively, resolves immunological efficiency and convulsive syndrome.

Conclusion: Rickets is a differential diagnosis that we should not leave aside. Even though it is less frequent, genetic causes exist. Not only endocrinologists should be familiar with it, but also pediatricians, neurologists, immunologists, geneticists, and pulmonologists due to its systemic repercussion. The beginning of treatment in long-term diseases has bone remodeling level consequences similar to patients post parathyroidectomy in hyperparathyroidism, which leads to bone remodeling unbalance due

to cessation of resorption stimulus, which is why it is important to early detect hungry bone syndrome: hypocalcemia, hypophosphatemia, hypomagnesemia and give prompt treatment.

P2-98

BUR-CL207: An Open-label, Multicenter, Non-randomized Study to Assess the Safety, Tolerability, Pharmacokinetics and Efficacy of Burosumab in Pediatric Patients from Birth to Less than 1 Year of Age with XLH

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Background: X-linked hypophosphatemia (XLH) is caused by mutations in *PHEX* which increases serum Fibroblast Growth Factor 23 (FGF23) concentrations leading to phosphate wasting and osteomalacia. Burosumab is a recombinant fully human IgG1 monoclonal antibody which selectively inhibits the activity of FGF23. In clinical trials burosumab demonstrated significant clinical improvements in radiological rickets severity, growth, and biochemistry among XLH children aged 1-12 years compared to those continuing on conventional therapy (Imel 2019). Burosumab is licensed by the European Medicines Agency for management of XLH in children >1 year. Early initiation of treatment in XLH improves height (Makitie 2003) and effective and sustained treatment improves dental and musculoskeletal outcomes. Study BUR-CL207 has been designed to evaluate the safety, tolerability, pharmacology and efficacy of burosumab in pediatric patients <12 months.

Methods: This study is enrolling and will include approximately 20 XLH infants (<12 months old) with a confirmed *PHEX* mutation. Baseline fasted serum phosphate below the age-adjusted normal range is required for inclusion. Infants receiving conventional therapy will discontinue medications >1 week before commencing burosumab treatment and for the duration of study. This study comprises three cohorts with a total treatment period of up to 48 weeks. Subjects will be enrolled into a cohort dependent on

their age. Cohorts 1 and 2 for subjects aged: ≥6 months to <12 months, and cohort 3 for subjects <6 months. Burosumab starting doses of 0.4 mg/kg (Cohorts 1 and 3) and 0.8 mg/kg (Cohort 2), administered every two weeks, will be studied in each subgroup in a staggered manner with up to 3 subjects per cohort (final number per cohort will depend on age of eligible patients as enrolled). Burosumab dose adjustments will be determined by serum phosphate levels. A Data Safety Monitoring Board will review data accrued in each cohort.

Outcome Measurements: The primary endpoint is the safety of burosumab in pediatric patients <12 months. The secondary endpoints include: PK assessments and change from baseline in serum phosphate and 1,25(OH)₂D, the clinical effects of burosumab on growth and prevention and/or healing of rickets and skeletal deformities. Exploratory endpoints include presence and appearance of bone and skeletal XLH related abnormalities in pediatric subjects starting treatment <12 months, anthropometric and motor development in pediatric subjects with XLH and characterizing the immunogenicity of burosumab following administration to pediatric subjects with XLH.

BUR-CL207 is conducted in Austria, France, Germany, Italy, Spain, Sweden, UK.

EudraCT: 2019-000469-19

Diabetes and Insulin

P2-99

Glycemic Dysregulation During Treatment of Childhood Hematologic Malignancies

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Background: Secondary forms of diabetes mellitus (DM) are underdiagnosed in children and adolescents with cancer because despite the whole body of evidence that asparaginase, steroids and total body irradiation increase the risk of developing DM, risk factors are missing and – asides from treatments – understudied (e.g., pre-existing obesity, sex, age, ethnicity, family history of DM). The objectives of our study were to assess the incidence and associated risk factors of developing dysglycemia in children and adolescents treated for leukemia or lymphoma.

Methods: We conducted a 15-years retrospective study of pediatric patients treated for acute lymphoblastic leukemia (ALL), Hodgkin's lymphoma (HL), and non-Hodgkin's lymphoma (NHL) immediately at treatment initiation. We studied risk factors for DM in univariate and multivariate analyses.

Results: Our study cohort included 267 patients corresponding to 179 patients with ALL, 48 with NHL and 40 with HL. Eighteen percent of ALL patients (32/179) and 17% of NHL patients (8/48) developed DM within 2 months of treatment (for >61% of cases).

Half of NHL patients and 36% of ALL patients presented impaired glucose tolerance (IGT). No DM or IGT was observed in HL patients. Multivariate analysis showed the following DM risk factors for ALL patients: overweight or obesity (OR 3.793) and pubertal onset (OR 4.269) at cancer diagnosis, steroid-resistant disease (OR 3.445) and hematopoietic stem cell transplant (HSCT) (OR 4.754). Advanced age ($p < 0.001$) and high-risk treatment ($p = 0.002$) significantly associated with DM onset, were no longer present after adjustment with other cofactors.

Conclusion: In our cohort, 18% of patients with ALL or NHL developed early-onset DM after chemotherapy/radiotherapy. Patients with ALL with increased DM risk can be readily identified by measuring BMI and puberty stage at cancer diagnosis. Also, glucose monitoring should be reinforced when patients show steroid-resistant disease and/or require HSCT.

P2-100

The knowledge and Confidence in Management of Diabetic Ketoacidosis (DKA) among Iraqi Paediatric Residents: a Cross Sectional Study

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Introduction: Diabetic ketoacidosis (DKA) is a common medical emergency and is the most common cause of death in children with type 1 diabetes mellitus due its complications. Paediatric residents are usually the first line whom managing paediatric emergencies in Iraqi hospitals. They form the backbone of the provided service. It is important to make sure they are practicing at the highest possible standard to ensure patients' safety. Therefore, it is crucial to check their knowledge and confidence in managing paediatric endocrine emergencies.

Objectives: this study evaluates the knowledge of Iraqi paediatric residents regarding DKA recognition and management. It also sheds the light on the areas that need further improvement.

Methods: An online survey was conducted. A survey link of the questionnaire using SurveyMonkey was sent to residents from different levels between first to fourth year of training (R1-4) in general paediatrics.

Results: The survey was completed by 47 residents. 60.9% of them completed more than 6 months of paediatric emergency training placement. Only 28.9% of the residents recognized the correct diagnostic criteria of DKA, with R4 trainees accounting for the highest percentage (45.5%). 83.3% of R3 and 81.8% of R4 responders chose 0.9% sodium chloride as a maintenance intravenous fluid without adding potassium chloride to it, 80.4% of residents would start the insulin infusion after 60 minutes from starting the intravenous fluids. 69.6% of residents are not routinely attaching their patients to a cardiac monitor unless the patient is unstable or deteriorating during the DKA management.

Majority of residents (73.9%) recognized that cerebral oedema is a life-threatening complication of DKA but failed in recognizing

other life-threatening complications such as hypokalaemia and aspiration pneumonia as these were identified by only 30.4% and 13% of residents, respectively. 66.7% of R1-3 doctors can detect symptoms and signs of cerebral oedema compared to 81.8% of R4 doctors. 69.6% of residents felt confident in treating children presenting with DKA; with the highest average score of confidence came from R3 residents. Saying that, the vast majority of responded paediatric residents (91.3%) think there is a need for more DKA teaching/educational sessions.

Conclusions: Gaps in knowledge of correctly diagnosing DKA and subsequently its management were identified. Lack of a standardized national protocol is a contributing factor. Educational sessions for the residents about DKA management deemed necessary and it was demanded by the residents themselves.

P2-101

Disturbances of glucose homeostasis in polytransfused beta-thalassemia patients

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Introduction: B-thalassemia is a hereditary chronic hemolytic anemia characterized by a defect in the synthesis of beta-globin chains, particularly common in the Mediterranean region, southern Asia, and the Middle East (1) Transfusion programs and chelating therapy have greatly extended the life expectancy of patients (2). This has led to an increase in the prevalence of endocrine complications, linked to iron overload (3) including abnormalities in glucose homeostasis (4). Glycoregulation disturbances range from insulin resistance and glucose intolerance to obvious diabetes mellitus. Regular follow up of ferritinemia is the most commonly biological component used to assess the degree of iron overload. The correlation between the ferritinemia rate and glycoregulation abnormalities is not well studied and deserves to be specified (5-6).

Objectives:

Main: Describe the frequency of glucose homeostasis abnormalities in patients with polytransfused β -thalassemia

Secondary: study the relationship between abnormal glycoregulation and:

- The ferritinemia level
- Average transfusion volume (MTV)
- Duration of transfusion therapy
- Splenectomy
- Compliance with chelating treatment

Method: It is a descriptive, analytical and mono-centric cross-sectional study which was carried out in the pediatric department of CHU Mustapha and which involved 87 patients (46 Girls and 41 Boys), followed for several years on a regular basis and treated by a transfusion regimen (more than 10 transfusions) combined with a chelating treatment. All patients were assessed by a clinical history, physical examination, fasting blood glucose and oral hyperglycemia test (HGPO) combined with a test of HOMA-IR (Homeostasis Model Assessment of insulin resistance).

Results: 28 (32.2%) patients presented glycoregulation disorders with 17 (60.7%) girls and 11 (39.3%) boys, there is no statistically significant relationship between the two genders ($p = 0.31$). The average age of patients with glycoregulation disorders is 13.4 ± 6.58 years, 16 (18.4%) patients had moderate fasting hyperglycemia (MGH), 8 (9.2%) patients had glucose intolerance (GI), and 4 (4.6%) patients had diabetes (3 patients diagnosed before the start of the study). 10 (12%) patients presented a positive HOMA test, there is no statistically significant relationship between ferritinemia and glycoregulation disorders ($p = 0.65$).

Conclusion: Our results suggest that children with β -thalassemia have a high incidence of glycoregulation disorder in the second decade of life or later.

P2-102

Unmet need in technology for diabetes management in the Middle East, Africa and South East Asia

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Introduction: Diabetes is a global disease with approximately 425 millions of people affected throughout the world. The treatment cost for diabetes constitutes a significant economic burden and is estimated to increase in areas of Africa, South East Asia and the middle east in parallel to the increase to the disease incidence. These regions contribute differently in the global market revenue for the use of continuous glucose monitoring (CGM) and insulin pump therapy.

Aim: We aim to assess the utilization of CGM and insulin pump therapy in countries within the South East Asia, Africa and the Middle East and North Africa. We also planned to study the main challenges leading to lack of access and utilization of technology and suggested measures to overcome these challenges.

Method: A survey was designed and sent to health professionals providing care to young people with diabetes in those countries. We approached the African Society of Paediatric Endocrinology (ASPAE), the Asian Pacific Pediatric Endocrinology Society (APPES), the Indian society of Paediatric Endocrinology (ISPAE) and the Arab Society of Paediatric Endocrinology (ASPED) to circulate the survey.

Results: We received 201 responses from 28 countries and analysed 197. Majority of responders were physicians (90%) with 23% of them practicing in big diabetes centres with more than 500 patients under the age of 18. Around half of responders have less than 5% of their patients using either CGM or pump with 8 and 19% having none on either CGM or pumps. There were 10% and 5% of responders having more than half of their patients on CGM and pumps respectively. Lack of funding was the main challenge indicated by 70% of responders. Other challenges included Lack of simplified technology, maintaining patient motivation, lack of continuity in training the training, paucity of local research lack of sales competition, low acceptance of usage of technology devices because of cultural reasons and lack of secure patient information storage.

Conclusion: Technology use in diabetes remains underutilized in Africa and some parts of Asia. Funding remains a major obstacle in technology access and use. In the MENA region, use of technology is variable due to the marked variation in the level of income among its countries. Various measures were suggested by participants to fill the gaps of technology use in diabetes.

P2-103

Diabetes in a child with infantile onset multisystem neurological, endocrine and pancreatic disease (IMNEPD)

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IMNEPD is a mitochondrial disease caused by homozygous mutations in the *PTRH2* gene, a nuclear gene coding for a primary mitochondrial protein. IMNEPD was first described in 2014. So far only 3 other case reports have been published, reporting on a total of 15 patients.

We report on two affected siblings of whom the girl developed an antibody negative diabetes at 13 years of age with typical symptoms (polyuria, polydipsia, weight loss of 1,5 kg), and without diabetic ketoacidosis, HbA1c 10,2%, glycaemia 240 mg/dl, c-peptide 1.7 ng/ml (1.1-4.4).

As the clinical examination revealed a severe psychomotor retardation (2 word sentences, unsteady walk at 13 years of age), a sensorineural hearing loss, a peripheral neuropathy (slowed SSEP) and coordination deficits as well, we performed genetic testing for mitochondrial diseases. Genetic analysis showed a new homozygous frame shift variant (c.127dupA, p.(Ser43Lysfs*11) in the *PTRH2* (NM_001015509.2) gene.

The same pathogenic variant was found in homoplasmy in her 2 years older brother, who suffered also from severe neurocognitive impairment, motor delay, sensorineural hearing loss, but has so far no diabetes. The clinically non affected parents are both heterozygous for this pathogenic variant.

In contrast to the IMNEPD case reports published, neither of our two patients had short stature, nor did the girl suffer from an exocrine pancreas insufficiency. Similar to a reported IMNEPD patient, she developed insulin dependent diabetes.

Conclusion: When auto antibody negative insulin dependent diabetes is diagnosed in an individual with neurocognitive impairment and hearing loss, patients should be tested for *PTRH2* pathogenic variants, while affected IMNEPD patients should be monitored for diabetes on a regular basis.

The clinical characteristics of hybrid diabetes (HD) in children and their response to treatment

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Introduction: The term hybrid diabetes (HD) describes a form of diabetes in which hyperglycemia occurs in obese children in the presence of positive autoimmunity against the beta cells. Few data are available about the clinical presentation and the course of disease in children with this form of diabetes.

Aim: We describe the clinical characteristics and response to treatment in 7 children with hybrid diabetes.

Results: Seven children with HD diabetic patients whose mean age 10.8 $\pm$ 0.98 years) were diagnosed and followed in our institution. At presentation, all patients were obese, with a mean BMI SD was 2.73 $\pm$ 0.58, and 71 percent had acanthosis nigricans. Six out of seven patients had a family history of at least one type of diabetes (type 1, type 2, or gestational diabetes). The was checked and it was found that 2 patients had 2 autoantibodies against beta cells, 4 patients had 3 positive autoantibodies, and one patient had all 4 autoantibodies positive. The mean HbA1c at diagnosis was 10.6 % $\pm$ 2.1%. Four patients presented with the classical symptoms of polyuria, polydipsia, and recent weight loss along with hyperglycemia. Three patients presented with moderate to severe DKA. All patients were started on insulin at diagnosis, and 5 patients received metformin in the first week after diagnosis. During their follow-up, 4 patients did not require any insulin therapy and the other 3 patients had a marked reduction in the insulin requirement up to less than 0.2 unit/kg/day (2.36 $\pm$ 2.79 months) after diagnosis. This was associated with a marked reduction of their HbA1c to 6.3% $\pm$ 0.7%. In addition, the mean BMI SD has dropped to 2.39 $\pm$ 0.5 in the first 2 months after diagnosis, with a delta change = -0.34.

The duration of either no insulin requirement or marked reduction in the total daily dose to less than 0.2 unit/kg/day continued for an average of 15 months. After this period 5 patients required initiating insulin or an increase in the insulin dose/kg. One child remained insulin-independent and one required a markedly low dose of 0.06 unit/kg/day to control glycemia.

Conclusion: The etiology behind hybrid diabetes is not well understood. We described the clinical characteristics of hybrid diabetes in 7 children and their response to treatment. All children with HD were obese at presentation and had easier control of their glycemia (long honeymoon period) and many did not require insulin during this period.

Recurrent episodes of hypoglycemia in an infant with type 1 spinal muscular atrophy after gene therapy: Beta oxidation defect exaggerated by hepatic dysfunction

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Introduction: Spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative disease. In 2016, nusinersen (Spinraza) was approved by the FDA. The first AAV9-based gene therapy (Zolgensma), was approved by the FDA (2019) for the treatment of infants with SMA. We report an SMA case with recurrent hypoglycemic events after gene therapy.

Case Report: A 22 months old boy, with SMA type 1 was born at term by CS for fetal bradycardia. Initially, he was fed orally well with progressive swallowing difficulties. He was floppy with a weak Moro reflex. He had a positive family history of confirmed SMA. Both parents were carriers for the SMA gene and had another 3 healthy children. He was started on Spinraza by day 12 of life after genetic diagnosis and received 7 doses. By 6 months of age, he received intravenous gene therapy (GT) and 1mg/kg/day prednisolone as per protocol. One week after GT, his liver enzymes (ALT and AST) were elevated (65 and 127U/L, respectively). Three weeks later, while on prednisolone therapy, he developed an episode of hypoglycemia (1.9 mmol/L) 1.5 hours after feeding. He was receiving high caloric formula for low BMI. During another attack of hypoglycemia (BG= 2.8 mmol/L), the levels of insulin = 2.4 mic unit/ml, B-hydroxybutyrate 0.06mmol/L(low), cortisol 33.8nmol/L (low), and GH 1.77ug/L(low). While on prednisolone therapy and continuous GJ feeding, he had no hypoglycemia. After discontinuation of prednisone, a trial of interrupted feeding resulted in an episode of hypoglycemia (2.2mmol/L) after 0.5hour. Critical sample showed BG =2.4mmo/L, B-hydroxybutyrate = 0.54mmol/L, insulin=0.9 mic uint/ml, cortisol=132 nmol/L, GH = 8.69ug/L, and no acidosis. Continuous glucose monitoring (CGM) showed a generalized tendency to low glucose readings with the lowest = 3 mmol/L. These data of non-kenotic hypoglycemic episodes supported the possibility of associated fatty acid oxidation defect. His amino acid pattern and acylcarnitine screening were normal.

Conclusion: Hypoglycemia is a major clinical sign in all fatty acid oxidation defects due to a reduced hepatic glucose output and an enhanced peripheral glucose uptake. Zolgensma, most common side effects are elevated liver enzymes and vomiting. It appears that these side effects of Zolgensma could amplify the hypoglycemic effect of the associated FAOD in these children.

P2-106**Knowledge of the Final Year Medical Students Compared to Interns about the Diagnosis and management of Diabetes Mellitus**

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Introduction: Since diabetes mellitus is one of the major non-communicable diseases, therefore it is important taking this subject in some details during the undergraduate medical course, to prepare the students for recognizing the disease and understanding its management. In Sultan Qaboos University, the medical students go through a pre-internship training period, immediately after their final year of clerkship and just before starting their internship.

Objectives: To study the knowledge of the final year medical students about diagnosis and management of diabetes mellitus and compare it with the knowledge of intern doctors practicing at Sultan Qaboos University Hospital. The outcomes may also help us understanding the retention and the use of the previously taught lessons about diabetes.

Methods: An observational cross-sectional study was conducted at Sultan Qaboos University using an online questionnaire via SurveyMonkey website that was sent to the final year medical students of (2019-2020) batch and the intern doctors of the same year.

Results: A total of 80 responses were received from 41 final year medical students and 39 intern doctors. The principal knowledge about diabetes was similar among both groups. However, more medical students were aware of post viral infection role in the development of T1DM compared to a small number of intern doctors (19 vs 6, p-value of 0.001). Medical students were more aware than intern doctors in knowing that HbA1c is reflecting on the glycemic status of the preceding 3 months (p-value 0.018). Medical students were better in their response to whether T1DM is curable disease or not with statistical significance (p 0.04). Response to other questions about management of diabetes mellitus showed no significant statical difference between the two groups. Choosing "I don't know" option was selected by more students than interns during this survey.

Conclusion: The study showed not much difference between the knowledge of the final year medical students and intern doctors about diagnosing and managing diabetes mellitus. Interestingly, intern doctors' attitude was towards answering almost all the questions and sometimes giving wrong answers compared to medical students who frequently said "do not know" when they did not know. Intern doctors to be reminded about their own limitations to avoid giving wrong decisions in the clinical practice. Pre-internship course may contain more material about diabetes mellitus, and Educators may consider different methods of teaching to consolidate the knowledge of their students and contributing in minimizing the knowledge regression.

P2-107**A paradoxical conundrum: diabetic ketoacidosis resulting in treatment-resistant hypokalemic alkalosis**

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From time to time pediatric endocrinologists may be confronted with paradoxical constellations. Here, we report on a 13-year-old boy with type-1 diabetes. He had polyuria and polydipsia for the previous 2 weeks. Three days before presentation, he got increasingly exhausted and developed recurrent vomiting. At presentation his weight was 41,4 kg (P 25-50) and his height was 154 cm (P 25-50). Initial labs were HbA1c 10.2%, glucose 530 mg/dl, pH 7.15, base excess -21.1 mmol/l, bicarbonate 9.8 mmol/l, Na 131 mmol/l, K 2.4 mmol/l. Type-1 diabetes was diagnosed and the boy treated with i.v. insulin, fluid and electrolyte substitution. However, despite a high potassium substitution of up to 6 mmol/kg body weight/24h, therapy-resistant hypokalemia with hypokalemic metabolic alkalosis persisted after regression of ketoacidosis: pH 7.48, base excess 10.8 mmol/l, bicarbonate 33.7 mmol/l, Na 136 mmol/l, K 2.7 mmol/l. Further lab diagnostics showed a plasma renin of >300ng/l and a serum aldosterone of 141.1 ng/dl.

The constellation of therapy-resistant hypokalemic alkalosis and secondary hyperaldosteronism with normal blood pressures made us think of the additional presence of Bartter's syndrome. Bartter's syndrome is a clinically and genetically heterogeneous renal salt loss disorder with hypokalemic metabolic alkalosis and secondary hyperaldosteronism. Bartter's syndrome type 3 is caused by pathogenic changes in the CLCNKB gene and is inherited as an autosomal recessive trait. Analysis by next generation sequencing showed a complete deletion of the CLCNKB gene in the homozygous state, which was confirmed by multiplex ligation-dependent probe amplification analysis.

To the best of our knowledge, we describe the first case of persisting hypokalaemia and alkalosis after regression of diabetic ketoacidosis due to a previously undiagnosed Bartter's syndrome. During the course of long-term therapy with spironolactone and potassium substitution, the potassium levels normalized.

P2-108**Impact of the COVID19 pandemic on Paediatric Diabetes Services in Arab Countries**

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Introduction: The COVID19 pandemic had an impact on different health services due to the lockdowns, curfews, or reducing

provision of some clinical services in order to minimise the infection spread. Cancellation of clinic appointments was observed. Some patients also did not attend their appointments due to the fear of contracting the infection.

Objectives: This study looked at the impact of the pandemic on the paediatrics diabetes services in Arab countries.

Methods: An online survey using SurveyMonkey was sent out to the paediatric endocrinologist consultants who run diabetes clinics in the Middle East and North Africa, serving the children and adolescents live with diabetes mellitus. The survey was active for a 2-week period in August 2020.

Results: 34 paediatric endocrinologist consultants, from 10 Arab countries, working in 29 different hospitals responded to the survey. 82% of them are tertiary or University hospitals from the Government sector. The median number of patients used to be seen in diabetes clinic pre-pandemic was 22 patients per clinic, 45% of the responders were running 2 clinics per week. During the pandemic, the median number of patients reduced to 4 patients per clinic, 39% of the consultants became running only 1 clinic per week and another 24% had suspended their clinics. Since the announcement of the pandemic, 69.7% of the consultants either introduced or increased the number of remote consultations (81.8% via telephone, 51.5% via WhatsApp/Viber/Skype, 36.4% using video-call consultations with majority using Zoom platform). 45.5% of the consultants ran their virtual clinics from home, 33% from their actual clinic space, and 21.2% from their offices. Only 9% of clinicians thought the virtual clinic was not useful. 45.5% of the consultants stated that they would “definitely” continue the virtual clinic in future when the pandemic is over and 42.4% “may” continue it.

Conclusion: The pandemic has led to decreasing the number of patients attending the diabetes clinics in Arab countries. However, virtual clinics and tele-consultations emerged evidently during the pandemic. Almost half of clinicians were able to run their virtual clinics from home. It is expected to see more virtual clinics in the MENA region in the post pandemic era.

P2-109

Clinical Case of Cystic Fibrosis-like and APECED-like Syndrome due to Gain-of-Function Variant in STAT1

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Background: *STAT1* mutations can cause an extensive spectrum of disease, varying from severe bacterial and viral infections to mild disseminated mycobacterial disease, also chronic mucocutaneous candidiasis. Many patients present with autoimmune manifestations as type 1 diabetes, hypothyroidism and systemic lupus erythematosus. There are risks of cancers and cerebral aneurysms.

Aim: To present the clinical manifestations of *STAT1* gain-of-function mutation.

Clinical Case: We present a girl, born to a first normal pregnancy with uneventful family history. Since early infancy she suffered with obstructive lung infections and pneumonias, clinically resembling cystic fibrosis, accompanied with mildly elevated sweat chlorides. She developed bronchiectasias very early. At age of 3 years she was hospitalized for autoimmune hepatitis and chronic diarrhea. Cystic fibrosis was genetically excluded. Antifungal therapy was introduced for oral and nail moniliasis. At the age of 10 years autoimmune diabetes debuted with ketoacidosis. Severe autoimmune thyroiditis was established at the same time. Systemic therapy consisted of hormone replacement, antifungal and antimicrobial therapy. At the age of 13 years she revealed several episodes of autoimmune hemolytic anemia (1-2 times per year), which needed intermittent corticosteroid courses. She was genetically tested for *AIRE* gene defect to establish APECED syndrome without positive result. Through the years chronic lung infection worsened and at the age of 15 hemolytic anemia was transformed to syndrome of macrophageal activation. Lung infection progressed to lung abscesses and empyema that needed surgical interventions. She died at the age of 17 years.

Final Genetic Results: By using targeted next generation sequencing (Agilent custom capture v5.3/Illumina NextSeq500) at Exeter Molecular Genetic Laboratory we established de novo arisen missense mutation of *STAT1* gene, Exon 14:c.1154C>T, p.(Thr385Met). This variant has been previously reported and is predicted to be pathogenic. This confirms a diagnosis of syndrome of immune dysregulation due to a gain-of-function variant in the *STAT1* gene with CF-like and APECED-like clinical course, rather than IPEX-like one.

Conclusion: We report our first patient with autoimmune monogenic diabetes, multiple endocrinopathies and other autoimmune phenomena in combination with immune deficiency and CF-like lung disease due to pathogenic variant of the *STAT1* gene. Complex clinical manifestation of reported patient with *STAT1* mutation shows an extensive role of this gene in autoimmune, hematopoietic, gastrointestinal and pulmonary systems.

P2-110

A quality improvement project of a Young Adult Diabetes (YAD) service at a UK specialist centre

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Introduction: The joint young adult diabetes (YAD) service at a specialist UK centre facilitates transition from paediatric to adult diabetes care for young people (YP) aged 16-25 years. Since 2018, quality improvement interventions have included focus groups with young people, joint paediatric and adult specialist nurse appointments and recruitment of a type 1 diabetes educator. We assess the impact of these interventions and changes imposed by

the Covid-19 pandemic on clinic attendance and diabetes control in the 19-25 year old cohort.

Methods: YAD service data was retrospectively collected for: April 2018-March 2019 (year 1), April 2019-March 2020 (year 2) and April 2020-March 2021 (year 3 – COVID-19 pandemic). Outcomes of interest included technology uptake, HbA1c and clinic attendance. 'Did not attend' (DNA) rates were calculated as a percentage of all appointments offered, excluding those rescheduled or cancelled prior to the clinic start.

Results: The number of YP within the service increased over the 3 years (n=57 (year 1); n=75 (year 2); n=88 (year 3)). All had type 1 diabetes mellitus with the exception of one who had early onset type 2 diabetes.

Table 1 summarises our key findings. Year 3 had the lowest overall DNA rate. Median HbA1c improved over the years, with greater proportions of YP achieving a target HbA1c <58mmol/mol. Over time, multiple dose injection (MDI) use declined and uptake of insulin pumps, FreeStyle Libre (FSL) and real-time Continuous Glucose Monitoring (rtCGM) increased.

Emergency department (ED) attendances and hospital admissions particularly reduced in year 3. Of all ED attendances, the proportion of YP presenting with diabetic ketoacidosis (DKA) also reduced over time.

Conclusion: There has been an improvement in engagement and diabetes control over time. Based on focus group outcomes, we plan to initiate group education sessions and permanently integrate flexible consultations, allowing YP the option of virtual or face-to-face appointments.

P2-111

Prevalence of skin reactions among pediatric patients with Type 1 Diabetes users of glucose sensors

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Introduction: Glucose sensors are medical devices used in glycaemic control of patients with type 1 diabetes (T1D). Its use prevents multiple capillary measurements, improving disease control and quality of life. However, these systems are not exempt from unforeseen events. The rise in the number of users has resulted in the increasing detection of local skin reactions by these devices, being the most frequent the eczematous ones, which may correspond to irritative or allergic contact dermatitis.

Among allergens with sensitizing capacity, the most important is isobornyl acrylate (IBOA). Other allergens are 2,6-Di-tert-butyl-4-cresol (BHT), colophon, abitol, mixture of sesquiterpenic lactones and N,N-dimethylacrylamide.

Objective: Study the prevalence of skin reactions to glucose sensors (GS) and evaluate which ones are allergic to these substances.

Methods and Patients: Descriptive observational, carried out between 2019-2020 in 156 paediatric patients with T1D. Patients answered a survey about the development of skin injuries, referring them to a contact dermatitis unit. Epicutaneous tests were performed on patients with suspicious allergic reaction.

Results: 93 patients (49 males) were tested (90= flash glucose monitoring system users, 1=Dexcom G6®, 1=Enlite®, 1=Guardian Connect 3®). Average age of patients was 11.8 (±3.7). Median time from the onset of DM1 to the date of the assessment was 5.2 years (IQR:1.9 – 7), and 2.8 years (IQR:1.3-4,1) from the start of the sensor.

36.6% (n=34) of the individuals had some kind of reaction (31=flash glucose monitoring system, 1=Dexcom G6®, 1=Enlite®, 1=Guardian Connect 3®), of which only 8.4% had a history of skin atopia. 57.6% reported itching; 87.9% erythema; 27.3% flaking; 24.2% vesicles; 30.3% wounds and 39.4% changes in skin colour.

Table 1. Summary of key findings

	Year 1 (n=57)	Year 2 (n=75)	Year 3 (n=88)
Min. 1 appointment attended in year, %	79	76	81
DNA rate, %	41	41	27
HbA1c <58mmol/mol, n(%)	8 (17)	15 (23)	18 (33)
Median HbA1c, mmol/mol (IQR)	76 (64-92)	71 (60-86)	66 (54-82)
MDI, n(%)	44 (77)	57 (76)	57 (65)
Insulin Pump, n(%)	12 (21)	18 (24)	29 (33)
FSL, n(%)	-	26 (35)	40 (45)
rtCGM, n(%)	-	7 (9)	15 (17)
Min. 1 ED attendance, n	12	20	7
ED presentations due to DKA, n(%)	18 (60)	20 (57)	0 (0)

48.4% of the individuals who suffered any form of reaction used barrier methods, seeing improvement after its use by 57%. Five patients discontinued its use due to skin lesions.

10 of 34 patients who suffered a skin reaction were referred to the contact dermatitis unit. 2= contact dermatitis, 4= allergic contact dermatitis caused to black rubber //colophony rosin // IBOA // colophony rosin + IBOA (all flash glucose monitoring system users), 2= allergic contact dermatitis to sensor element – not parched- and 2= non-contact dermatitis.

Conclusions: Skin dermatitis is a frequent presenting complaint among glucose sensors users. The results of this study indicate that an evaluation of the skin area where the glucose sensor is placed must be introduced in our daily T1D clinics in order to improve and provide adequate care of our diabetic patients.

P2-112

A single-centre evaluation of remote video consultation for children and young people with diabetes

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Background: Throughout 2020 telemedicine was rapidly deployed across health services and, during the COVID-19 pandemic, replaced many face-to-face (FTF) medical consultations. Children and young people (CYP) with diabetes present a unique opportunity for this type of consultation, due to the ability to interpret and share glucose data via other platforms. This study describes both CYP and parent experience of a new telemedicine service for CYP with diabetes.

Methods: Data were collected from a patient cohort looked after in a single paediatric diabetes service between April 2020 and August 2020. This period followed the rapid introduction of telemedicine consultations for all paediatric clinics due to COVID-19. Telemedicine clinic appointments were offered using the Attend Anywhere platform. Parents and young people were contacted by telephone after their telemedicine consultation and data regarding their experience were collected via semi-structured interviews. Results were analysed both quantitatively and qualitatively.

Results: Data were analysed from 42 semi-structured interviews for 42 separate CYP, with an age range of 6-18 years. 60% of consultations were with more than one healthcare professional. 64% of interviewees described the video call quality as being just as good as FTF, with 36% describing it as satisfactory but not as good as FTF. The median time saved for patients was 1.5 hours (IQR 1.0-2.0 hours). "Time saved" was the most frequently expressed positive feedback. "Preferring face to face" was raised 8 times by responders as the most commonly reported negative feedback with "lack of HbA1c" the second most reported negative feedback. Overall, 45% interviewed described preferring remote consultation, 26% expressing no preference and 29% preferring FTF consultation. 93% of interviewees reported that they would be happy to use remote consulting again. Regarding the mode of

consultation 81% reported their preference would be for video consultation, 5% reported a preference for telephone consultation and 10% expressed no preference for mode of remote consultation.

Conclusions: CYP and parents reported a high degree of satisfaction and acceptability with both the technical aspects of video consultation and the overall consultation. Ability to share diabetes data through online platforms makes telemedicine consultations effective. Some aspects of FTF diabetes consultation such as HbA1c measurement are more challenging. Video consultation is likely to increase in prevalence in the future not just with physical distancing secondary to COVID-19 but also with aims to reduce emissions from travel and reduce the healthcare time burden associated with chronic disease.

P2-113

Health Outcome Indicators in Children with Diabetes Mellitus during the SARS-CoV-2 Pandemic

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Objectives: The SARS-CoV-2 pandemic has resulted in major cutbacks in service provision to patients. This could be detrimental to children with diabetes mellitus (DM), whose condition could deteriorate from poor access to healthcare. The lockdown has also potentially caused changes in diet, sedentary behavior and psychological burden due to the stress associated with the pandemic, which can have negative effects on glycemic control. Thus, this study compares clinical processes and patient care markers for paediatric patients with DM pre- and post- pandemic.

Study Design: A clinical audit of diabetes care provided to paediatric patients was conducted in a tertiary children's hospital in London. The indicators of care were based on the 9 care processes recommended by the National Institute for Health and Care Excellence. Data was collected retrospectively for 270 patients and compared between the pre-pandemic (October 2019 to March 2020) and post pandemic (October 2020 to March 2021) periods. Newly diagnosed, transitioned, permanently discharged patients were excluded. Paired sample t-tests were used for data analysis.

Results: There were 207 patients with T1DM, 18 with T2DM, 11 with MODY and 34 with others. The mean BMI and HbA1c values of patients who had data for both periods, are as follows:

Expectedly, the mean number of BMI and HbA1c measurements taken for the entire cohort dropped drastically over the 2 time periods, from 1.40 (95%CI 1.32-1.48) to 0.70 (95%CI 0.62-0.77) and 1.46 (95%CI 1.39-1.53) to 0.93 (95%CI 0.87-0.99) respectively (p<0.001).

Of the patients assessed during both periods, 55.9% required psychological support pre-pandemic versus 57.7% post. Of those receiving input, mental health staging declined for 38.6%, remained

	Total	T1DM	T2DM	MODY
Mean BMI Pre-pandemic (95% CI)	22.42 (21.45-23.39)	21.15 (20.36-21.94)	33.40 (29.48-37.32)	nil
Mean BMI Post-pandemic (95% CI)	23.42 (22.41-24.43)	22.23 (21.36-23.10)	32.92 (28.99-36.85)	nil
P value	p<0.001	p<0.001	p=0.787	nil
Mean HbA1c Post-pandemic/ mmol/mol (95% CI)	61.7 (59.4-64.0)	63.7 (61.3-66.1)	51.4 (44.2-58.6)	40.6 (37.3-43.9)
Mean HbA1c Pre-pandemic/ mmol/mol (95% CI)	62.1 (59.7-64.5)	63.5 (61.1-65.9)	57.8 (46.5-69.1)	40.9 (36.6-44.5)
P value	p=0.286	p=0.614	p=0.052	p=0.397

unchanged for 42.1% and improved for 19.3% (p=0.092). Of those who declined, 52.4% were primarily due to the lockdown.

Conclusions: During the pandemic, the BMI of patients with T1DM and the HbA1c of patients with T2DM increased significantly. It also impacted the percentage of patients with completed care processes, the frequency of monitoring of key indicators and the patient's mental wellbeing.

P2-114

Evaluation of serum myostatin levels in patients with insulin dependent diabetes mellitus

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Objective: We aimed to evaluate the relationship between serum myostatin levels and metabolic parameters in children with insulin dependent (Type 1) diabetes mellitus and to show the relationship with sarcopenia in children with insulin dependent diabetes mellitus.

Methods: Forty -four patients aged between 8 and 16 years, and 45 control patients were enrolled in the study. Anthropometric measurements and laboratory analysis were performed. Serum myostatin levels were studied in both groups. Body analysis was done to the patient and control groups. Lean body mass ratio was detected.

Results: There was a statistically significant difference between the patient and control groups in terms of the myostatin level (p <0.01). The mean "Myostatin" value of the participants in the patient group (33,17 ng/ml) was significantly higher than the mean "Myostatin" value of the participants in the control group (13,60 ng/ml). There was a statistically significant difference between the patient and control groups in terms of "CPK" (p <0.05). The mean "CPK" value in the patient group was lower than the control group. Although there was no statistically significant relationship between

myostatin values and "HbA1c", "C-peptide", "Insulin" and "CPK" variables, there was a negative correlation with "CPK", "insulin" and "C- peptide" levels and positive correlation with "HbA1c".

Conclusions: Serum myostatin levels were higher in children and adolescents with insulin dependent diabetes mellitus than in control group, regardless of muscle mass. It was found to be positively correlated with HbA1c. This result may indicate that serum myostatin levels may have potential new pathological effects on muscle mass and metabolism, especially in children and adolescents with poorly controlled insulin dependent diabetes mellitus. Further studies are needed on the subject.

P2-115

HbA1c and Glucose Management Indicator relationship: can HbA1c determination be avoided?

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Introduction: Continuous Glucose Monitoring (CGM) devices have introduced new metrics to assess metabolic situation of patients with type 1 diabetes mellitus (T1DM). Among them, the glucose management indicator (GMI) provides a proxy to HbA1c, however, these measures do not always match.

Purposes: To evaluate the concordance between GMI and HbA1c, and determinate in which scenarios GMI could replace HbA1c.

Subjects and Methods: Retrospective study of children and adolescents aged <18 years with T1DM using FreeStyleLibre® Flash Glucose Monitor. Data of the CGM are collected from the Libre-view® cloud system and correspond to 2 weeks period and sensor active ≥70% of the time.

The HbA1c is measured capillary by the DCA® Vantage analyzer.

Variables Analyzed: average glucose, CV, GMI, HbA1c, time above range (TAR), time very high (TVH), time in range (TIR), time bellow range (TBR), time very low (TVL), time sensor is active, and glucose lectures/day.

Inclusion criteria: DM last ≥6 months, time between HbA1c determination and CGM evaluation ≤15 days.

Variables are analyzed with the Stata14 software. Qualitative and quantitative variables are described as frequencies and mean (SD) respectively. GMI and HbA1c are compared by the t Student-Fisher test. Linear regression analysis examines the influence of the reported variables on the HbA1c-GMI difference, in case of association the cutoff point of each variable at which GMI and HbA1c can be considered to be equivalent is determined by the t Student-Fisher test: first not significant value. A $p \leq 0.05$ is considered significant.

Results: 201 subjects are enrolled (56.72% males), with 4.59 years (3.12) of T1DM evolution.

The time elapsed between the determination of HbA1c and the CGM evaluation is 0.0003 days (0.01). The mean HbA1c is 7.2% (0.8) and the mean GMI is 7.49% (0.72), and they are significantly different ($p < 0.001$). In 32.85% of the patients the HbA1c-GMI discordance is $\leq 0.2\%$.

Influence on HbA1c and GMI difference		
Variables	Linear regression	Cut-off point
Average glucose	$p=0.001$	≤ 161 mg/dl
CV	$p=0.181$	
TAR	$p=0.002$	$\leq 30\%$
TVH	$p=0.004$	$\leq 6\%$
TIR	$p=0.03$	$\geq 70\%$
TBR	$p=0.002$	$\leq 0\%$
TVL	$p=0.13$	
Time of sensor active	$p=0.098$	
Glucose lectures/day	$p=0.017$	≥ 30

Conclusions: In case of average glucose ≤ 161 mg/dl, TAR $\leq 30\%$, TVH $\leq 6\%$, TIR $\geq 70\%$, TBR $\leq 0\%$ or lectures/day ≥ 30 , GMI agrees with HbA1c, and HbA1c does not add any information compared to the sensor, avoiding its determination is both time and cost saving.

P2-116

Sex differences over two decades for glycaemic control, pump use and insulin dose in patients aged 10-20 years with type 1 diabetes

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Background: Therapy in type 1 diabetes has undergone a fundamental change over the last several decades, especially by the use of technical devices. Another change that took place is the growing awareness of sex differences of all kind, e.g. as influencing factors of metabolic control.

Our study aimed to evaluate sex differences over two decades with regard to changes in glycaemic control, with regard to trends in insulin pump use and insulin dose. Migration background was taken into account.

Methods: Via DPV database, type-1-diabetes patients aged 10-20 for the time period 1999-2018 were identified. Linear regression analyses adjusted for age, duration of diabetes, migration background and repeated measurements were used to create HbA1c-trends, trends about insulin pump use and insulin dose. Subsequently, stratification by migration background was made.

Results: For the cohort's characteristics see table. Both, girls and boys showed an HbA1c-decrease over the period examined: from 8.30 (8.24 – 8.35) to 8.07 (8.04-8.10)% in girls and from 8.15 (8.10-8.21) to 8.00 (7.98-8.04)% in boys. After stratification for migrant background a clear HbA1c-convergence between boys and girls was seen in those without migrant background as of 2016, but not in adolescents with migrant background. Use of insulin pumps increased continuously from 3% in 1999 (boys and girls) to 47% (boys) and 54% (girls), respectively in 2018. Adolescents with migration background used insulin pumps less frequently, with the girls being in the majority (2018: 48% girls, 40% boys). The daily insulin dose increased continuously from 1999-2018. An insulin dose levelling between boys and girls was seen.

Conclusion: The gap in metabolic control between boys and girls with type 1 diabetes seems to close, but in adolescents without migrant background only. HbA1c improvements are accompanied by increased insulin pump use, especially in girls. Sex differences in people with type 1 and migrant background needs to be addressed.

Table. Data are presented as median and lower-upper quartile or as percentage and represent the 1st year available per patient

Parameter		N
1 st year of analysis	2009 (2004-2014)	68,662
Age (years)	12.0 (10.4-14.6)	68,662
Female/male sex (%)	46.8/53.2	68,662
Migration background (%)	17.0	68,662
Diabetes duration (years)	1.9 (0.2-5.6)	68,662
Insulin pump use (%)	19.5	65,498
HbA _{1c} (%)	7.73 (6.87-9.02)	67,095
Insulin dose (U/Kg/d)	0.75 (0.57-0.95)	64,534

P2-117

Cardiovascular risk factors in adolescents with type 1 diabetes: Prevalence and gender differences

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Introduction: Obesity may increase the risk of cardiovascular disease (CVD) in patients with type 1 diabetes (T1DM). Risk of CVD in girls with T1DM is suggested to be higher than boys, however data pertaining to risk of CVD in boys are limited. The aim of this study is to determine the prevalence of obesity and risk factors of CVD in adolescents with T1DM as well as the impact of gender on these parameters.

Methods: This is a retrospective analysis of 345 cases (190 girls) aged 10-18 years, with T1DM of at least 3 years, using intensive insulin therapy. Patients were divided into lean and overweight/obese groups according to body mass index (BMI). Risk factors for CVD (obesity, dyslipidemia, hypertension) were compared between groups, and impact of gender was also analyzed.

Results: Prevalence of overweight/obesity was 22.3% which was significantly higher in girls (26.8% vs 16.8%, $p<0.001$). Age, duration of treatment, and HbA_{1c} levels of two groups were similar. Daily dose of insulin was higher in overweight/obese group (1.4 ± 0.3 U/kg vs 0.9 ± 0.2 U/kg, $p<0.001$). Mean LDL and TG levels were highest in overweight/obese girls, followed by overweight/obese boys, lean girls and lean boys, respectively ($p=0.002$, and $p=0.003$, respectively). Prevalence of LDL and TG elevation was similar between overweight/obese girls and boys, followed by lean girls and then lean boys (for LDL 74.5%, 69.2%, 36.7%, 23.3%, respectively, $p=0.008$, and for TG 29.4%, 23.1%, 13.7%, 4.7%, respectively, $p=0.009$). Mean HDL levels did not differ among groups. Prevalence of low HDL was similar in overweight/obese girls and boys which was higher than lean girls and boys ($p=0.006$). Prevalence of hypertension was highest in overweight/obese girls followed by overweight/obese boys, and similar in lean boys and girls ($p=0.01$).

Conclusion: Prevalence of obesity in this cohort is higher than the national prevalence of the same age. Overweight/obese girls with T1DM have the highest risk for CVD, followed by overweight/obese boys. Even lean girls have higher risk for CVD than lean boys. Control of weight during intensive insulin therapy is crucial in T1DM. Special attention should be paid to girls.

P2-118

Bilateral severe proliferative retinopathy, macular oedema, and lack of macrocytosis in an adolescent male with thiamine-responsive megaloblastic anaemia

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Thiamine-Responsive Megaloblastic Anaemia (TRMA) is a rare autosomal recessive disorder emerging due to mutation in the thiamine transporter 1 gene. It presents with sensorineural hearing loss, non-immune diabetes mellitus and megaloblastic anaemia. Ocular manifestations of TRMA described so far include optic atrophy and cone-rod retinal dystrophy.

This paper presents a case report of a British-Pakistani adolescent boy unexpectedly diagnosed with bilateral severe proliferative retinopathy and macular oedema just 3 months after being diagnosed with diabetes due to TRMA. His parents are first cousins and both were born in UK after grandparents migrated from Kashmir. He was diagnosed with bilateral sensorineural hearing loss at 2 years of age following a normal hearing test at birth. He subsequently presented at 14 years of age with mastoiditis, when he was also found to be in diabetic ketoacidosis (DKA). HbA_{1c} was 147 mmol/mol. Glutamic acid decarboxylase antibodies were negative. He was diagnosed with non-immune diabetes and was started on insulin.

First retinal screening (3 months after presentation with DKA) identified bilateral high-risk proliferative retinopathy and macular oedema. At the same time, he was admitted with breathing difficulties and was found to have anaemia, thrombocytopaenia and reticulocytopenia.

Investigation	Patient's results
Haemoglobin	40 g/L
RBC count	$1.49 \times 10^{12}/L$
Mean corpuscular volume	79.9 fL
Platelets	$42 \times 10^9/L$
WCC	$4.1 \times 10^9/L$
Reticulocyte count	$4 \times 10^9/L$

Peripheral smear revealed marked poikilocytosis with fragments, target cells and tear drop cells. Comprehensive evaluation for cause of pancytopenia revealed normal clotting, lactate dehydrogenase, vitamin B12, folic acid and ADAMTS-13 levels

and test results for autoantibodies and PCR for several viruses were negative. Bone marrow examination revealed erythroid dysplasia and numerous ring sideroblasts, and this eventually led to the diagnosis of TRMA. Red-cell thiamine level was 60 nmol/L (67–200). He was started on high-dose thiamine therapy (50 mg/day). Haemoglobin, red cell and platelet count improved and normalised within 3 weeks. Red-cell MCV increased from 79.9 to 100 fL. He is homozygous for a pathogenic SLC19A2 nonsense variant NM_006996.2:c.196G>T p. (Glu66Ter) and both his parents are heterozygous for the same mutation. He has had pan-retinal photocoagulation and his diabetes is better controlled since starting thiamine, though he continues to require insulin therapy.

Proliferative retinopathy within 3 months of diabetes diagnosis in adolescence is highly unusual. It may be due to the combined effect of intracellular thiamine deficiency and severe hyperglycaemia.

This case report also highlights the extensive haematological investigations that were required in view of patient's presentation with normocytic rather than macrocytic anaemia. Thus, macrocytosis should not be considered as an essential prerequisite while evaluating a patient for TRMA syndrome.

P2-119

First Survey About Pediatric Diabetes Services in Iraq

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Background: Diabetes mellitus is the second most common chronic disease of childhood. It requires appropriate management and follow up to reduce the complications. Type 1 diabetes mellitus (T1DM) is the most common type of diabetes that affects children. Most of the developed countries launched registries. In Iraq, there is no access to statistics or national report about the provided service. Rather, there is no standardization of the practice.

Purpose: This study aims to overview the provided service for children and young people living with diabetes in Iraq.

Methods: Online survey was sent out to colleagues from different Iraqi provinces. Responses were collected between November and December 2019.

Results: 18 responses from 10 provinces. All of them are working in government led pediatric diabetes units (PDUs). Respondents were 8 pediatricians, 6 consultant pediatric endocrinologists, 2 consultant adult endocrinologists and 2 pediatric endocrine specialists. Median number of patients in each center was 1000 ranging roughly between 100 and 3000. Total number of diabetic patients under 18 years old was approximately 15.4K. Median age before transferring patients to adult services is 16 years, ranging from 14-19 years. Majority (77.7%) have no transition policy in their health care centers. Team composition was variable between the PDUs. Median number of consultants, resident and administrator/secretary for each PDU was 1. 66% of PDUs do not have pediatric diabetologists, diabetes specialist nurses or diabetes educators. 77.8% are not having dietitians and 94.4% function

without psychologists. Basic facilities were limited; stadiometers were available in 78%, and different sizes of sphygmomanometers in 33% of PDUs. Similarly not all investigations were available as celiac screen was available in only 39%, urine for albumin/creatinine measurement in 22%, and HbA1c in 67% of PDUs. Only 56% of centers run an annual screening for their patients. Glucometers are provided in 50% of centers, glucometers' strips in 44%, insulin-syringes in 67% and insulin-pens in 44%. Lente insulin was available in all centers. 61% of PDUs do not organize any sort of activities for their patients.

Conclusion: There is a strong need to improve health services for children and young people live with diabetes in Iraq. Standardization of care is a big desire. Auditing the practice regularly is advisable to identify the gaps and poor compliance in order to be highlighted for the decision makers, working on improving the quality of care.

P2-120

Effect of metabolic control on the presence of Nonalcoholic Fatty Liver Disease (NAFLD) in adolescents with type 2 Diabetes

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Background: Type 2 diabetes (T2D) is an emerging disease in the pediatric population. The association between T2D and non-alcoholic fatty liver disease (NAFLD) has been described; the mechanisms responsible for the development and progression of NAFLD are incompletely understood. Evidence of high Haemoglobin A1c (HbA1c) levels and the risk of diabetes complications has been demonstrated. Recent evidence suggests that metabolic control may have a role in the development and progression of NAFLD.

Objective: To evaluate the effect of metabolic control on the percentage of liver fat in T2D youths.

Material and Method: This Cross-sectional study included a total of 47 adolescents with T2D, who attended the Diabetes Care Clinic of the Children's Hospital of Mexico Federico Gomez. The protocol was approved by the local Ethics and Research Committees. The characteristics of the study were explained to all the participants; a complete clinical history, anthropometry and physical examination were performed. To evaluate the average of liver fat, the imaging estimated proton density fat fraction (PDFF) was determined by magnetic resonance (MR). The HbA1c levels were analyzed by high performance liquid chromatography; we obtained an average of 12 HbA1c levels per patient (2 years).

Results: Mean age was 15.6 ± 1.75 years, and body mass index (BMI) was 25.1 ± 4.6 kg/m². Considering the average PDFF threshold of 6.5% or higher, we had 31 adolescents with NAFLD and 16 without NAFLD. The frequency of NAFLD was 66%, 45% was mild, 39% moderate, and 16% severe. The HbA1c% average

was higher in subjects with NAFLD ($7.3 \pm 1.0\%$ vs. $8.2 \pm 2.2\%$, $p = <0.05$). We observed an association between the percentage of liver fat and HbA1c% ($p = 0.001$). After a multivariable analysis, the association was non-significant when we adjusted for age, sex, BMI or Tanner score. With the exception of the association between the percentage of liver fat and HbA1c which remained significant after adjustment for diabetes duration and severity of NAFLD.

Conclusions: In adolescents with T2D, high HbA1c levels are associated with increased of the percentage of liver fat (PDF). Further investigation is warranted to determine if the metabolic control of pediatric patients with T2D has a role in the development and progression of NAFLD.

P2-121

The effect of glycemic variability on DNA damage in pediatric patients with type 1 Diabetes Mellitus

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Increased glycemic variability is an important risk factor in terms of complications independent of HbA1c. The aim of this study was; to investigate the relationship between continuous glucose monitoring system (CGMS) indices and clinical data, to investigate DNA damage in patients with diabetes and to evaluate the effect of glycemic variability on DNA damage.

Fifty patients with T1DM, aged under 18 years old, who were followed up at least one year in Pediatric Endocrinology Department of Pamukkale University Faculty of Medicine and 21 healthy control objects were included in the study. "Medtronic iPro^{TM}2, Enlite Glucose Sensor®" was inserted and CGMS indices were calculated. Mean sensor glucose, standard deviation (SD), glucose management indicator (GMI), coefficient of variation (CV), time in range (TIR), time below range (TBR), time above range (TAR) indices were evaluated. Blood samples were taken for DNA damage, fasting lipids and HbA1c.

Total 50 patients with a mean age of 13.69 ± 2.99 (F/M:30/20) were included to the study. Mean diabetes duration and HbA1c level were 4.39 ± 2.39 years and $9.23 \pm 2.16\%$, respectively. Mean sensor glucose was 167.1 ± 28.93 mg/dL, TIR was $58.88 \pm 15\%$, TAR was $36.46 \pm 15.53\%$, TBR was $4.64 \pm 4.51\%$, SD was 64.64 ± 15.22 mg/dL, CV was 39%, GMI was $7.45 \pm 1.01\%$.

The measured HbA1c value was higher than the GMI. There was a positive correlation between HbA1c and mean sensor glucose, GMI ($r = 0.3$, $p = 0.03$; $r = 0.29$ $p = 0.03$). No relationship was found between HbA1c and other sensor indices. TBR and SD of the patients with stable glycemic variability ($CV < 36\%$) were lower than that of the unstable glycemic variability ($\geq 36\%$).

DNA damage parameters were similar between type 1 diabetes and healthy control groups. Tail length which is one of the parameter of DNA damage was higher in patients with poor metabolic

control (HbA1c $< 7.5\%$) than that of the good metabolic control (HbA1c $> 7.5\%$). No significant difference was detected between stable and unstable glycemic variability groups regarding DNA damage parameters, however a positive correlation was found between the tail length, tail intensity and tail migration and % CV ($p = 0.043$, 0.034 , 0.027).

It was shown that DNA damage increased as glycemic variability increases. DNA damage of patients with poor metabolic control was higher than patients with good metabolic control.

P2-122

Parental insulin resistance is associated with unhealthy lifestyle behaviours independently of body mass index in children: The Feel4Diabetes study

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Introduction and Aim: Parental health is associated with children's health and lifestyles. Thus, the aim of the present study was to assess lifestyle behaviours of children from parents with insulin resistance (IR) and at risk of type 2 diabetes.

Methods: 2117 European parents from six countries included in the Feel4Diabetes-study measured in 2015 and identified as being at risk for diabetes with the FINDRISC questionnaire were included. Parental IR was considered when homeostasis model assessment (HOMA) was higher than 2.5. Children's screen-time, physical activity and diet were assessed and clustered by K-means. For children, a Healthy Diet Score (HDS) was calculated. Regression and multilevel logistic regression analyses were performed in 2021.

Results: Children from parents with IR had higher body mass index (BMI) ($p < 0.001$) and spent more screen time ($p = 0.014$) than those from non-IR parents. Children from parents with IR had a lower value in the breakfast and vegetable components of the HDS ($p = 0.008$ and $p = 0.05$). Four lifestyle clusters were found. Children from IR parents had higher odds of being in a non-healthy cluster (OR: 1.19; 95%CI: 1.001-1.437).

Conclusion: Having an IR parent was associated with a high screen time and an increased probability of having an unhealthy lifestyle pattern in children. Thus, in those families with IR parents, children's lifestyles should be assessed to prevent the development of IR in children.

P2-123**Use of the whole country insulin consumption data in Israel showed a reduced prevalence of type 1 diabetes in children aged <5 years during universal Rotavirus vaccination**

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Background: Recent studies showed that Rotavirus vaccination may affect the prevalence of type 1 diabetes (T1D). Our aim is to determine the prevalence of early childhood (<5 years) T1D before and during the introduction of Rotavirus vaccination in Israel by syndromic surveillance.

Methods: Data on insulin purchases reported by Israel's four health care organizations (HMOs) was retrieved from the National Program for Quality Indicators in Community Healthcare (QICH).

Results: During the pre- vaccination years (2002-2007) a steady increase of insulin purchases was reported in the young (<5 years). The period percent change (PC) of children aged <5 years old diagnosed with T1D inferred from purchased insulin prescriptions increased by 50.0%, and the annual percent change (APC) increased by 10.0% ($p=0.01$).

During the period of free, universal Rotavirus vaccination (2011-2018), the PC for T1D diagnoses among children aged <5 years decreased by 3.8% with an APC of -2.5% ($p=0.14$). There was a significant difference ($p=0.002$) between the increasing trend in insulin use before vaccination versus the decreasing trend after vaccination.

Conclusion: Rotavirus vaccination correlated with attenuation of the increasing rate in the prevalence of T1D in <5 year-old children in Israel.

P2-124**Psychological changes in youth with diabetes: comparison between preadolescents and adolescents**

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Background: The course of type one diabetic disease (T1DM) varies according to the period of life and in response to various external or internal factors. Adolescence is an evolutionary phase that involves important developmental changes and identity construction. Diabetes disease and its management, especially in this life period, can lead to psychological distress and impact on Self-redefinition.

Method: We conducted a retrospective analysis on psychological data that emerged within the school camps conducted in recent

years (2013-2019) with preadolescents (PA 12-14 years) and adolescents (A 15-17 years). We investigated: adaptation to diabetes (PAID, PA=213, A=209); self-esteem (Culture-Free Self-Esteem Inventory for Children Form, PA=158, A=154); mood (WHO-5, PA=205, A=211); anxiety (RCMAS-2 / SAFA-A, PA=166, A=167) and disordered eating behaviors (DEPS-R, PA=124, A=124).

Results: Psychological scores were within normal range but with a wide dispersion and vary according to age. Diabetes related distress (PAID) was greater in PA compared to A ($p = .03$). Significant lower self-esteem levels were found in A than in PA ($p = .0002$). Lower emotional wellbeing scores emerged in A compared with PA ($p < .0001$). Anxiety, tested by two different questionnaires among years, didn't show significant differences between PA and A. Concerning to eating disorder behaviors, difference between the two groups was found to be not quite statistically significant ($p=0.06$), with an occurrence of clinical cases equal to 18% (PA) and 23% (A).

Conclusions: Our data highlighted a vulnerability in the areas investigated, with variations according to the age and developmental needs of the young patients. For the younger ones, the most complex aspect seems to be the adaptation to diabetes, probably due to their level of self-management skills and psycho-developmental challenges. Teens seem to be more aware of T1DM management, while their difficulties are more focused on mood and self-esteem. These aspects could be linked to the need to integrate the chronic condition in the vision of themselves and in the process of building identity. Data about eating disorders showed a frequency in line with literature but must be deepened in a larger group. Camps can improve psychological processing of the DMT1 condition giving the opportunity for peers of sharing the same daily life experience, decreasing sense of diversity. The data must be studied in a larger sample, also involving those who do not attend the camps but can be a starting point for planning interventions differentiated by age.

P2-125**Focal Congenital Hyperinsulinism in Infancy is Directly Linked to Increased Numbers of Islet Pancreatic Polypeptide Cells in Islets**

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Congenital Hyperinsulinism (CHI) is primarily associated with defects in the regulated release of insulin from β -cells but little information is available about the role of other islet cell types. Pancreatic polypeptide (PP) cells represent a minor component of the islet endocrine cell population. PP causes satiety, decreases gastrointestinal tract motility and suppresses glucagon release. Since CHI is associated with feeding problems and loss of glucagon-mediated

counter-regulatory responses to hypoglycaemia, we hypothesised the involvement of PP in the pathophysiology of CHI and investigated the expression of PP cells in pancreatic tissue.

Methods: We analysed tissue from 28 patients with either focal (CHI-F) (n=17) or diffuse (CHI-D) (n=11) CHI. All patients had confirmed mutations in either *KCNJ11* or *ABCC8*. Gene expression studies were performed using Affymetrix Human Transcriptome Arrays (HTA 2.0) and protein expression was assessed by immunohistochemistry and electron microscopy.

Results: All patients experienced feeding problems during the early stages of diagnosis and treatment of CHI. These were identified as difficulty with sucking, swallowing, vomiting, and feed aversion (or a combination). In 82% of CHI-F cases, feeding problems ameliorated within 4-8 weeks following surgery. By contrast 80% of patients with CHI-D continued to experience feeding difficulties for more than 2 years after surgery. In CHI-D patients with genomic defects in all islet cells in the pancreas, we found no alteration in either the expression of *PPY*, the incidence of PP cells within islets (<1% of cells, n=46,960) or the fraction of islet cells expressing pancreatic polypeptide ($33 \pm 5\%$, n=8 cases, n=425 islets) compared to age-matched control tissue. In marked contrast, in CHI-F lesions (resulting from somatic events that cause expansion of β -cells and the paternal inheritance of *ABCC8/KCNJ11*) defects trigger a marked increase in *PPY* expression ($P < 0.0001$) and a greater than 30-fold increase in the population of PP cells. We found no evidence from gene transcript profiling for the loss of β -cell identity and PP secretory granules were not seen in other populations of islet cells by electron microscopy.

Conclusion: We conclude that increased islet PP cell frequency is not directly and causally correlated to *ABCC8/KCNJ11* defects. The consistent association of increased islet PP with CHI-F may indicate that inappropriate endocrine signalling has a significant impact upon the phenotype of disease and may prove valuable in diagnosing CHI-F.

P2-126

Oral administration of CRN04777, a nonpeptide selective SST5 receptor agonist, suppresses insulin secretion and rescues hypoglycemia in neonatal rat models of congenital hyperinsulinism

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CRN04777 is an orally administered nonpeptide that is a potent and selective agonist of somatostatin 5 (SST5) receptors and is currently under development for the treatment of congenital hyperinsulinism (HI), the most common cause of persistent hypoglycemia in newborns and infants. Congenital HI arises from mutations within the insulin secretion pathway and is characterized by excessive and/or inappropriate insulin secretion by pancreatic islet beta cells. This excess insulin can result in profound hypoglycemia which can lead to neurological impairment, coma, and even death if not treated promptly.

The neuropeptide somatostatin is an important modulator of hormonal signaling in the pancreas, and SST5 activation has been shown to suppress insulin and raise blood glucose, thus providing a potential treatment mechanism for patients with congenital HI. We characterized the ability of CRN04777 to raise blood glucose and lower plasma insulin in preclinical models using neonatal (PND7-11) rats. Oral administration of CRN04777 in neonatal rats suppressed insulin secretion and dose-dependently increased blood glucose levels for up to 6 hours after a single dose. Furthermore, the CRN04777 mediated increase in blood glucose was sustained over 5 days of repeated oral administration.

The most common mutations underlying congenital HI are found in the genes encoding the ATP-sensitive potassium (KATP) channel, which controls the membrane potential of pancreatic beta cell, and children with KATP-dependent HI are typically unresponsive to diazoxide, the only FDA-approved drug for HI. Sulfonylurea drugs, such as glyburide, close KATP channels and can be used to induce a hyperinsulinemic hypoglycemic state in rats that mimics some of the characteristics of KATP-HI. As expected, a single administration of glyburide in neonatal rats induced a pronounced increase in plasma insulin levels, with a concomitant decrease in blood glucose that persisted for several hours. Oral administration of CRN04777 rescued the glyburide-induced hyperinsulinemic hypoglycemia, lowering insulin levels and restoring blood glucose levels to >60 mg/dL.

These findings provide evidence that CRN04777 is an efficacious nonpeptide SST5 agonist that suppresses insulin and increases blood glucose in neonatal rats. In addition, oral administration of CRN04777 rescued hypoglycemia in a neonatal rat model of congenital HI, demonstrating its potential as an oral therapeutic for children with congenital HI.

P2-127

Thiamine-responsive megaloblastic anemia: a rare presentation of an uncommon disease!

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Background: Thiamine-responsive megaloblastic anemia syndrome (TRMA) is characterized by a triad of megaloblastic anemia, progressive sensorineural hearing loss, and diabetes mellitus (DM). It is due to an inherited mutation in *SLC19A2* gene, encoding a high-affinity thiamine transporter 1 in charge of facilitating the uptake of thiamine by the cells. Other manifestations including optic atrophy and stroke are rarely reported.

We herein report an extremely rare case of TRMA without megaloblastic anemia, with associated stroke, and optic atrophy.

Case History: A 1-year-old girl born to consanguineous parents presented with right focal convulsions, hemiplegia, and photophobia. She was diagnosed with left-sided stroke and epilepsy. Her thrombophilia profile was normal, apart from heterozygous MTHFR gene mutation with normal homocysteine level. Within

the period of her admission, hyperglycemia was incidentally discovered and she was diagnosed with DM, with low C-peptide (0.1 ng/ml), and HbA1C 7%. Her fundus examination revealed bilateral optic atrophy. After discharge, she started having difficulty hearing. Audiometry was done showing profound sensorineural hearing loss at high frequencies.

At the age of 3 years, she presented with fever, pallor, and purpuric spots all over her body. She had been receiving iron therapy for 3 months, but with no improvement. On examination, she had mild hepatosplenomegaly. Her blood count showed normocytic normochromic anemia (MCV 81 fl) with reticulocytic count 3.6%, thrombocytopenia (plt 15.000/ μ l), neutropenia (ANC 700/ μ l), and activated lymphocytes. Cytomegalovirus-induced pancytopenia was suspected to be the cause of her hematological findings with positive CMV IgM, IgG. Other investigations including urine analysis, ANA, anti-dsDNA, C3, D-dimer, fibrinogen were normal, and Coomb's test was negative. Pancreatic autoantibodies were done to confirm non-type 1 DM and were negative.

Despite that she didn't have macrocytic anemia, bone marrow with Prussian blue stain revealed sideroblastic anemia with ringed sideroblasts confirming the diagnosis of TRMA. On thiamine therapy (50 mg/day), her hematological findings, and her HbA1c normalized (5.6%) on insulin requirement 0.5 U/Kg/day. Later on, her genetic testing confirmed the diagnosis with homozygous mutation for a pathogenic non-sense variant of SLC19A2 gene.

Conclusions: TRMA syndrome should be kept in mind in the differential diagnosis of DM with deafness. It does not always have to be a classical presentation with all the cardinal features, so a high index of suspicion is needed. BM with Prussian blue stain demonstrating ringed sideroblasts is helpful in diagnosis-even if no megaloblastic anemia is present.

P2-128

Daily Meal Size Variation Does Not Affect Glycemic Control In T1D Adolescent Patients Equipped With The Closed Loop DBLG1 System

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The aim of this study was to assess the impact of meal size on glycemic control for T1D adolescent patients equipped with Diabeloop's Closed Loop, DBLG1 System [1], based on data from the clinical trial NCT04190277.

Among this dataset we isolated 37 adolescents. Only days with $\geq 70\%$ available CGM data and $>50\%$ of time in closed-loop were included in the analysis, resulting in an average duration of 18 days per patient for a total of 668 days of treatment.

To assess the impact of patient meal size (the daily sum of Carbohydrates (CHO) declared by each patient on his device) on glycemic control, we computed the difference in percentage point between patient daily value and patient daily mean value of both Time In Range (TIR, [70-180 mg/dL]) and Time In Hyperglycemia (TIHYPER, > 180 mg/dL) and plotted it against each daily CHO as a percentage of the mean daily CHO for this patient. This way we could observe the effect of larger and smaller than average meals and determine if they tended to increase or decrease TIR and TIHYPER.

We observed no correlation between the TIR and the daily amount of ingested CHO ($r=-0.05$), nor between the TIHYPER and the daily amount of ingested CHO ($r=0.05$).

In conclusion, Diabeloop's DBLG1 System's performance was not altered by the variations in daily amount of carbohydrates ingested by T1D adolescent patients.

[1] Benhamou, P.Y., et al. "Closed-loop insulin delivery in adults with type 1 diabetes in real-life conditions: a 12-week multicentre, open-label randomised controlled crossover trial." *Lancet Digit Health* 1;1 (2019): e17-e25.

P2-129

Evaluation of continuous glucose monitoring for the diagnosis of cystic fibrosis related diabetes (CFRD). A prospective and longitudinal study

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Introduction: Continuous-glucose monitoring (CGM) is becoming a useful tool to evaluate glucose profiles in real-life conditions and to detect glucose abnormalities undetected by OGTT in CF patients.

Objectives:

- Evaluation of OGTT and CGM results longitudinally
- Evaluation of BMI z-score and %FEV1 changes in relation to OGTT and CGM results.
- Analysis of 6 proposed criteria to classify glucose abnormalities by CGM results.

Patients and Methods: Prospective longitudinal and cross-sectional study. Patients with genetically-confirmed CF >10 years old, visited between November/2012 and November/2019. Fifty patients (28 female), age: 13.79 ± 2.43 years. Patients receiving insulin, lung transplant; or treatment with corticosteroids, GH and/or immunosuppressants or having disease exacerbation in the previous 4 weeks were excluded.

OGTT and GCM performed yearly. BMI and %FEV1 assessed at the time of testing (± 2 months) and at the previous year (± 2 months).

OGTT classifies patients into normal glucose tolerance (NGT), abnormal glucose tolerance (AGT) or CFRD. After OGTT, CGM (IproTM2) was carried out for 6 days with regular exercise and diet.

Comparison, by ROC curve, of sensitivity and specificity of the proposed criteria to classify glucose abnormalities by CGM results. Statistical analysis performed with SPSS v.24 program.

Results: Cross-sectional study: 26% homozygous and 50% heterozygous for F508del mutation. 80% pancreatic insufficiency.

- OGTT: 28 patients (56%) NGT, 19 (38%) AGT and 3 (6%) CFRD.
- CGM: One patient (2%) with NGT and 11 (22%) with AGT had glucose peaks >200mg/dl

To classify glucose abnormalities by CGM the following criteria were chosen (Specificity: 71.43%, Sensitivity: 86.36%), AGT: glucose between 140-199 mg/dL $\geq$ 4.5% of monitoring time or one peak of glucose $\geq$ 200mg/dL; CFRD: $\geq$ 2 glucose peaks $\geq$ 200mg/dl on different days.

Prospective Study: in 21 patients at least 2 pairs of tests (CGM and OGTT) were performed (second test age: 15.33 $\pm$ 2.38 years) and in 12 of them (third test age: 16.01 $\pm$ 1.71 years) 3 pairs of tests.

BMI and %FEV1 according to CGM results.

2nd CGM	Difference in BMI z-score in 3rd test (median)	p
NTG	0.13	0.024
AGT/CFRD	-0.30	
3rd CGM	%FEV1 in 3rd test (median)	
NTG	106	0.024
AGT/CFRD	94	

NGT n=8; AGT/CFRD n=4.

Conclusions:

- CGM is a useful method to evaluate glucose abnormalities in CF patients.
- Criteria to diagnose glucose abnormalities using CGM are proposed.
- CGM is more sensitive than OGTT in detecting glucose abnormalities that are related with lung function variations and predicting future nutritional changes (decreased BMI).

P2-130

Blood lipid concentrations of newborns and their mothers with gestational diabetes

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It is noted that with gestational diabetes mellitus, lipids cross the placenta in a limited amount. It is assumed that their concentration in maternal blood correlates with the concentration of lipids in the fetus.

The purpose of this study was to compare the levels of the main indicators of the lipid profile, such as cholesterol, triglycerides and high and low density lipoproteins, in newborns and similar indicators in their mothers with gestational diabetes.

Patients and methods. The study included 127 mother-child pairs. All infants were born with gestational age less than 37 full weeks. Birth weight ranged from 2800 to 3600 grams.

Levels of cholesterol, triglycerides, high and low density lipoproteins were studied during the neonatal period. LiquickCor-CHOL test systems were used to quantify cholesterol, triglycerides were measured using LiquickCor-TG test systems, high and low density lipoproteins were determined using CORMAYHDL-DIRECT test systems.

Results: The relationship of maternal and neonatal indicators of the lipid spectrum in the neonatal period has not been identified. The only exception was the concentration of triglycerides, which showed a statistically significant negative relationship between the content of triglycerides in the blood of mothers (Me - 0.005mmol/l) and their babies (ME - 0.001mmol/l).

Conclusions: The results of this study do not strongly confirm the relationship between the lipid content in the blood plasma of mother with gestational diabetes and her newborn.

However, in order to draw final conclusions regarding the correction of lipid metabolism in newborns, longitudinal studies with sufficient power are necessary.

P2-131

Comparison between hybrid diabetes (HD) and type 2 diabetes (T2DM) in children; Patient's characteristics at diagnosis: a retrospective observational study

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The "Hybrid Diabetes (HD)" is a new term that emerged in the last few years to describe diabetes with combined features of type 1 and type 2 diabetes. The etiology behind hybrid diabetes is not well understood, and clinical characteristics for these unique patients were not described before. Differentiating HD from other forms of diabetes will lead to a better understanding of the disease process and course, as well as knowing the most appropriate management plan to prevent future complications.

Patients and Methods: Seven children who were identified as HD were compared to 59 children who were diagnosed with type 2 diabetes (age 7 to 18 years). Their clinical and biochemical data at presentation were collected and analyzed to delineate the difference between the 2 groups.

Results: The age at presentation did not differ between the 2 groups. The mean BMI SD of T2DM was significantly higher than the DD group (p< 0.04). None of the T2DM patients presented with DKA, while 28% of children with HD presented with DKA. No significant difference among the two groups was found regarding, family history of DM, presence of AN, presence of polyuria, and polydipsia or HbA1C concentration. The mean C peptide level at presentation was significantly higher in T2DM versus HD group. (p 0.01)

	HD	T2DM	p-value
	7	59	--
Age (yr)	10.8	11.28	0.50
BMI SD	2.73	4.5	0.04
acanthosis	71%	90%	0.16
+ family history	85.70%	87%	0.29
Polyuria/polydipsia	57.10%	78%	0.22
ketosis no acidosis	14.20%	22%	0.64
DKA	28.60%	0%	< .00001
C-peptide	1.42	3.88	0.01
HbA1c at diagnosis	10.63%	10.05%	0.61

Discussion: Our study showed that children with HD were less obese and has lower C peptide levels and a higher risk to present with DKA compared to T2DM.

Conclusion: HD is a newly recognized subtype of diabetes and has special characteristics that differentiate it from other types of diabetes. Further studies are needed to investigate the long-term prognosis and management plans for this group.

P2-132

Features of the manifestation of type 1 diabetes in children in COVID-19 pandemic

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Type 1 diabetes is one of the common chronic diseases of children's age. In recent years there is an increase in the rate of primary morbidity of 1 type diabetes in children with a displacement of peak manifestation for age 5-9 years. Medical History of 110 patients aged from 0.5 to 18 years diagnosed with 1 type diabetes have been analyzed in the Republican Center for Pediatric Endocrinology with a division into comparison group (2018- 2019) and control group (2020). Comparison of the number of patients admitted to the hospital with the first time identified type 1 diabetes haven't got statistically significant differences, in 2018 - 30, 2019 - 40, 2020 - 39 patients. The duration of complaints before the admission to the hospital was in 2018 - 19.64 ± 15.09 days, 2019 - 31.16 ± 31.04 days, 2020 - 23 ± 16.17 days. T-criterion in all cases less than unit, which indicates statistically not significant differences. Among all patients in 2018 year boys are 56.7%, girls - 43.3%, in 2019 patients were distributed on the sex equally: boys - 50% and girls - 50%, in 2020 girls insignificantly prevailed - 54%, boys - 46% (statistically significant differences in the sex distribution were not found). Among girls the share of children under 10 years old amounted to 70%, among boys - 47%. Significant hyperglycemia was revealed in the hospital: in 2018 - 18.71 ± 6.23 mmol/l, 2019 - 20.88 ± 8.4 mmol/l, 2020 - 22.3 ± 10.45 mmol/l.

The level of glycated hemoglobin was higher than the norm in all patients and did not have statistically significant differences (2018 - 11.3 ± 2.09%, 2019 - 11.5 ± 2.78%, 2020 - 11.64 ± 2.54%).

During the period 2018-2019 a correlation dependence was revealed between the length of complaints and the level of the glycated hemoglobin (Person's criterion = 0.408) and the level of glycated hemoglobin and age (Person's criterion = 0.276, correlation 95%).

In 2018 36% of children were in a state of laboratory and clinical acidosis, which is confirmed by the data of the acid-base state of the blood, in 2019 - 32%, in 2020 - 25%, statistically significant differences were not found.

During COVID-19 pandemic the age displacement of the peak of manifestation of type 1 diabetes is preserved for the age of pre-pubertal, more pronounced in girls. There is a correlation dependence between the level of glycated hemoglobin and the age of patients, the duration of complaints.

P2-133

Risk factors of autoimmune thyroid disease in children with type 1 diabetes mellitus

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Background and Aims: The incidence and prevalence of childhood type 1 diabetes (T1D) increases all over the world. The disease is often combined with other autoimmune lesions. The most common is autoimmune thyroid diseases. The combination of several autoimmune diseases significantly worsens diabetes control in children with T1D. The aim of the study: to identify risk factors of autoimmune thyroid diseases in children with T1D based on the study of the features of anthropometric, metabolic and immunological parameters in children with polyglandular autoimmunity.

Methods: 49 children with combined autoimmune pathology (main group, age 12.64±3.68 years) and 81 patients with only T1D (comparison group, age 11.82±3.41 years) were recruited. Groups were comparable in age (p=0.09) and T1D duration (p=0.99). Assessment of anthropometric parameters; glycosylated hemoglobin (HbA1c), vitamin D, thyroid hormones, antibodies to thyroid peroxidase (anti-TPO), and zinc transporter8 (ZnT8A) levels was carried out. The assessment of height and body mass index (BMI) was carried out using the z-criterion (who, 2007). Results were processed using Excel 10.

Results: In the main group girls predominated (69.4%). In 46 children T1D coexisted with autoimmune thyroiditis and in 3 patients - with Graves' disease. The odds ratio (OR) of developing thyroid pathology in puberty patients was 2.381; 95% confidence interval (95% CI) 1.341-3.438; in girls - OR 3.076, 95% CI 1.487-6.362. We found higher BMI z-criteria in the main group (p=0.019) and a greater prevalence of overweight (26.5%) compared to patients with only T1D - 12.3% (p=0.029). There was a tendency to lower vitamin D levels in the main group compared to the comparison group (15.62±8.82 ng/ml vs 18.08±6.67 ng/ml, p=0.12). A higher frequency of severe vitamin D deficiency (<10 ng/ml) was noted in the children with combined endocrinopathy than in the comparison group (27.3% vs. 7.5%; OR=3.566; 95% CI

1.066-5.464, $p=0.009$). The patients of the main group with severe vitamin D deficiency were more likely in having poor glycemic control (glycated hemoglobin > 9%) compared to patients with vitamin D concentration > 10 ng/ml (OR =7.00; 95% CI 1.496-32.721, $p=0.011$). The main group showed higher levels of ZnT8A than the comparison group (643.52 ± 771.88 vs 334.43 ± 507.84 U/ml, $p=0.018$). A higher prevalence of ZnT8A>1500 U/ml was found in patients with thyroid pathology (OR=3.502, 95% CI 1.223-10.032, $p=0.019$).

Conclusion: Female gender, puberty, overweight, severe vitamin D deficiency, high level of ZnT8A were identified as the risk factors of autoimmune thyroid diseases in children with T1D.

P2-134

Does SARS-COV-2 outbreak increase diabetic ketoacidosis in new onset T1DM

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Introduction: Diabetic ketoacidosis (DKA) is a life-threatening acute complication of type 1 diabetes mellitus (T1DM) and infection is the most common precipitating factor for DKA and is responsible for more than 50% of cases.

Aim: We evaluated the frequency and severity of DKA in children with T1DM, before and during the coronavirus disease 2019 (COVID-19) outbreak, in order to identify its indirect effects on DKA incidence.

Method: A single-center, retrospective study; including children with new onset T1DM < 18 years of age was carried out. The COVID-19 pandemic group comprised those presenting from March 2020 to March 2021. The control groups included those newly diagnosed with T1DM from March 2016 to March 2020. DKA was defined according to ISPAD criteria.

Results: Whole study group consists of 199 newly onset T1DM. Demographics and clinical characteristics of patients were specified in table1. The rate of DKA at presentation was similar during the pandemic period compared to the pre-pandemic years (58,3% in 2020 vs 55.3% in 2019, 45.5% in 2018, 44.8% in 2017, 64.3% in 2016, $p=0.393$). The rate of severe DKA in the last 2 years was higher than previous years (30.4% in 2020 vs 45.7% in 2019, 24.2% in 2018, 18.5% in 2017, 17.1% in 2016, $p=0.027$).

Conclusion: No increase in DKA percentage and severity was detected during pandemic period when compared to previous 4 years. We thought that pandemic measures and lock-down did not delay the diagnosis of diabetes and did not cause disruption in the functioning of the healthcare system.

P2-135

Heterozygous mutation in the PAX4 gene: a first case description of MODY9 in Vietnam

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Maturity onset diabetes of the young (MODY) is a clinically heterogeneous disorder characterized by noninsulin-dependent diabetes diagnosed at a young age (<25 years) with autosomal dominant transmission and absence of pancreatic autoantibodies. Due to the relatively low prevalence in the general population and atypical clinical manifestations, MODY is often misdiagnosed with type 1 diabetes and type 2 diabetes. Currently, distinguishing MODY from type 1 and type 2 diabetes is still challenging for clinicians. We report 14 years old girl in an obese family. She presented with overweight (BMI 23.6 kg/m²), hypertension, and acanthosis nigricans. A fasting blood glucose was elevated and her HbA1c was 13%. Her mother has type 2 diabetes at 40 years old. At the first

		2020–2021	2019–2020	2018–2019	2017–2018	2016–2017
Newly diagnosed T1DM	(n)	48	47	33	29	42
Sex	Male	28(58,3%)	24(51,1%)	14(42,4%)	15(51,7%)	24 (57,1%)
	Female	20(41,7%)	23(48,9%)	19(57,6%)	14(48,3%)	18(42,9%)
BMI (SDS)		-0.78 ± 1.69	-0.51 ± 1.59	-0.25 ± 1.25	-0.52 ± 1.72	-0.21 ± 1.34
Age at diagnosis (years)	Mean ± SDS	8,94± 4.65	7,62± 4,54	9,53±4.27	8,88± 4,16	9,21± 4.86
	Median	30	10	10	8.5	20
Duration of symptom (day)	(min-max)	(2-90)	(1-90)	(1-90)	(4-90)	(0-90)
	<5 years	11(23.4%)	14(30.4%)	6 (18.2%)	6 (20.7%)	12(28.6%)
	6-11 years	19(40.4%)	21(45.7%)	14(42.4%)	14(48.3%)	12(28.6%)
Age group (n)	12-18 years	17 (36.2%)	11(23.9%)	13(39.4%)	9 (31.0%)	18(42.9%)
	CSII	11(22.9%)	13(27.7%)	4 (12.5%)	7 (25%)	5 (12.5%)
Treatment Modalities	MDI	37(77.1%)	34(72.3%)	28(87.5%)	21 (75%)	35(87.5%)

CSII: Continuous Subcutaneous Insulin Infusion

MDI: Multiple Dose Insulin

admission, she was diagnosed with type 2 diabetes. Insulin and metformin treatment was started. Because of side effect of metformin, we stopped it and replace with diamicron. According to ADA recommendations, we discontinued insulin after glycemic control. Then, the patient failed to reach recommended glycemic goals. After calculating the probability of a girl's MODY based on a MODY calculator with 9 criteria: diagnosed age, current age, BMI, HbA1c, being on insulin or medication, time of insulin treatment, population race, parental history, and associated syndromes, we found a probability up to 75%, thus she was consulted for genetic testing. She has a heterozygous mutation in the PAX4 c772-3del gene, a mutation in the intron region. PAX4 is an important regulator of early pancreatic development in the embryonic stage and plays an important role in the differentiation and development of islet β -cells. Insulin therapy was restarted and her glycemia improved. To our knowledge, the present case demonstrates that a mutation of PAX4 is likely to be associated with diabetes and it is the first case to be reported in Vietnam. Following the reclassification of the diabetes subtype, her family has received genetic testing counseling.

P2-136

Evaluation of the Effect of Carbohydrate Count on Nutritional Habits and Metabolic Control in Adolescents with Type 1 Diabetes

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Aim: Type 1 Diabetes Mellitus (T1DM) is a chronic disease and requires lifelong care and management. Carbohydrate (CHO) counting is one of the meal planning methods that can be preferred in the treatment of diabetes. We aimed to investigate the effect of carbohydrate counting on the nutritional habits and metabolic control of adolescents with Type 1 DM.

Subjects and Method: Patients with Type 1DM diagnosis who applied to our Pediatric Endocrinology outpatient clinic and wanted to participate in the study voluntarily were included in the study. A questionnaire form (Food Consumption Frequency Form) aimed at evaluating the nutritional habits of the patients was administered through face-to-face interviews. HbA1c level was used to evaluate metabolic control.

Results: Fifty (58% female) adolescents diagnosed with T1DM with a mean age of 13.3 ± 2.6 years (10-19) were included in the study. 54% ($n = 27$) of the cases had received CHO count training, while 42% ($n = 21$) were performing CHO count. The average age of the patients who performed the CHO count was 13.1 ± 2.3 years (10-19), 66.7% ($n = 14$) of them were female. The average age of the group that did not perform the CHO count was 13.5 ± 2.7 years (10-19), and 51.7% ($n = 15$) were female. The mean duration of diabetes was 5.2 ± 3.5 (1-12) years in the group using the CHO count, and 4.9 ± 3.0 (1-12) years in the group that did not, and did not differ between the groups ($p = 0.16$). While there was no difference between the number of daily snacks and snacks

and the amount of CHO consumed in the main meal between the group that used the CHO count and the group that did not use the CHO count, it was found that the group that used the CHO count consumed more CHO in snacks (respectively $p = 0.40$, $p = 0.37$, $p = 0.50$, $p = 0.04$). The mean HbA1c level was $8.4 \pm 1.8\%$ (6.1-13.7) in the group that used the CHO count, and $8.4 \pm 1.7\%$ (6.4-14.1) in the group that did not, and it was not different between the groups. ($p = 0.95$).

Conclusions: We found that CHO count causes an increase in the amount of CHO consumed especially in snacks in adolescents with T1DM, but does not have a significant effect on nutritional habits and metabolic control.

P2-137

Nutritional evaluation of children with type 1 diabetes on admission to the Endocrinology-Diabetology and Nutrition Department

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Introduction: Nutritional education is a cornerstone in the management of the type 1 diabetic patient in combination with insulin and physical activity. The objective of our study was to explore the nutritional profiles of type 1 diabetic children during their first hospitalization.

Materials and Methods: This is a retrospective descriptive study carried out 100 type 1 diabetic patients less than 15 years old hospitalized in the Endocrinology-Diabetology and Nutrition Department of the Mohammed VI University Hospital Center of Oujda, in the eastern of Morocco. The data collected were analyzed using SPSS 21 software.

Results: The main age was 11.1 ± 3.6 years with a sex ratio M/F at 1.17. The average BMI was $17.2 \pm 3.1 \text{ kg/m}^2$, with an average duration of diabetes of 3.1 ± 2.9 years. The HbA1c was over 10% in 40.9% of patients. Analysis of the lipid profile revealed hypertriglyceridemia in 10.8% of cases, and hypoHDLemia in 26% of cases. Fifty-six percent of patients had three main daily meals associated with a snack in 52% of cases with a notion of snacking in 50%. The diet was normo-caloric in 41% of cases. Carbohydrate intake was unsuitable in 85% of cases, with a high carbohydrate index food intake in 53%, and a misunderstanding of carbohydrate equivalence in 93% of cases. Dietary fibre intake was inadequate in 75% of patients. Only 27% of patients practiced physical exercise.

Discussion-Conclusion: A high total energy intake with poor knowledge of carbohydrate equivalence was noted in most children, which is consistent with the data in the literature. The presence of dyslipidemia can be explained by excessive lipid intake with insufficient nutritive fibre and lack of physical activity.

Therefore, dietary advice should be individualized for each child with type 1 diabetes based on age, physical activity and body size.

Correlation between antiinsulin autoantibodies and clinical presentation in T1DM

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Introduction: The pathogenetic process in type 1 diabetes mellitus includes a complex mechanism between genetic and immunological factors. Chronic autoimmune reaction relies upon the detection on autoantibodies in the patient's serum long before initiation of the disease. Autoimmune markers include mainly 4 types of antibodies - GAD65, IAA, ICA and IA-2, some present in children less than 10 years (IAA, ZnT8), and some later in life (GAD, IA-2). The presence of more than 2 autoimmune markers predicts earlier presentation of the disease, but there is no clear data between autoantibodies and severity of clinical presentation at the time of diagnosis.

Materials and Methods: A cohort of 50 children aged 3-18 years with T1DM during the first hospital admission was analyzed. The presence of antibodies was evaluated in all patients, and data were correlated with other clinical and biochemical parameters upon hospitalization. Clinical presentation of the disease in patients was classified as mild, moderate and severe ketoacidosis. Correlation between amount of autoantibodies and basic clinical data that determine severity of ketoacidosis was made with linear regression using *GraphPad Prism 9.0.0*.

Results: In most of the children at least two autoimmune markers were present. Positive antibodies GAD65 for were found in 65%; IAA in 55%; ICA in 62,5% and IA-2 in 77,5% of patients respectively. Non-significant correlation was found between all autoimmune markers and both clinical presentation and biochemical markers (HbA1C, c-peptide and insulinemia) in patients. Slightly elevated correlation was found between concentration of IAA and glycaemia.

Conclusion: concentration of all autoimmune antibodies at the time of the diagnosis of T1DM is not a good predictive factor for the progression of the disease. High values of GAD65 and ICA in patients indicate greater degree of cell destruction and therefore demand higher insulin dose.

Different schemes of insulin therapy (CSII and MDII) in children with DM1 in a Dnipro city

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Background: Due to the Ukrainian Pediatric Diabetes Register (UPDR) the number of children with DM1 0-17 y.o. in 2019 was 9860 (1 in 769), with DM2 36 (1 in 210,547) with neonatal DM (NDM) 66 (1 in 115,000), with MODY 40 cases (1 in 114,844). The diabetes prevalence rates increased from 9.3 (per 1000) in 2007 up to 12,57 (per 1000) in 2018. CSII is well established in pediatric patients with DM1. Most studies focus on such parameters as HbA1c levels, hypoglycemia and quality of life, whereas no investigation of chronic complications has been widely described.

Materials and Methods: The UPDR was created in 2004. It contains all information about children with DM1 aged 0-17 including HbA1c levels, the frequency of acute complications (diabetes ketoacidosis and severe hypoglycemia), chronic complications (cataract, retinopathy, nephropathy, peripheral neuropathy, steatohepatosis, cheiroarthropathy, angiopathy of legs etc). We studied the frequency of acute and chronic complications among 292 children aged 0-17 y.o. who were treated with CSII (n=22) vs MDII (n=270) and in different age groups (0-14 and 15-17 y.o) in the city of Dnipro.

Results: The incidence of diabetes in the city of Dnipro increased from 0.69 (per 10,000) in 2008 up to 1.07 (per 10,000) in 2018. At the same time, the pediatric population of Ukraine decreased from 10.3 million in 2002 to 7.6 million in 2018. The total number of patients with DM1 in Dnipro is 292. Among them, there are 190 children aged 0-14 years old (17 of whom receive CSII), and 102 adolescents (5 of whom receive CSII).

The results of study showed the absence of a significant difference in the frequency of diabetes complications and HbA1c levels between CSII and MDII groups ($p>0.05$), despite the fact that the duration of DM1 and age were similar.

However, a significant increase ($p<0.05$) of the frequency of complications (e.g. angiopathy of legs, peripheral neuropathy, cheiroarthropathy and HbA1c levels) was found in the 15-17 y.o. group (vs 0-14 y.o.) with the increase of the duration of DM1 ($p<0.05$).

Conclusions: The study did not reveal any difference in the frequency of acute and chronic complications and HbA1c levels among patients with DM1 treated with CSII and MDII. The frequency of chronic complications and HbA1c level increases with age and duration of DM1 ($p<0.01$). Further treatment modalities should be studied in a pediatric cohort with DM1, especially in adolescents (15-17 y.o.).

HbA1c of T1DM Patients before and after Transition - Single Center Experience

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Introduction: More than 1.1 million children and adolescents are living with Type 1 diabetes mellitus (T1DM) in 2019 world-wide¹. Transition period is considered a crucial phase in management of T1DM, where movement of adolescents to adult health care is initiated. During this period, physical, psychological and behavioral changes may make this interval becoming more challenging by which diabetes management can be affected. HbA1c worsening was reported 1-year post-transition² by which there is continuous invitation to improve the transitioning process in order to avoid any deterioration in the management of diabetes and keeping the momentum.

Aim: Retrospective evaluation of HbA1c; 2 years before and 2 years after transition of patients living with T1DM.

Method: Retrospective Cohort study included all transitioned patients in 2017 and 2018 (Total 22 patients, 3 lost follow up). Their HbA1c results were reviewed two year before and after the transition. Data were obtained from Sultan Qaboos University Hospital electronic medical records. Data was analyzed by using SPSS and Excel.

Results: Total of 22 patients with T1DM transitioned to adult care, three of them lost follow up. 19 patients were included in our study (11M). Median age at transition was 16 years, ranged between 14 and 18 years.

Median HbA1c showed a steady improvement over 2 years before transition, from 77.2 to 73.8 mmol/mol (9.21% to 8.9%) in the last visit during pediatric follow up. But then a sudden worsening of HbA1c was observed one year after transition, median 76.9 mmol/mol (9.19%). These results could be attributed to multiple factors, but mainly the lack of a proper transition process.

Conclusion: Transition period is a crucial interval that needs extra attention. Those results motivated both paediatric and adult diabetology teams in our center to take active steps towards a structured transition process.

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Glycated Hemoglobin Variability and Microvascular Complications in Patients with Type 1 Diabetes Mellitus

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Introduction-Objective: Nephropathy, retinopathy, neuropathy are long-term microvascular complications of diabetes. Glycated hemoglobin (HbA1c), used as a glycemic control indicator, have proven to be indicative in the development of microvascular complications. In this study, the contribution of HbA1c variability to complication development was evaluated.

Method: Twenty one cases with type 1 diabetes mellitus (T1DM) who developed microvascular complications and 39 cases without complications, that were similar in terms of age, gender, age of diagnosis, insulin treatment regimen, insulin doses (U / Kg), and mean HbA1c (%) levels were included in the study. Student t test and Mann Whitney U methods were used for statistical analysis and ROC analysis were used to determine limit values.

Results: Mean age of 21 cases (15 girls, 6 boys) who developed microvascular complications was 18.11 ± 4.39 years, and the mean duration of diabetes was 5.87 ± 3.93 years. Mean age and duration of diabetes of 39 control patients (24 girls, 15 boys) were 13.25 ± 5.22 and 4.63 ± 3.33 years respectively. Nephropathy was detected in 17 cases, neuropathy in 8 cases, and retinopathy in 1 case. Nephropathy occurred at a mean age of 11.52 ± 4.12 years; neuropathy at 14.13 ± 5.68 years and retinopathy at 18.41 years. Mean age of Type1 DM diagnosis in the complication group was 5.87 ± 3.93 years and 4.63 ± 3.33 years in the control group ($p = 0.20$). Insulin infusion pump therapy (CSII) was initiated 3.12 ± 2.91 years after the diagnosis of diabetes and mean duration of CSII use was 7.45 ± 3.78 years. In the complication group 40% of the patients and in the control group 32.5 % were using CSII.

The mean HbA1c during follow up was similar in both of the groups ($8.60\% \pm 0.63$ vs $8.84\% \pm 1.32\%$). Adjusted HbA1c-Standard deviation (SD) and HbA1c-Variation coefficient (CV) values were 1.30 ± 0.65 and 14.36 ± 6.23 in the group with complications, and 0.91 ± 0.37 and 10.59 ± 4.01 in the control group ($p < 0.05$). In the ROC-analysis for microvascular complications, the limit value HbA1c-CV value was 11.99. (sensitivity: 61.9%, specificity: 71.9; Youden index J: 0.3370). This value for HbA1c-SD was 0.9699. (sensitivity: 71.43%, specificity: 66.67; Youden index J: 0.3810)

Conclusion: This study has shown that long-term fluctuations in HbA1care associated with the development of microvascular complications in type 1 diabetes. However, new studies with more patients are needed in this area.

Affective response of newly diagnosed Type1 diabetes parents: An experience of a developing country

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Background & objectives: An important aspect of managing type 1 diabetes is to identify and address the apprehensions of patients and parents of newly diagnosed type 1 diabetes. Understanding parental difficulties in managing type1 diabetes and promptly dealing them will surely affect the short and long-term outcome in children.

The aim of this study was to determine the affective response of parents after the diagnosis of type 1 diabetes in a developing country like Pakistan.

Methods: Questionnaire analysis of economic and psychosocial aspects of all newly diagnosed type 1 diabetes parents presenting in a tertiary care unit.

Results: A total of 79 parents were enrolled in the study. The monthly family income of 66/79 (83%) children was less than Rs.50,000 while 10/79 (13%) had more than Rs.50,000 and only 3/79 (4%) had income more than Rs.100,000. The economic standards were used in view of the economic background and their income level which added to their psychosocial stresses in the management of children on one hand and economic support on the other for sustainable health of the child.

62/79 (78%) parents felt depressed, 11/79 (14%) felt sense of guilt and 6/79 (8%) were in denial after diagnosis. 73/79 (93%) were not accepting injectable insulin as first line treatment and wanted to try some other form of treatment like oral medications and homeopathy mainly because of financial constraints. 66/79 (83%) of parents main concern was regular injections and continuous glucose monitoring. This was again due to affordability of glucose strips and insulin injections. Therefore these 83% families asked for complete financial support for treatment of their child while 4% needed only partial support.

All parents showed concerns about their child life expectancy and long-term medical complications. 64/79 (81%) were worried about coping of studies and schooling with type1 diabetes, 6/79 (8%) about their marriage and 2/79 (3%) about future career and jobs. 55/79 (69%) parents were inquiring about inheritance and worried about chances of sibling to be affected.

Conclusion: Parents of type 1 diabetes are prone to psychosocial affects with depression being the most common followed by sense of guilt and denial. Main stressing aspect was daily insulin injections, regular 4-6 times monitoring with pen-pricks fear, affording of glucose monitoring strips and their impact on child's daily life, schooling, physical activities and psychological well-being.

Short-term glycaemic changes from continuous glucose monitoring among children and adolescents with type 1 diabetes mellitus during fasting in Ramadan month

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Objectives: The study aimed to observe and compare the short-term glycaemic outcome among Muslim type 1 diabetes mellitus (T1DM) children and adolescents using retrospective continuous glucose monitoring (CGM) before and during Ramadan month. The selection of retrospective CGM over real-time CGM conferred the benefit of representing the actual glycaemic impact of Ramadan fasting, especially relevant to developing Muslim nations that have less access to personal CGM.

Methodology: This observational prospective study was conducted in both Hospital Putrajaya and Hospital Universiti Sains Malaysia in west and east peninsular Malaysia, respectively, from February to May 2020, including Ramadan (23/4/20-23/5/20). Muslim T1DM children and adolescents who intended to fast were included. They were given structured pre-Ramadan focused education and standardised glucometers (Contour Plus One®) with glucose strips for self-monitoring of blood glucose (SMBG) at home. IPro2® (Medtronic) was used for retrospective CGM. All participants were followed up and advised to break their fast when indicated.

Results: Due to COVID-19 pandemic, out of the initial 32 participants, 8 were dropped, as 4 defaulted and another 4 had incomplete CGM pairs. Only 24 participants were analysed. Mean age was 13.6 ± 3.06 years old and mean baseline HbA1c $9.6 \pm 1.85\%$. 91.7% were on multiple daily injections (MDI) and 8.3% on continuous subcutaneous insulin infusion (CSII). Mean basal insulin dose was 0.34 ± 0.11 unit/kg/day during Ramadan compared to 0.41 ± 0.12 unit/kg/day before. SMBG frequency was 3.8 ± 0.8 times-per-day during Ramadan and 3.9 ± 0.7 times-per-day before. All had fasted successfully for at least 7 days during CGM period and none had required emergency visits or hospitalisations. Total sensor readings were 1613.9 ± 416.1 during Ramadan and 1739.8 ± 366.9 before. Mean absolute relative difference (MARD) was $15.0 \pm 9.45\%$ during Ramadan and $14.3 \pm 7.69\%$ before. Further CGM analysis had indicated increases in time in non-severe hyperglycaemia (level 1; $>10\text{mmol/L}$), mean sensor glucose and estimated A1c during Ramadan fasting as compared to the non-fasting period before. However, no difference was observed between both periods for time in severe hyperglycaemia (level 2; $>13.9\text{mmol/L}$), time in mild hypoglycaemia (level 1; $<3.9\text{mmol/L}$), time in severe hypoglycaemia (level 2; $<3.0\text{mmol/L}$) and time in range (level 1; $3.9\text{--}10.0\text{mmol/L}$).

Conclusion: Muslim T1DM children and adolescents who were given pre-Ramadan focused education and compliant to SMBG could fast safely during Ramadan without short-term glycaemic deterioration, except for the increase in non-severe hyperglycaemia that reflects the general approach taken to buffer the greater concern of hypoglycaemia.

Is Type 1 Diabetes Mellitus Predictable? Investigation of Predictive Markers in Siblings of Proband with Newly Diagnosed Type 1 Diabetes Mellitus

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Background/Aim: Type 1 diabetes Mellitus (T1DM) often presents with clear clinical signs after a long-term asymptomatic autoimmune process. This long and silent period has been leading to an increase in awareness day by day in order to prevent and predict the development of the disease. Among the well-known genetic and environmental risk factors, close relatives of the index cases constitute a population that is quite suitable for predicting and preventing the development of T1DM. There is an increased risk of T1DM for first-degree relatives of patients that endure into the advanced years. This study focused on the clinical characteristics, serological and biochemical predictive markers that reflect the potential risk for T1DM in the asymptomatic siblings of index patients with newly diagnosed T1DM

Materials and Methods: A total of 112 siblings of 82 index cases were included in the study. The siblings consisted of 69 healthy asymptomatic and 43 T1DM children. The following serological and biochemical markers were screened: Islet cell antibodies containing HbA1C, C-peptide, anti-glutamic acid decarboxylase (anti-GAD), anti-insulin (anti-IA), and islet cell antibodies (anti-ICA). Participants were classified into three groups according to the age group screened: 0-4, 5-10, and ≥ 11 years. Three groups were evaluated in terms of clinical serological and biochemical markers. The following criteria were considered as risk factors: At least one antibody positivity, C-peptide $< 0.4 \mu\text{g/L}$ and HbA1C > 5.7 .

Results: The seropositivity rates for anti-GAD, anti-ICA and anti-IA in patients with T1DM (index cases plus siblings of index cases) were 58%, 37.3%, and 33.33%, respectively. At least one autoantibody for islet cell antibodies was positive in 5 (7.2%) of the asymptomatic siblings, while HbA1C levels were found above 5.7 in 14 (20.2%) of them. C-peptide level was not low in any of the asymptomatic siblings.

Conclusion: This study showed that siblings of index cases had high rates of islet cell antibody positivity and high HbA1C levels, indicating the need for long-term close follow-up in terms of predicting, preventing, and even evaluating potential therapeutic options in siblings of index cases with T1DM.

Dealing with hypoglycaemia during acute DKA management by paediatric residents from Bahrain, Iraq and Saudi Arabia

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Introduction: During management of Diabetic ketoacidosis (DKA), and after starting the insulin infusion, it is crucial to monitor the blood glucose level frequently. If the glucose level drops quickly or below certain limit when there is still an evidence of ketonemia, it is recommended to add dextrose to the maintenance fluids and continuing the insulin infusion to switch off the ketosis process. However certain measures are required when the glucose continues to drop, and the patient becomes truly hypoglycaemic with a glucose level below 4mmol/L. These measures include giving a dextrose bolus intravenously, stopping the insulin infusion temporarily and adding more dextrose to the maintenance fluids.

Objectives: This study aims to evaluate the performance of Bahraini, Iraqi, and Saudi paediatric residents throughout their different levels of training (year 1 to 4), regarding how to manage a DKA patient who drops a glucose below 4mmol/L whilst the patient is still ketonemic and still on intravenous fluids and insulin.

Methods: An online survey using SurveyMonkey was sent out to the paediatric residents practicing in Bahrain, Iraq, and Saudi Arabia between May and July 2020, giving a scenario to evaluate their management when a DKA patient drops the glucose below 4mmol/L. Responses received anonymously.

Results: 142 residents responded (41 from each Bahrain and Iraq, and 60 from Saudi Arabia). Correct answers were given by only 19%, 22% and 27% of the responded Iraqi, Saudi, and Bahraini paediatric residents respectfully. 15%, 24%, and 32% of Saudi, Bahraini and Iraqi residents respectfully preferred giving a dextrose bolus intravenously only, and 10-12% of the responders wanted just stopping the insulin infusion temporarily. Majority of the residents (90%, 83%, and 66% from Iraq, Saudi Arabia, and Bahrain) feel that further educational sessions about details of DKA management is definitely needed. Whereas the rest may attend such educational activities if provided.

Conclusion: Gap in knowledge of managing hypoglycaemia during the treatment of DKA was evident among junior and senior residents from the three studied countries. Further training and education are recommended, and perhaps adding more details about management of hypoglycaemia to the existing protocols in the studied countries will raise more awareness and give guidance on dealing with the possible outcomes and complications.

A Rare Clinical Case Of A Combination Of Monogenic And Autoimmune Diabetes Mellitus

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Introduction: Type 1 diabetes mellitus (T1D) is the most common form of carbohydrate metabolism disorder in childhood. There are also monogenic forms of diabetes. In the world literature, there are isolated mentions of the combination of monogenic and autoimmune forms of diabetes mellitus.

Clinical Case: A 10-year-old obese patient presented with hyperglycemia. At hospitalization: height 168 cm, weight 87 kg, SDS BMI +3.0. Glycemia 14.4 mmol/l, HbA1c - 8.9%. Mixed-meal tolerance test (MMTT): fasting glucose 12.8 mmol/l, C-peptide 2.46 ng/ml; after 2 hours - glucose 17.2 mmol/l, C-peptide 3.21 ng/ml. GAD autoantibodies - 4.5 U/ml (N 0-1), IA-2 - 25 U/ml (N 0-1). HLA typing: DRB1*01:07-DQA1*0101,0201-DQB1*0501:0201 (haplotypes: predisposing and neutral). The patient was diagnosed with T1D and started on insulin therapy at a daily dose of 0.2 U/kg.

On examination at the age of 11: height 174 cm, weight 108 kg, SDS BMI +3.35, HbA1c 10.6%. The daily dose of insulin was 0.95 U/kg/day. Due to the presence of obesity and intact insulin secretion, metformin was started at a dose of 1000-1350 mg/day. The daily dose of insulin was reduced to 0.60-0.65 U/kg.

At the age of 15: height 168.5 cm, weight 90 kg, SDS BMI +3.4; HbA1c 10.7%; MMTT: fasting glucose 9.5 mmol/l, C-peptide 0.83 ng/ml; after 2 hours - glucose 17.6 mmol/l, C-peptide 1.66 ng/ml. Autoantibodies: ZnT8 72.9 U/ml, IA-2 81.6 U/ml, GAD 44.6 U/ml.

We believe the patient has high HbA1c levels due to low compliance, as glycemia were always stable (4-10 mmol/l) in the hospital when the patient maintained the diet and insulin therapy.

Whole exome sequencing revealed a likely pathogenic heterozygous variant c.40-41dupGC (p.Val15GlnfsTer41) in the *KLF11* gene.

Mutations in the *KLF11* gene may lead to MODY7. To date, fewer than 10 mutations in the *KLF11* gene have been described, and therefore, data on the clinical picture are rather scarce. Basically, the disease proceeds similarly to type 2 diabetes. Although, there are references to insulin requirements.

Conclusion: This clinical case is a combination of monogenic and autoimmune diabetes mellitus. We suppose the patient presented with MODY7 at first with later onset of autoimmune diabetes mellitus due to mild disease course, relatively low titer of

pancreatic autoantibodies, average T1D risk based on HLA typing, and presence of insulin secretion at the beginning.

Thrombocytopaenia induced by diazoxide treatment in a toddler with Hyperinsulinism-Hyperammonemia syndrome: a rare side-effect

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Introduction: Diazoxide is the first-line drug for Hyperinsulinemia-Hyperammonemia (HI/HA) syndrome, a disease due to a mutation in the glutamate dehydrogenase-1 (GLUD1) gene. Diazoxide, an opener of the pancreatic β -cells KATP-channels reducing insulin release, is uncommonly associated with thrombocytopaenia.

Aim: We describe a toddler with HI/HA syndrome who developed thrombocytopaenia on diazoxide treatment.

Subjects and Methods: A 13-month-old boy was transferred to our department from a District Hospital (DGH) due to two episodes of tonic-clonic seizures associated with loss of consciousness, staring, hypoglycaemia (blood glucose (BG) 32mg/dl (1.7mmol/l)). Treatment was intravenous (iv) Dextrose and oral feeds; continued to have asymptomatic hypoglycaemia (BG <60mg/dl (3.3mmol/l)). On admission, he was alert, had normal physical examination and development, growth (15th percentile). He was born at 39 weeks gestation, small for gestational age (birth weight 2210gr), first child of unrelated parents. His 28 year-old mother had epilepsy since the age of five years old, on antiepileptics; father 45 years old, healthy. Episodes of sweating, restlessness, and upper limbs tremor were reported the last four months prior to admission. Hypoglycaemia screen when BG 36mg/dl (2mmol/l) revealed inappropriately high insulin and C-peptide levels (17,8 μ IU/ml and 3,3ng/ml respectively) with negative blood and urine ketones. Septic screen was negative, cortisol, thyroid function, growth hormone, metabolic screen, carnitine, acylcarnitine, imaging studies, electroencephalograph were normal. Hypoglycaemia and hyperammonaemia (92mmol/l) were confirmed by a glucagon and protein-loading test leading to a suspected diagnosis of HI/HA syndrome. He was treated with iv dextrose 10%, oral feeds and oral diazoxide (max dose 6.7mg/kg/d) and hydrochlorothiazide (7 mg/kg/d). He responded well to medication and was discharged. He presented at the DGH on day 12 of diazoxide treatment with a two-day history of petechial rash and nose bleeds, no signs of infection. Platelet count (PLT) was 2K/ μ L (NR 150-450K/ μ L); treated with corticosteroids. On re-admission PLTs were 4K/ μ L; he received iv platelets, immunoglobulin, prednisolone, diazoxide was discontinued. On day 5 PLTs increased to 226K/ μ L, he had hypoglycaemic episodes. Diazoxide was replaced with octreotide and later with lanreotide. He has been well since with no hypoglycaemia +/- seizures, growth is on the 5th centile; normal development.

Results: Genetic testing confirmed HI/HA syndrome to the patient and his mother. The thrombocytopaenia was ameliorated five days after diazoxide discontinuation (PLT 226 K/ μ L).

Conclusions: Diazoxide is a well-tolerated, oral medication for hyperinsulinaemic hypoglycaemia, thrombocytopenia is a rare side effect. In such cases, second-line treatment with other agents, such as octreotide, may be required. A full blood count should be obtained periodically.

P2-148

Nephrotic Syndrome and Type 1 Diabetes: a Therapeutic Approach

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Background: Paediatric nephrotic syndrome has an estimated incidence of 2 per 100,000 children per year and type 1 diabetes had a reported incidence of 9.5 per 100,000 inhabitants in Portugal (2018 data). To the best of our knowledge, the simultaneous occurrence of nephrotic syndrome and type 1 diabetes is rare – we found 13 published cases in paediatric age worldwide.

Clinical Case: A 5-year-old boy with personal history of nephrotic syndrome was admitted to the emergency department with complaints of palpebral oedema and proteinuria (+++) in the urine dipstick test. At admission, he was stable, with no alterations in his physical exam besides the palpebral oedema. Urinalysis showed protein (+++) and glycosuria (+++++) by dipstick. He denied polyuria, polydipsia, weight loss and polyphagia. Further blood evaluation reported cetoneuria 1.2 mmol/L, HbA1C 8.6%, insulin 2.0 pmol/L and blood gases without alterations. The child was diagnosed with relapsing nephrotic syndrome and inaugural type 1 diabetes without ketoacidosis. Oral prednisolone 60 mg/m²/day and multiple insulin injection therapy were started. It was challenging to maintain glycaemia on the target during corticoid treatment. When he started to take it every other day, our option was to diminish 10% of the basal insulin in the days without corticoid, with satisfactory results (HbA1 7.6%). Eight months after the diagnosis, continuous subcutaneous insulin infusion was initiated, achieving a HbA1C of 6.5% with a total daily dose of insulin of 0.68 IU/kg, without corticoid. In his latest nephrotic syndrome relapse it is reported a better glycaemic control, achieved using temporary basal rates in the insulin pump (HbA1 7.3%). To note that total daily dose of insulin increased to 1.14 IU/kg. In addition to the described, he exhibited positivity for human leucocyte antigen (HLA) DQA1 and DQB1, both associated with DQ2 heterodimer.

Conclusions: The aim of this case is not only to report a new case of nephrotic syndrome and type 1 diabetes mellitus, but also to make known a different approach concerning patients with diabetes mellitus insulin-treated and nephrotic syndrome. We report a better glycaemia control with insulin pump compared to multiple insulin injections in our patient, besides stating our approach during corticosteroid progressive weaning when in multiple insulin injection therapy.

P2-149

Assessment of the percentage of T lymphocytes and B lymphocytes with the expression of selected activation markers in patients with type 1 diabetes mellitus depending on the presence of antibodies against EBV antigens

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Introduction: After contact with the antigen, lymphocytes require activation for proliferation and differentiation into effector cells. Activation of lymphocytes results in the expression of activation markers.

The CD69 antigen appears first on the surface of lymphocytes. This occurs one hour after receiving the activation signal. The CD69 molecule acts as a cellular stimulating signal, causing further activation and proliferation of cells, stimulating the synthesis and release of cytokines, and the induction of the CD25 molecule.

At a later stage, about 2 hours after the recognition of the antigen, the CD25 molecule appears on the surface of activated lymphocytes. The CD25 antigen plays the role of the interleukin-2 receptor alpha chain, thus participating in the proliferation of T cells.

Materials and Methods: The study included 43 children diagnosed with type 1 diabetes, hospitalized at the Department of Pediatric Endocrinology and Diabetology, Medical University of Lublin. This group included 21 girls and 22 boys. The age of children during the tests ranged from 3.9 to 18 years.

The material for the research was venous blood in the amount of 9 ml. The collected material was used to evaluate the immunophenotype of cells with regard to activation markers (CD69 and CD25) by flow cytometry.

Results: A significantly lower percentage of CD8 + T cells expressing the CD 69 antigen was demonstrated in the group of patients with anti-VCA IgG antibodies compared to the group of patients without IgG anti-VCA antibodies ($p = 0.029$). However, no differences were found in the percentage of T and B lymphocytes expressing the CD69 antigen in people with type 1 diabetes depending on the presence of anti-VCA IgM antibodies and anti-EBNA-1 antibodies in the IgG class.

In the group of patients with type 1 diabetes with anti-EBNA-1 antibodies in the IgG class, a significantly lower percentage of CD8 + T cells expressing the CD25 antigen was demonstrated ($p = 0.042$). There were no significant differences in the percentage of T and B lymphocytes expressing the CD25 antigen in people with type 1 diabetes depending on the presence of anti-VCA IgM antibodies and anti-VCA IgG antibodies.

Conclusions: The finding of a lower percentage of CD8 + T cells with the expression of the CD69 molecule and the expression of the CD25 + molecule in patients with antibodies to EBV antigens may indicate a limited control of the immune system in the course of EBV infection in these patients.

PIMS-TS [Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 (Covid-19)] in a child with new onset type 2 diabetes

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Introduction: PIMS-TS [Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2] is a unique clinical complication of COVID-19 infection in paediatric patients. We report a case of a child presenting with PIMS-TS and new onset type 2 diabetes.

Presentation: A previously healthy 15 year old boy of Bengali-Indian origin presented to the hospital with polyuria, polydipsia, dry cough, abdominal pain and 1 episode of haemoptysis. He was febrile and tachycardic. Blood glucose was 41mmol/l but he was not ketotic or acidotic. Diabetes was diagnosed and he was started on subcutaneous insulin. Diabetes antibodies were negative, c-peptide was raised, he was obese with acanthosis nigricans and a strong family history of type 2 diabetes. A diagnosis of type 2 diabetes was made.

He was started on antibiotics and initially temperature settled but tachycardia and tachypnoea persisted, he also became hypotensive with lactic acidosis. Inflammatory and cardiac markers for PIMS-TS came back significantly elevated along with abnormal coagulation studies. His neurological status deteriorated and hypertonic saline was given. CT scan of the brain was normal and his neurological status returned to normal in 12 hours. Echocardiogram showed globally severely impaired biventricular systolic and diastolic function hence inotropic support was started. He tested positive for SARS-CoV2 IgG antibodies.

Management: As he fulfilled the criteria for PIMS-TS, he received treatment with Methylprednisolone as per RECOVERY trial regime with prophylactic dalteparin and low dose aspirin. Due to the increasing level of glucose, he was switched to IV insulin. His diabetes management was quite challenging as he had significant insulin resistance and needed IV insulin doses of up to 2 units/kg/day. Requirements improved once Methylprednisolone was discontinued. 72 hours after treatment with IVIG and methyl prednisolone, his clinical course improved and inflammatory markers gradually normalised. His final insulin dose on discharge was 1.2

units/kg/day. Metformin was not started due to initially deranged liver function tests.

Discussion: This is the first reported case of new onset type 2 diabetes and PIMS-TS. The patient had symptoms of diabetes before presenting to the hospital and would have eventually presented with diabetes, but the hyperinflammatory pathway of PIMS-TS may have accelerated the process. Interestingly, he did not develop diabetes ketoacidosis. Low grade inflammation seen in obesity could have contributed to presentation. Corticosteroids used to treat PIMS-TS along with increased hepatic glucose production through increased counter-regulatory stress hormones made management quite challenging.

The impact of COVID-19 lockdown on glycaemic control and BMI in children with type 1 diabetes mellitus (T1DM)

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Introduction: National lockdowns to prevent the spread of coronavirus disease (COVID-19) in United Kingdom was first introduced in March 2020. Consequently, the routine management of children and young people with Type 1 diabetes mellitus (CYPD) changed with a move towards virtual clinics. The period also resulted in lifestyle changes relating to reduced physical activity and dietary habits. To-date there is little data on the effects of lockdown on BMI and HbA1C in CYPD (see ref). There are no reports from the UK. We undertook this local study to investigate the effects of the lockdown on HbA1C and BMI of children with T1DM

Methods: A retrospective analysis of children with T1DM attending the Paediatric-diabetes service in an inner-city hospital. We included CYPD with paired values of hospital-measured BMI and HbA1C during 2 periods covering pre and post-lockdown (January-June 2020 versus November2020-April 2021). Children without paired values were excluded. HbA1C is expressed in DCCT% units. BMI calculated in absolute values, given the short study period.

Results: 49 children with T1DM were included (55% male and 45% female, mean age of 12.86 years (range 4-18 years). The mean duration of diabetes was 6.39 ± 3.13 years. 21/49 (42.8%) patients had an increase of HbA1c $>0.5\%$ (range 0.5- 3.7%) whilst 8/49(16%) patients showed an improvement in HbA1c $>0.5\%$ (range 0.5-2.4%). There was a non-significant trend to higher HbA1C in the second period compared to the first (8.74 ± 1.76 vs 8.53 ± 1.91 ; mean-difference 0.02 ± 1.29 ; $p=0.27$). Patients who had a decrease in their mean HbA1c had better control prior to lockdown (8.86% vs 10.66% ($p=0.004$)). The mean change in BMI was $+1.21$ kg/sqm (range -2.9 to 9.0 kg/sqm) in absolute values, with a pre-lockdown mean BMI of 19.90 ± 4.39 kg/sqm versus 21.11 ± 5.10 kg/sqm in the post lockdown period.

Discussion: COVID-19 lockdown was not associated with a significant worsening of glycaemic control in CYPD. BMI trended upwards during lockdown, although not statistically significant.

Further evaluation of the effect of the pandemic on BMI and HbA1C should be studied carefully through national audits. This will also reflect the impact and analysis of virtual clinics.

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P2-152

Timing of Consulting Paediatric Endocrinologist or Diabetologist During the Management of Acute DKA; Response of Bahraini, Iraqi, and Saudi Paediatric Residents

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Introduction: Diabetic ketoacidosis (DKA) is a known complication of diabetes mellitus, mainly type 1. It is a medical emergency condition. The recent British paediatric DKA guideline clearly recommends involving a senior clinician at time of diagnosis, usually either an emergency medicine or general paediatric doctor. There is no clear recommendation of when to consult the on-call paediatric endocrinologist or diabetologist who covers the admission of diabetic cases.

Aim: This comparative analytic study aims to review the response of Bahraini, Iraqi, and Saudi paediatric residents throughout their different levels of training, regarding when they would consult the on-call consultant covering diabetes.

Methods: An online survey was sent out to the paediatric residents practicing in Bahrain, Iraq, and Saudi Arabia between May and July 2020. The questionnaire included a question asking about the timing of when to consult the paediatric endocrinologist during management of acute DKA, giving them four different options.

Results: 142 residents responded to this questionnaire (41 from Bahrain, 41 from Iraq and 60 from Saudi Arabia). Majority do involve their seniors at time of diagnosis but timing to consult the paediatric endocrinologist varied (Table 1). The highest responses of consulting the endocrinologist whilst the patient is still in the emergency room received from the Saudi residents (28, 47%). 12 residents from Bahrain (29%) would run the consultation only if the child requires intensive care unit admission and 29% of Iraqi residents were not sure when to consult.

Table 1. Variable responses of residents to a question of 'When to consult the endocrinologist during management of DKA?'

	Bahraini residents (n=41)	Iraqi residents (n=41)	Saudi Residents (n=60)
Whilst the patient is still in emergency room	12 (29%)	16 (39%)	28 (47%)
Within 2 hrs of admitting the child	10 (24%)	7 (17%)	12 (20%)
Only if the child required PICU admission	12 (29%)	6 (15%)	9 (15%)
Not sure	7 (17%)	12 (29%)	11 (18%)

Conclusion: There was a noticeable variation of approaches from the paediatric residents. Uncertainty of when to consult the on-call clinician who covers diabetes was evident. Exploring the practice from different countries would be warranted and a recommendation from the international societies could be useful to unify the approach and ensuring patients' safety.

P2-153

Prevalence and factors associated with microalbuminuria in type 1 diabetic children and adolescents on follow up at Pediatric Endocrinology Clinic in Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia

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Background: An increased urinary albumin excretion rate of 30 to 300 mg/24h (microalbuminuria) constitutes an early stage of nephropathy, especially when it becomes persistent. The main modifiable initiation and progression factors of diabetic nephropathy are hyperglycemia and hypertension. There is limited information on the burden of diabetic nephropathy in developing countries. To date there are no studies that show the magnitude of microalbuminuria in the pediatric population of Ethiopia with only very few in Africa. This study aimed to determine the prevalence and factors associated with microalbuminuria among diabetic children and adolescents attending an outpatient clinic in Addis Ababa, Ethiopia.

Objective: This study determined the prevalence of microalbuminuria and associated factors among type 1 diabetic patients attending paediatric endocrinology follow up clinic (PEC) at Tikur Anbessa Specialized Hospital.

Methodology: This is a cross sectional hospital based descriptive study which was conducted among T1DM patients aged 11 years and above at the study period and had at least 2 years of diabetic duration. The children were consecutively recruited from paediatric endocrinology clinic between May 1, 2017 and July 30, 2017. Structured questionnaires were used to collect socio-demographic characteristics and information pertinent to diabetes. Spot urine was used to determine microalbuminuria using Combilyzer13

automated urine analysis machine. Retinopathy and neuropathy screening was done for all patients with microalbuminuria.

Results: A total of 120 T1DM children were recruited into this study. Sixty two (51.7%) were female. Mean age of participants was 14.3 ± 2.2 years. 67 children (55.8 %) had poor glycemic control. Thirteen children (10.8%) had persistent microalbuminuria. Prevalence of persistent microalbuminuria was noted to be significantly higher among children with poor glycemic control ($p < 0.02$). Those with and without persistent microalbuminuria did not differ significantly in age, age at onset of diabetes and diabetes duration.

Conclusion: This study highlights the difficulties of achieving good glycemic control and the early occurrence of persistent microalbuminuria in Ethiopian diabetic children.

P2-154

Neonatal Diabetes Secondary to Isolated Pancreatic Agenesis

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Background: Pancreatic agenesis has been reported as a cause of neonatal diabetes. Most commonly it was associated with severe neurodevelopmental problems caused by homozygous mutations in the transcription factor PTF1A. Isolated pancreatic agenesis was related to biallelic mutations in an enhancer located near PTF1A gene, which suggests that the enhancer is tissue specific to the pancreas.

PDX1 is another transcription factor gene in which biallelic mutation resulted in neonatal diabetes in the absence of exocrine pancreatic insufficiency.

Case Report: 2 siblings (Currently, 16 and 13 years old) from consanguineous parent diagnosed with early onset neonatal diabetes. They presented on the first 2 days of life with high blood glucose not related to stress or medications and started on Insulin during the first week. Insulin doses were adjusted based on their need. Clinically, there were no dysmorphic features or impaired neurological manifestations.

Throughout their clinical course, they were evaluated for short stature and failure to thrive. Celiac screening was positive in the older boy but negative for the girl. They were complaining of recurrent foul-smelling diarrhea, diagnosed with malabsorption and ADEK vitamins deficiency and started on replacement therapy. US abdomen showed pancreatic agenesis.

With treatment, their diabetes was controlled, but they ended-up short and the diarrhea persist. Whole exome sequencing showed a homozygous missense mutation (exon1: c.571C>A: p.P191T) in both siblings causing isolated pancreatic agenesis. This mutation

had been reported once as hypomorphic PTF1A mutation in four individuals from two separate families from Saudi Arabia and Kuwait with same presentation.

Conclusion: Hypomorphic PTF1A missense mutations can cause isolated pancreatic agenesis. This mutation should be considered in patients presenting with neonatal diabetes without neurological manifestations especially in a child with consanguineous parent. Patients with this mutation has been reported in our region which could be a founder mutation.

P2-155

Dyslipidaemia in children with type 1 diabetes mellitus

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Dyslipidemia is one of the major risk factors for cardiovascular disease in diabetes mellitus. The characteristic features of diabetic dyslipidemia in adults are a high plasma triglyceride concentration, low HDL cholesterol concentration and increased LDL cholesterol. Dyslipidaemia in children with type 1 diabetes mellitus (T1D) have been little studied (P. Lozano et al., 2016; J. D. Schofield et al., 2016; M. Kinoshita et al., 2018; C. Elkins et al., 2019). DECODE studies (Diabetic Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe, 2003) have shown that postprandial hyperglycemia and postprandial hypertriglyceridemia is strongly associated with occurrence of cardiovascular diseases.

Purpose: To study the features of changes in the blood lipid levels in children with type I diabetes.

Patients and Methods: The blood lipid and lipoprotein spectrum was biochemically studied in 60 children with T1D aged 6-19 years. The total cholesterol, triglycerides, lipoproteins of the low density (LDL) and high density (HDL) and glycemic profile were determined. The study was performed in accordance with the Declaration of Helsinki. Data was analyzed using SPSS Statistics v 24.0.0.0. A $p < 5$ was considered to be statistically significant.

Results: Depending of the level of postprandial glycemia (PPG) all patients were divided into three groups: group I – with PPG 5-10 mmol/l and group II – children with PPG >10 mmol/l. In group I dyslipidemia was determined in 16%, in group II – in 71% ($p < 0.001$). Hypercholesterolemia, hypertriglyceridemia and low HDL were present in surveyed patients. Hypertriglyceridemia was positively correlated with PPG level in group II ($r = 0.55$).

Conclusions: Hypertriglyceridemia and low HDL cholesterol is common in children with T1D and high postprandial glycemia levels (above 10 mmol/l). This suggests that children with T1D, high postprandial glycemia levels and dyslipidemia need specific management.

P2-156**The relationship between metabolic parameters atherogenic parameters, atherogenic index and vitamin D levels in children with insulin-dependent diabetes mellitus**

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Objective: Vitamin D plays an important role in hyperlipidemia, cardiovascular disease risk, and glucose/insulin metabolism. The aim of this study is; to investigate the relationship between serum vitamin D levels and metabolic profiles of children with T1DM, atherogenic index, and cardiovascular disease risk.

Materials and Methods: T1DM patients were included in the study retrospectively. Anthropometric and clinical measurements, biochemical parameters, atherogenic plasma index (AIP) values, and serum vitamin D levels were evaluated.

Results: The study included 307 diabetic patients, 152 (49.5%) females and 155 (50.5%) males, with a mean age of 11.5±3.87. Vitamin D deficiency (77.5%; (n=193)) was detected in the majority of our patients. The mean daily insulin dose of patients with low vitamin D levels was 0.91±0.31 U/kg/day; mean hemoglobin A1C (HbA1C) level 11.77%; in those with normal vitamin D levels, the mean insulin dose is 0.94±0.28 U/kg/day; the HbA1C level was found to be 12.19% (p>0.05).

While the mean AIP level in females was 0.28±0.33; it was 0.25±0.31 in males (p>0.05). While the mean AIP of cases with vitamin D deficiency was 0.29±0.31, the mean of AIP in those without vitamin D deficiency was found to be 0.13±0.28 (p<0.001).

Conclusion: AIP was higher in patients with vitamin D deficiency. According to the data obtained as a result of the study; low vitamin D and high AIP levels are important predictors of cardiovascular complications. It is thought that close monitoring of these parameters will be a guide in preventing long-term morbidity in children with T1DM.

and lipaemia retinalis. Severe hypertriglyceridemia likely accounts for 1-10% of acute pancreatitis cases in adults but there is limited data in children. We report a case of new-onset type 1 diabetes mellitus (T1DM) presenting in diabetic ketoacidosis (DKA) with acute pancreatitis owing to severe hypertriglyceridemia.

Case: A previously healthy 13-year-old boy (34 kg, 4th percentile) presented to his local hospital with a short history of lethargy and abdominal pain. He was found to be in severe DKA (pH: 6.88, glucose: 21.5 mmol/L, bicarbonate: 5.3 mmol/L, ketones: 5 mmol/L). He received intravenous insulin and fluids. He was later transferred to our institution owing to reduced consciousness and agitation.

Subsequently, CT head ruled out cerebral oedema. His blood was lipaemic with a maximum triglyceride level of 53 mmol/L (normal <1.7mmol/L) and cholesterol 16.1mmol/L. His amylase peaked at 989 IU/L (normal 25-125 IU/L), but CT abdomen was relatively unremarkable. His mild pancreatitis was managed conservatively. On day 2 of admission, he was transitioned to subcutaneous insulin with initiation of strict low-fat oral diet (fat <10 g/day). Serum triglycerides and amylase levels decreased to 4.21 mmol/L and 282 IU/L respectively by discharge. Incidentally, he was noted to have undetectable vitamin D and high parathyroid hormone (12.2pmol/L, normal 1.6-7.2pmol/L) levels. T1DM was confirmed by positive GAD and IA2 antibodies. He received intensive dietetic input after discharge. Post-discharge monthly lipid profiles showed gradual improvement. With cautious dietary fat liberalisation and adequate insulin treatment, triglycerides (0.81mmol/L) and cholesterol (3.2mmol/L) normalised by three months at which point he returned to full fat intake of 70-80 g/day. Vitamin D returned to normal after high dose replacement. Owing to strong family history of T1DM and heart disease, he had a familial chylomicronaemia syndrome gene panel which was negative.

Discussion: Although very rare in children, hypertriglyceridaemia can occur in T1DM owing to metabolic derangements and severe insulin deficiency. Increased hepatic free fatty acid uptake produces high very low density lipoprotein which causes hypertriglyceridaemia. It can lead to acute pancreatitis, especially with levels above 10mmol/L. Insulin treatment to facilitate lipoprotein lipase mediated metabolism and careful dietary fat restriction are the mainstay of management. Refractory cases warrant urgent plasmapheresis. Our case illustrates that early recognition and timely intervention lead to satisfactory outcomes.

P2-157**A case of severe hypertriglyceridaemia complicating new-onset type 1 diabetes mellitus**

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Introduction: Extreme hypertriglyceridaemia is uncommon in the paediatric population but can have devastating consequences. It can lead to acute pancreatitis, cutaneous eruptive xanthomas

A novel variant HNF1A gene (HNF1A-MODY) in a patient presenting with hyperglycaemia and glycosuria

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Introduction: HNF1A-MODY (MODY3) is a common subtype of the Maturity Onset Diabetes of the Young (MODY), a monogenic autosomal dominant disease presenting as a non-ketotic diabetes with onset usually during adolescence, or early adulthood. HNF1A-MODY is less common among children as the hyperglycaemia usually manifests after 10th year of life.

Aim: We describe a young girl presented with hyperglycaemia and glycosuria.

Subjects and Methods: An 8.5-year-old girl was referred to our Department by a District Hospital with abdominal pain, nausea, urine glucose (++++) and elevated serum blood glucose (BG) (288mg/dl-16mmol/l), with the suspicion of a newly developing type 1 diabetes (T1D). She received intravenous N/S 0.9%. She was one of twins, born at 36 weeks gestation, birth weight 2310gr; unrelated parents. Her father, 51 years old, had been on treatment for arterial hypertension and presumed type 2 diabetes (T2D) diagnosed 10 years ago, her mother and twin brother were healthy. On admission she had mild abdominal pain. Growth was on the 50th percentile, prepubertal; BG normal, pH 7.44, HCO₃ 22.4mmol/L, BE -2.3mmol/L, biochemical and hormonal screening normal. Urine testing showed glycosuria, no ketones; subsequently negative for both. An oral glucose tolerance test (OGTT) is shown below:

Time (mins)	0'	60'	120'
BG(mg/dl)	76	191	230
(mmol/l)	(4.2)	(10.6)	(12.7)
Insulin (μIU/ml)	5.6	21	34.4
C-peptide(ng/ml)	1.42	4.47	5.74
HbA1c (%)	6		

During her hospitalization pre-and post-prandial BG testing was within normal range. Renal ultrasound revealed a renal cortex cyst with a calcified wall on the right, distension of the renal pelvis on the left kidney. Anti-GAD, IA2, ICA antibodies were negative. She was discharged on home BG (BMstix) self-monitoring and follow-up in Clinic. She has been well since with normal pre-and post-prandial BG, last HbA1c 5.5% (4.8-6). Patients' DNA were tested employing an NGS Targeted Gene Panel of 7 MODY genes. The variant identified was confirmed by Sanger Sequencing exon 2 of HNF1A gene in patient's and her father's DNA.

Results: Genetic testing revealed that our patient and her father were heterozygotes for the novel HNF1A,c.454A>C, p.T152P, variant, classified according to ACMG criteria as Likely Pathogenic.

Conclusions: HNF1A-MODY patients could easily be misclassified as T1D or T2D. Most patients will need pharmacological treatment as they show progressive deterioration in glycaemic control; they are extremely sensitive to sulfonylureas. Molecular genetic diagnosis of the MODY subtype is of outmost importance for clinical diagnosis, disease progression prognosis and family counselling.

Glucose 6 phosphate dehydrogenase deficiency diagnosed with hemolytic anemia triggered by diabetes mellitus type 1

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Background: Glucose 6 phosphate dehydrogenase (G6PD) is expressed in all tissues and is necessary for the oxidant stress capacity of cells. G6PD deficiency is the most common enzymopathy in humans; it is among the important causes of hemolytic anemia. It has been reported that severe hemolytic anemia due to G6PD deficiency may develop in newly diagnosed diabetes, especially during the correction of hyperglycemia. To date, 9 cases have been described in the literature. We present a case of hemolytic anemia due to G6PD deficiency secondary to newly diagnosed diabetes.

Case Report: A 4-year-old male patient presented with the complaint of polyuria-polydipsia. Blood glucose was 750 mg/dl. He was tachypneic and weak. In laboratory examination, hemoglobin (Hgb) 13.1 g/dl, glucose 750 mg/dl, Na 126 meq/l, K 4.55 meq/l, HbA1c 15.3%, insulin 2.2 mIU/ml, C peptide 0.3 ng/ml, urine ketone positive, pH 7.29, HCO₃ 12.4 mmol/l. The patient was diagnosed with diabetic ketoacidosis. Islet and Glutamate Decarboxylase (GAD) autoantibody were positive. On the 10th day of his hospitalization, while receiving subcutaneous insulin therapy, his hypoglycemia was accompanied by tachycardia. After his hypoglycemia resolved, his tachycardia continued. The patient, whose tachycardia continued after the hypoglycemia resolved, was examined. There was no jaundice and organomegaly on the physical examination. The patient was examined. Hgb 8.3 g/dl, thrombocyte 639,000/mm³, leukocyte 13.170/mm³. Anisocytosis and normoblasts were seen in the peripheral smear. Reticulocytosis (10%) was found. Hemolytic anemia was considered with these examinations. G6PD level was found to be low at 0.56 U / gr Hgb. Control Hgb was 7 g/dl, erythrocyte suspension was given,

hemoglobin level was found to be 12.2 g/dl. Genetic examination of our patient was performed, and C.653C>T(p.S218F)(p.Ser218Phe) hemizygous mutation was detected in the G6PD gene.

Conclusions: It should be kept in mind that G6PD deficiency may occur in diabetic individuals in the presence of severe anemia and hemolysis may develop with blood glucose regulation.

Key Words: hyperglycemia, anemia, glucose-6-phosphate dehydrogenase, diabetes mellitus

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P2-160

HbA1C stability – is posting samples reliable?

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For the safe delivery of Paediatric Diabetes services at DBTH during the COVID pandemic a postal HbA1c service with patients collecting capillary blood samples to send to the laboratory for analysis was proposed. The aim of this pilot study was to assess stability of HbA1c at ambient temperature in capillary whole blood samples collected into Sarstedt Microvette EDTA tubes. Samples were analysed on the day of collection on the TOSOH G11 analyser and then re-assayed daily for up to 6 days to allow for postal delays. Acceptable stability was taken as a change of ≤ 4 mmol/mol from the day of collection. The study indicates that a valid result can be expected to be obtained in 82% of samples analysed within 3 days of collection, which reduced to 50% after 4 days.

P2-161

Not every obese child has type 2 Diabetes Mellitus

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Background: Maturity onset Diabetes of the young (MODY) is a rare form of diabetes with specific features that distinguish it from diabetes mellitus type 1 (DM1) or type 2 (DM2). Research studies suggest that 5% of subjects diagnosed with diabetes before the age of 45 years have MODY, with 80% of them having been incorrectly diagnosed as having DM1 or DM2. Genetic testing may enable correct diagnosis and treatment, optimize glycemic control, reduce the risk of hypoglycemic events and long-term complications, and enable proper genetic counseling.

Case description: We present the case of a 11.84 year old female, who presented with obesity and a history of gradual weight gain since the age of 8 years. Her mother had obesity (BMI: 32 kg/m²) and a history of gestational diabetes mellitus (GDM) that progressed to DM2, which was difficult to control despite treatment

with insulin and metformin. Her elder 13 year old brother had impaired fasting glucose despite normal BMI, while her uncle had also been diagnosed with DM2. On clinical examination she had obesity (BMI: 31.5 kg/m², BMI z-score: 3.55), mild acanthosis nigricans and hypertension. Endocrinologic evaluation revealed elevated fasting plasma glucose (FG: 122 mg/dL), and impaired glucose tolerance on OGTT (glucose @ 120': 182 mg/dL, insulin 0' = 43.38 μ UI/ml). Despite the implementation of a personalized intervention program of diet and exercise, her glycemic control deteriorated. At 11.14 years, her FG (118 mg/dL) and insulin concentrations (31.5 μ UI/mL) remained elevated. A repeat OGTT confirmed the diagnosis of diabetes (glucose @ 120': 225 mg/dL) and the patient was commenced on metformin. Her HbA1C (5.5%) and C-peptide (3.8 ng/mL) were normal, and the antibody screen for DM1 was negative. The diagnosis of MODY was suggested by the strong family history, and genetic testing was undertaken. A heterozygous mutation in HNF1A gene was detected, thereby confirming the diagnosis of MODY3. The management plan now includes institution of sulfonylurea treatment.

Discussion: Patients with MODY may present with obesity and may be difficult to distinguish from DM2. Genetic testing allows confirmation of the correct diagnosis and leads to optimal treatment.

P2-162

Does insulin pump therapy improve glycaemic control in type 1 diabetes children: one year follow up

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Introduction: Since its introduction in the 1970s, insulin pump therapy became more and more recommended in patients with type 1 diabetes, in order to achieve and maintain an optimal glycemic control, by mimicking the physiological release of insulin through continuous infusion. The aim of our study was to determine the effectiveness of insulin pump therapy in improving the metabolic control in children with type 1 diabetes.

Patients and methods: A retrospective and descriptive study including children with type 1 diabetes treated with insulin pump therapy followed-up in the Department of Endocrinology-Diabetology-Nutrition of Mohammed-VI University Hospital Center of Oujda, in the eastern of Morocco, between 2017 and 2021. All patients received a clinical evaluation, capillary blood glucose monitoring and HbA1C testing. The statistical analysis was done by SPSS version 21.

Results: We collected 05 children with type 1 diabetes, followed up in our department. The mean age was 9.4 ± 4.7 years old, 4 girls and 1 boy. The duration of diabetes progression was less than 3 years for 60% of patients, with a mean duration of 5.6 years. No statural or ponderal abnormalities were noted. The mean HbA1C has decreased at 6 months going from 7.4 ± 0.5 % to 7.2 ± 0.9 .

However, we noted that an increase at 12 months by 0.4%. The frequency of hypoglycemia decreased from 7.8 ± 2.8 episodes/week to 1.5 ± 0.7 episodes/week at 6 months, and to 0.5 ± 0.7 episodes/week at 1 year. No severe hypoglycemia was noted during this period.

Discussion and Conclusion: Insulin pump therapy appears to be reliable and effective when used appropriately, combined with intensive therapy education and continuous monitoring. The results of studies that have looked for a long term effect are conflicting; some of them have reported a metabolic control mainly in the first 6 months to one year. Our results showed that there was an improvement in glycemic control with pump therapy in children with type 1 diabetes followed-up for one year in our department.

P2-163

Mauriac syndrome: a complication that still exists in children with type 1 diabetes. Report of a case

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Background: Mauriac Syndrome (MS) is currently an extremely rare complication in type 1 diabetes mellitus (DM1). It is characterized by the triad: poor metabolic control, dwarfism and hepatomegaly. Other findings are elevated transaminases, dyslipidemia, cushingoid features and delayed puberty.

Case: Male patient with DM1 since 5 years age. Coinciding with a family breakdown, from the age of 7 his metabolic control deteriorated significantly (HbA1c ~12% / recurrent ketoacidosis). At 12 years of age, he persisted with poor metabolic leading frequent hospitalizations for ketoacidosis and a progressive increase in insulin doses up to 2.7U/kg/day with MDI therapy. Despite this, poor metabolic control and multiple hospitalizations persist. From the age of 8 years there is a lack of growth and weight together with hepatomegaly with increased transaminases. At 15 years, his height was 130.3 cm (-4.9SD), BMI 16.2 kg/m² (-1.8SD); he had protruding abdomen with a smooth, firm consistency and not painful hepatomegaly of 5-6 cm under the costal margin, testes 2 cc, no pubic hair, thin limbs and hypotrophy of muscle masses. Laboratory: total cholesterol 253 mg/dl, HDL 92 mg/dl, LDL 134 mg/dl, triglycerides 134 mg/dl, AST 369 U/L, ALT 369 U/L with normal liver function. Normal blood count, celiac study, thyroid function and creatinine. Hepatitis A, B and C virus infection was ruled out. Basal GH 2.89 ng/ml (reference value (VR) < 1), clonidine-stimulated GH 10.7 ng/ml, IGF-1 346 ng/ml (VR 358 – 870), IGFBP-3 5246 ng/ml (VR 2590 – 7280). Bone age with 2-year delay. Treatment with an insulin pump is started. Improved metabolic control and normalization of liver tests were obtained. Unfortunately, patient abandons controls. A follow-up carried out at 21 years of age he remains using an insulin pump with poor adherence, HbA1c ~11% and new hospitalizations for ketoacidosis. He reached a final height of 156.9cm (-2.9SD; target height -0.9SD).

Conclusions: MS is the consequence of serious metabolic compromise in poorly controlled DM1 patients. Despite the advances

in therapies, MS can still appear. Differential diagnosis such as viral hepatitis or glycogenosis should be considered. Growth impairment due to resistance to the action of GH, and a global and hepatic pro-inflammatory environment could be reversed with appropriate therapy, but it can be definitive without it. Despite the large percentage of adolescents with poor metabolic control MS is rare. This leads to suppose the existence of certain genes that predispose to this pathology.

P2-164

The Impact of COVID 19 Pandemic on Type 1 Diabetes Mellitus: An experience of a Tertiary Care Hospital in a resource limited country

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Background and Objectives: Managing type 1 diabetes (T1DM) in covid pandemic is a real challenge in resource limited countries like Pakistan. This study was aimed to determine the effects of covid 19 in managing type 1 diabetes in resource limited countries.

Methods: Cross-sectional observational study, included all type 1 diabetes patients who were already enrolled in endocrine and diabetes clinic and were on regular follow up.

Results: Eighty-three patients of T1DM (48 from rural area) were included in this study. 64% belonged to lower middle or lower class (monthly income less than PKR 50,000) while 36% belonged to middle class (monthly income = or > than 50,000 but less than PKR100,000). Thirteen out of 83 were doing daily blood glucose monitoring 4 times; 15 patients 3 times; 33 patients 2 times, and no monitoring was done by 16 patients. Only 6 cases were monitoring blood glucose 6 times/day (pre and most meal).

Most of the patients had poor glycemic control with 16/83 (19%) between 300-350mg/dl; 25/83 (30%) between 250-300mg/dl and 33/83 (40%) between 200-250mg/dl. Patients showing glucose levels less than 200 mg/dl were only 9%. HbA1c was more than 10% in 59/83 (71%) patients and 24/83 (29%) had less than 10%. Fifty-five cases have no telemedicine access to doctor and 28 were having partial access.

Conclusion: Covid 19 seems to have a huge impact on managing type-1 diabetes. Due to lockdown, fear of coming to hospital and lack of telemedicine clinic, many patients are not properly monitoring blood glucose thus leading to poor control which can lead to complications like diabetic ketoacidosis.

Co-existence of new onset diabetic ketoacidosis with severe hypertriglyceridemia in a 9 year old girl

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Introduction: Insulin regulates the activity of lipoprotein lipase, the enzyme responsible for triglyceride metabolism. Although mild hypertriglyceridemia is seen in diabetic patients, severe hypertriglyceridemia (>1000 mg/dL) is extremely rare in the pediatric population. We present a case of co-existence of new onset diabetic ketoacidosis (DKA) with severe hypertriglyceridemia, together with therapeutic outcome.

Case: A 9-year-old, previously healthy girl presented with a 1-month history of epigastric pain, 3 kg weight loss and a 10-day history of polydipsia, polyuria, and vomiting.

On initial examination, she had dry mucous membranes while other system examinations were normal. Capillary glucose was 440 mg/dL, capillary beta-hydroxybutyrate 6 mmol/L, pH was 7.18 and bicarbonate was 8.7 mmol/L, indicating DKA. It was noted that the blood specimen was lipemic. Due to this lipemia, serum glucose and electrolyte levels were not accurately measured. Fluid replacement and insulin infusion were started.

Analysis of the sample after ultracentrifugation showed glucose was 410 mg/dL, sodium was 123 mmol/L and triglyceride was 15495 mg/dL. Amylase and lipase were normal. There were no findings associated with hyperlipidemia, such as xanthelasma, eruptive xanthoma, and lipemia retinalis, on examination. The patient did not have a family history of remarkable cardiovascular disease and/or hyperlipidemia. Parental lipid levels were normal. Although DKA resolved at the 24th hour of treatment, insulin infusion was continued. Triglyceride levels decreased rapidly. At the 72nd hour of treatment, she was allowed to start a low-fat diet and started subcutaneous insulin, omega 3 and gemfibrozil therapy. On the 5th day of hospitalization, triglyceride levels returned to normal. Pancreatitis did not develop on follow-up. Gemfibrozil was stopped after three weeks. We did not perform genetic analysis for disorders of lipid metabolism because of the rapid improvement in hyperlipidemia with insulin therapy and the absence of a family history of hyperlipidemia and early cardiovascular events. In subsequent follow-up, there was no increase in triglyceride levels and the last triglyceride measurement was 50 mg/dL.

Conclusion: To the best of our knowledge this case is one of the most extreme elevations of hypertriglyceridemia reported in a pediatric patient with DKA. Triglyceride elevation was thought to be secondary to DKA, due to the absence of family history and hyperlipidemia phenotype coupled with rapid recovery with insulin therapy. We suggest that insulin infusion should be continued in children with DKA and severe hypertriglyceridemia, even after resolution of the DKA.

How Does Continuous Glucose Monitoring Systems Effect Metabolic Control In Type 1 Diabetes: Single Center Experience

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Introduction: Continuous Glucose Monitoring System (CGMS) takes place increasingly in the daily routines of diabetic patients. It has been shown that metabolic control improves when CGMS is used consistently. We aimed to show the effect of CGMS in patients using MDI therapy.

Materials - Methods: All patients using multiple-dose insulin therapy at our center and continued their regular follow-up and using CGMS for at least three months were screened through their files. Eight of the 70 patients were excluded from the study because they switched to insulin pump therapy, 17 patients were on their honeymoon period, one patient was diagnosed with MODY, three patients were diagnosed with type 2 diabetes who only used metformin, and six patients were using for less than three months, so 35 patients were included in the study. Anthropometric measurements, insulin doses, HbA1c and sensor data of all cases were compared with the data of the last two weeks when they were actively using the sensor.

Results: It was shown that patients' weight, weight SDS increased with the use of sensors, and a statistically significant decrease was achieved in HbA1C (Table 1). In addition, the increase in the duration of sensor use correlated with a decrease in glucose variability, an increase in TIR, and a decrease in TAR (Table 2). While a decrease of 8.6% is observed in TIR with the use was less than 15 months, the benefit of using the sensor > 15 months is clearly seen, and a 7.2% increase is observed in TIR (p: 0.016). However, a significant decrease in TBR was not detected. After using the sensor, the awareness of the patients about hyperglycemia raised, they intervened more to reduce their blood glucose values and probably they consume more food because they can monitor blood glucose levels more closely.

Table 1. Comparison of the first 2 weeks after sensor insertion and the last 2 weeks of sensor use

	Beginning	After	p
Weight (kg)	44,6	51,7	<0,001
Weight SDS	0,22	0,47	0,034
BMI SDS	-0,03	0,26	0,072
HbA1C	8,02	7,4	0,01

Table 2. Correlation with Sensor Lifetime and Glycemic Control Parameters

	Pearson Correlation Coefficient	P
Glucose Variability (CV)	0,599	0,001
Time Between 70-180 mg/dl	-0,41	0,014
Time Between 180-250 mg/dl	0,373	0,027
>250 mg/dl elapsed time	0,345	0,046

P2-167

Blood level of Vitamin D and metabolic control of type 1 diabetes mellitus

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Background: There are some studies about vitamin D level and type 1 or type 2 diabetes mellitus (DM). Its effect on metabolic control of patients with type 1 DM is the subject of this study.

Patients and Method: In 339 patients with type 1 DM, 192 cases (99 males, 93 females) randomly enrolled in the study. The age of males was 9 ± 4.4 yr and age of females was 8.3 ± 4.3 yr. Their HbA1C and 25(OH) D3 were measured by HPLC method. Vitamin D level was divided into group 1: ≤ 10 ng/mL, group 2: $11 - 20$ ng/mL, group 3: $21 - 30$ ng/mL, group 4: > 30 ng/mL. HbA1C level was compared in different vitamin D groups.

Results: Mean $\pm$ SD of HbA1C was 10.2 ± 2.3 in group 1 that was significantly higher than group 3 (8.2 ± 1.6) (P value: 0.001) and group 4 (8.8 ± 2.4) (P=0.024). It was 9.7 ± 2.3 in group 2 that was significantly higher than group 3 (P: 0.003) and group 4 (0.045). There was no significant difference between group 1 and 2 and also between group 3 and 4.

Conclusion: Vitamin D level more than 20 is accompanied by better metabolic control of type 1 diabetes mellitus.

P2-168

Newly-onset type 1 diabetes mellitus triggered by COVID-19: Original case report

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Introduction: During this year, scientific research revolves around COVID-19, with so many unanswered queries in term of pathogenesis; complications, and mortality rate; in light of limited pediatric evidence. The close relation between COVID 19 and new-onset diabetes especially in children is still an unresolved issue. Our paper, exhibits an unique presentation of DKA misleading COVID 19 diagnosis at this age

Case Presentation: A three-year-old boy admitted for a history of acute dyspnea besides vomiting and weight loss, without abdominal discomfort. His vital parameters were monitored: temperature was 38°C, respiratory rate up to 50 breaths per minute without Kussmaul breathing however he had obvious respiratory distress signs particularly nasal flaring and chest retractions, his oxygen saturation was initially about 93 % under 3 liters of oxygen provided by a simple facial mask. The child's capillary blood glucose was checked; reaching 3 g/l with 3+ of ketones besides 3+ of glucose in the urine test. The remainder of his physical examination was uneventful. The diagnosis of a mild DKA was obviously assessed (pH: 7,25, Bicarbonate : 13,2 meq/l with decreased alkaline reserve : 8 meq/l). However, obvious respiratory distress signs didn't disappear even though glycaemic levels were normalized and acidosis was resolved. The boy was tested positive for Covid-19 just as his parents while they were asymptomatic. Then, the patient underwent a Chest computed tomography revealing bilateral ground-glass opacities especially in subpleural region with left consolidations; graded CO-RADS 4 by the radiologist. After 48 hours in the intensive care; his clinical condition gently improved. The patient started breathing room air; and was moved to an isolation COVID-19 care unit with his mother. Basal bolus insulin regimen was started, and diabetes education was provided and evaluated through sessions pursued even after the hospital's discharge. Our boy's HbA1c value was 10,3% ; and his islet autoantibodies were positive. After 10 days in the hospital, the patient and his mother were discharged with quarantine recommendation.

Conclusion: As a diabetologist; the correlation between COVID 19 and new-onset diabetes especially in children is still an unresolved issue. Higher attention is required to enhance COVID-19 linked diabetic ketoacidosis prognosis and the global registry of cases with COVID-19-related diabetes (Cov-iDIAB project) should be enriched in order to conduct further studies.

P2-169

Case of HNF1B MODY

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Background: MODY *HNF1B* variants are most frequently associated with extra-pancreatic manifestations like renal cysts [leading to renal cysts and diabetes (RCAD) syndrome], abnormalities of the uro-genital tract and hypomagnesemia, but may also cause MODY or renal structural disease in isolation, therefore cases of *HNF1B* MODY still remained largely undiagnosed. In Ukraine, there are currently three patients with MODY *HNF1B* *de novo* whole gene deletion.

Clinical Case: A 17 year old male, was admitted to the nephrology department for a routine examination. According to the anamnesis, he has been observed by a nephrologist since the age of 7 with chronic pyelonephritis and congenital anomaly in the development of the kidneys (doubling of the right kidney).

In the nephrology department the routine examination revealed hyperglycemia (10.5 mmol/l), there were no ketones in the urine. Due to hyperglycemia, the patient was transferred to the endocrinology department. The results of a general examination: height 176 cm (+0.1 SD), weight 58 kg, BMI 18.7 kg/m² (15 p.c.), Heart rate – 80/min, BP – 125/80 mm (75-90 p.c.). He had normal male external genitalia, Tanner 4. The blood glucose level was 15.7 mmol/l, he also had glycosuria without ketonuria. There are no cases of diabetes in the family; however, the father suffers from chronic pyelonephritis.

The results of an additional examination revealed high HbA1c (13.5%), low C-peptide 0.25 ng/ml (0.7-1.9). Insulin was administered at a dose 0.6 U/ kg.

The ultrasound examination of abdomen confirmed a doubling of the right kidney, as well as a neoplasm in the liver (hemangioma?). Subsequent CT scan excluded a liver pathology.

To continue the diagnostic search, the patient was tested for specific antibodies (GAD, IA2, ZnT8), the results of which were negative. Hereafter genetic testing using tNGS MODY panel was done, where it was found heterozygous pathogenic *HNF1B* whole gene deletion variant (NM_000458.4: c. (?_1)_(*4_?)del, p.(0?). The *HNF1B* whole gene deletion variant was also not detected in parents, and this result suggests that the variant has arisen *de novo*.

Follow up management is needed to control BP and lab tests (liver function tests, magnesium, uric acid, renal function (eGFR, urea and creatinine), fecal elastase, PTH, urinary albumin), ultrasound of abdomen, CT of abdomen. Early treatment with ACE inhibitors should be also considered.

P2-170

Diabetes Ketoacidosis Recovery in Youth with Newly Diagnosed and Established Type 1 Diabetes

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Objective: To describe the differences in metabolic parameters and in time to recovery from Diabetes ketoacidosis (DKA), between children and adolescents with newly diagnosed compared with established Type 1 Diabetes (T1DM).

Methods: A single center, retrospective study. The cohort comprised 356 children and adolescents with T1DM who had DKA during 2008-2018. Data were obtained from the patients' medical files. Recovery of DKA was defined as the resolution of acidosis (PH>7.3 and bicarbonate>15 meq/L).

Results: The mean time to recovery from DKA was significantly longer in patients with newly diagnosed than established diabetes (13± versus 8.5± hours) (p<0.001). This difference was maintained in an analysis according to DKA severity: mild, moderate, and severe. PH at presentation did not differ between the groups, but bicarbonate at presentation was significantly lower in patients with newly diagnosed diabetes than in those with established diabetes, 9.9± versus 12± mmol/L (p<0.001). Potassium and phosphorus levels were lower, and sodium and chloride levels were higher in patients with newly diagnosed diabetes than in those with established diabetes (p<0.001).

Conclusion: DKA is associated with shorter recovery time in patients with established compared to newly diagnosed diabetes. This important finding can help clinicians plan treatment. Specifically, regardless of the severity of the DKA, clinicians can prepare for shorter intravenous treatment in patients with established diabetes, with the expectation of fewer complications.

Fat, Metabolism and Obesity

P2-171

Association of calprotectin with obesity in prepubertal children

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Background: Perturbation of inflammation is critically linked to nutrient metabolic pathways and obesity-associated complications, such as insulin resistance and type 2 diabetes (T2DM). The S100 family of proteins, including S100A8/A9 (calprotectin), have

been implicated in disease pathogenesis and investigated as potential markers of inflammation. In adults, increased circulating levels of calprotectin have been reported in obesity-related chronic low-grade inflammation. The present study aimed to investigate the relationship between serum calprotectin levels and overweight/obesity in prepubertal children.

Methods: We enrolled 59 prepubertal children aged 6-9 years. The patients of hypothyroidism, Cushing syndrome, Prader-Willi syndrome, and T2DM were excluded in this study. The subjects were divided into two groups: normal-weighted group (BMI <85 Percentile, n=26) and overweight/obese group (BMI ≥85 Percentile, n=33). Calprotectin and IL-6 were measured using Commercial ELISA kit (Bühlmann Laboratories AG, Schönenbuch, Switzerland) and ELISA assay (R&D System, Minneapolis, MN, USA), respectively. Pearson's coefficient of correlation (r) between calprotectin and clinical parameters were calculated. Multiple linear regression analyses was used to evaluate the independent association between calprotectin and obesity.

Results: The serum calprotectin concentrations were significantly elevated in children with overweight/obesity compared to those with normal weight. The serum IL-6 concentrations were significantly elevated in children with overweight/obesity compared to those with normal weight. The serum calprotectin concentrations were significantly positively correlated with weight SDS, WC SDS, BMI SDS, and IL-6 in unadjusted Pearson's analyses. The serum IL-6 was significantly positively correlated with weight SDS, WC SDS, BMI SDS, and calprotectin in unadjusted Pearson's analyses. In the multiple linear regression analyses, the calprotectin was significantly associated with BMI SDS after adjustment for age, sex and IL-6.

Conclusions: Our results showed that the calprotectin was independently associated with obesity after adjustment for age, sex, and IL-6. Our results confirm a potential utility of calprotectin as a marker of obesity-associated chronic low-grade inflammation in children.

P2-172

Metabolic syndrome and birth anthropometric data in Prader-Willi syndrome

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Introduction: Previous studies showed that non-obese children and adults with Prader-Willi syndrome (PWS) have a low frequency of metabolic syndrome (MetS), while obese ones have a frequency similar to that of non-PWS obese. It is known that individuals born small for gestational age (SGA) have a greater predisposition to the development of MetS. Recent neonatal percentiles of subjects with PWS (Salvatori *et al*, *Am J Med Genet Part A*, 2019) documented a defect in weight of half kg and in length of 1 cm compared to general population. Moreover, females with a 15q11-13 deletion (DEL15) resulted shorter than those with maternal uniparental maternal disomy of chromosome 15 (mUPD15).

Aim of the Study: To establish whether PWS SGA subjects, defined on the basis of neonatal PWS's percentiles, have a greater risk of developing MetS.

Methods: We evaluated the presence of the components of the MetS in 91 PWS subject (32 males), aged 27.6 (5.3) years, with a BMI of 37.6 (16.9); 69 (76%, 28 males) had DEL15 and 22 (24%, 4 males) mUPD15. The patients were divided into two groups according their birth weight SDS (BW-SDS): SGA (BW-SDS <-1.5; n=17), appropriate for gestational age (AGA) (BW-SDS -0.682 / +1.5; n=74). In accordance with the literature (Alberti *et al.*, *Circulation*, 2009; 120: 1640-5), we defined subjects with MetS as having three abnormal findings out of the following five parameters: central obesity, high systolic BP and/or diastolic BP, high triglycerides, low HDL-C and raised fasting plasma glucose. We reported median (IQR) of continuous variables. Statistical analysis was performed by chi square and Mann-Whitney test.

Results: On overall SGA and AGA groups showed similar BMI, weight, length and MetS frequency (40%). The prevalence of MetS in SGA-born obese subjects (7/17; 41%) was similar to that of AGA-born obese (28/74; 38%). Obese girls with DEL15 showed significantly lower frequency of MetS than obese girls with mUPD15 (41% vs 67%; p<0.05).

Conclusion: Birth weight does not seem to significantly affect the frequency of obesity and MetS in young adults with PWS. Obese females with DEL15, who typically have a shorter birth length than mUPD15, appear to have a lower risk of developing MetS. These data would suggest a direct correlation between length at birth and metabolic risk.

P2-173

Evaluation of the BigO system during the COVID-19 outbreak in Greece

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Background: Since December 2019, the world has witnessed a global pandemic due to SARS-CoV-2 coronavirus (COVID-19), which has led to lifestyle changes as a result of Public Health Regulations and Guidelines introduced by governments worldwide.

Objective: To determine the body mass index (BMI) trajectory in children and adolescents with overweight and obesity with respect to the COVID-19 outbreak in Greece.

Methodology: The study was carried out as part of the four-year European project BigO (<http://bigoprogram.eu>, Horizon2020, No. 727688). Overweight and obese children and adolescents aged 9-18 years participated in the study following approval by the local Committee on the Ethics of Human Research. Written informed consent was obtained by parents/guardians in all cases. The data collection system included the BigO technology platform, which interfaces with a Smartphone and Smartwatch, and records data objectively (using inertial sensors and GPS) for each patient. Participants used the BigO system for 4 weeks in order to take photographs of the food they consumed, as well as food advertisements, and wore the watch for specific periods during the week (at least 2 weekdays, 1 weekend and 3 nights). Subsequently, they entered a personalized lifestyle intervention program of diet, physical exercise and sleep for 3-4 months and used the system again for

4 weeks. For our analysis we have taken into consideration those patients that have participated from March 2020 until February 2021, who contributed data twice.

Results: The study population consisted of 251 children and adolescents (137 males, 114 females; mean age $\pm$ SD: 12.786 $\pm$ 2.559 years). At initial evaluation, the percentage of subjects with obesity was 76.9% and overweight 23.1%. A higher number of boys had obesity compared with girls (54.9% vs. 45.1%). Following the use of the BigO system twice, the proportion of subjects with obesity decreased by 3.1 % (76.9% vs. 74.5%), while the proportion of overweight and normal-BMI subjects increased by 8.7% and 40%, respectively (23.1% vs. 25.1%, 0% vs. 0.4%). Similar changes were observed in both boys and girls. In general, BMI decreased by 1.4% (28.1 kg/m² vs 27.6 kg/m², $p < 0.001$) in all subjects.

Conclusions: These novel tools and interventions record the behavior of overweight and obese children and adolescents in an objective way. They were proven to be effective at managing childhood obesity despite the implications and lifestyle changes owing to the COVID-19 pandemic.

P2-174

The relationship between sleep time and obesity in childhood

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Childhood obesity (CO) is an important risk factor for the development of many chronic metabolic diseases in adulthood. Sleep patterns are known to affect leptin and ghrelin levels in the body. Recent studies using Functional Magnetic Resonance Imaging (fMRI) have shown that insufficient sleep time leads to unhealthy eating behaviors in the brain. The aim of this study is to investigate the association between sleep time in childhood and obesity. Consistent with this association, the effects of early sleep time on insulin resistance and lipid profile are the first questions that arise. Accordingly, we are investigating whether early sleep prevents obesity."

The study included 115 obese children with a BMI > 95th percentile. Biochemical (fasting serum glucose, lipid profile) and hormonal (fasting insulin) panels were queried after detailed history, anthropometric assessment, and physical examination in 115 cases presenting to our Pediatric Endocrinology clinic. Clinical assessments included insulin resistance measured by HOMA-IR ([fasting blood glucose (mmol/L) x fasting serum insulin (mIU/L)] / 22.5). We also measured the triglyceride and HDL levels of each patient. We also divided our cases into two groups: sleepers between 21:00-21:30 and late sleepers.

The mean weight and BMI SDS were 72.31 kg and 2.98, respectively, and the mean triglyceride and HDL levels of those who slept between 21:00 and 21:30 were 84.13 mg/dl and 49.67 mg/dl, respectively. Moreover, the mean triglyceride and HDL values of the patients who slept after 21:30 were 106.31 mg /dl and 44.34 mg/dl, respectively. Accordingly, the TG levels of patients who slept between 21:00-21:30 were lower than those who slept later

($p = 0.067$). In contrast, HDL levels of patients who slept between 21:00-21:30 were significantly higher than those who slept later ($p = 0.019$). While the mean HOMA-IR index of sleepers between 21:00-21:30 was 4.78, the mean HOMA-IR index of late sleepers was 5.21 ($p = 0.527$). The analysis shows that patients who sleep earlier (21:00-21:30) have lower HOMA-IR index and lower triglycerides and higher HDL levels. The results further show that early sleep reduces insulin resistance and prevents dyslipidemia.

In this study, we demonstrate that early sleep reduces insulin resistance and prevents dyslipidemia. Demonstration of this mechanism may be the goal of future studies in this regard.

P2-175

The relationship between acanthosis nigricans and vitamin D in obese children and adolescents

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Studies show that vitamin D deficiency can have negative effects on glucose homeostasis, although the mechanism for this is still unclear. The possible mechanism may be related to the presence of vitamin D receptors and their metabolizing enzymes in insulin-sensitive cell types, such as pancreatic cells and adipocytes. The aim of this study is to compare how serum 25-OH D level and HOMA-IR index are related to acanthosis nigricans (AN) and which of them is a better marker for acanthosis nigricans (AN).

The study included 115 obese children with a BMI > 95th percentile. After a detailed history, anthropometric evaluation, and physical examination of 115 cases presenting to our Pediatric Endocrinology clinic, we divided the cases into two groups according to whether they had acanthosis nigricans or not. Clinical examinations included insulin resistance measured by HOMA-IR ([fasting blood glucose (mmol/L) x serum fasting insulin (mIU/L)] / 22.5) and serum 25-OH D level.

Mean weight and BMI SDS were 72.31 kg and 2.98, respectively, and our sample included 47 patients with AN and 68 patients without AN. The mean HOMA-IR and serum 25-OH D levels of the patients with acanthosis nigricans were 5.11 and 14.46 ng/mL, respectively. In addition, the mean HOMA-IR and serum 25-OH D values of the patients who did not have acanthosis nigricans were 5.19 and 18 ng/mL, respectively. The serum 25-OH D levels of patients with AN were significantly lower than those of patients who did not have AN ($p = 0.032$). In contrast, the HOMA-IR indices of patients with AN and without AN were not significantly different from each other ($p = 0.866$). While patients with AN had significantly lower serum 25-OH D levels, the HOMA-IR index was not significantly different between children with and without AN. The results further indicate that serum 25-OH D level is more strongly related to AN than HOMA-IR.

Our results suggest that vitamin D insufficiency and vitamin D deficiency should be investigated in patients with acanthosis nigricans. Our results also suggest that a decrease in serum 25-OH D level may be observed before an increase in HOMA-IR index in patients with acanthosis nigricans.

P2-176

Exploring Urinary Bile Acids as Potential Markers of Metabolism: Reference Values in Children by Targeted LC-MS/MS

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Bile acids (BA) are C₂₄ steroids synthesized from cholesterol in liver. Originally, they were mainly considered to function as emulsifiers supporting resorption of lipophilic food compounds and excretion of metabolic products. Recently, their additional biological and endocrine functions in the regulation of metabolism have aroused interest of researchers. In contrast to BA in blood, it is surprising that hardly any data exist on BA in the most accessible human biofluid urine. Therefore, a targeted liquid chromatography/tandem mass spectrometry (LC-MS/MS) method was developed and validated to analyze 18 BA simultaneously. The method contains the measurement of the primary BA cholic acid (CA) and chenodeoxycholic acid (CDCA) and the secondary BA deoxycholic acid (DCA) and lithocholic acid (LCA) as well as glycine and taurine conjugates of these four BA (GCA, TCA, GCDCA, TCDCA, GDCA, TDCA, GLCA, TLCA). Furthermore, ursodeoxycholic acid (UDCA) and five BA in their sulfated forms (LCA-S, GLCA-S, TLCA-S, GCDCA-S, GDCA-S) were analyzed.

The method required 2 mL of urine and sample preparation consisting of protein precipitation and solid phase extraction. The method achieved good linearity ($R^2 > 0.99$) and recovery (90.49% - 113.99%). LOQ was determined as 6.25 ng/mL for each compound (except for GCDCA: 18.75 ng/mL). Intra-day/inter-day precision and accuracy ranged from 0.42% to 11.47% and 85.75% to 110.99%, respectively. No significant matrix effect was observed.

The method was successfully applied to samples of 80 healthy children of various age groups. CA (median: 55.2 ng/mL) and GCA (48.9 ng/mL) were the two dominant non-sulfated BA. However, sulfated BA showed much higher concentrations, with GCDCA-S (337.5 ng/mL) showing the highest levels among all BA, followed by GLCA-S (197.4 ng/mL) and GDCA-S (183.2 ng/mL). In total,

86.5% of quantified BA were sulfated. The total concentrations of glycine amidated BA measured were higher than taurine amidated and non-amidated ones. No obvious trends between urinary BA and age or sex, respectively were observed.

We established a method for profiling concentrations of urinary BA in humans. Our data showed that urinary BA are mostly present in their sulfated form in children's urine, indicating hepatic sulfation to be the major metabolic pathway for urinary BA excretion in humans. The study provides important information on the ontogenesis and metabolism of human BA. Our reference data for urinary BA from healthy children lay the foundation for further investigations into their potential role as metabolic and hepatic biomarkers.

P2-177

A novel mitochondrial tRNA^{Thr} 15894G>A mutation is potentially risk factor in a Chinese family with obesity

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A Chinese family of Han with symptoms of matrilineally-inherited obesity was assessed and its clinical, genetic, and molecular profiling was conducted. Obesity was observed in matrilineal relatives (3 out of 14) of a single generation (of 3 alive generations) of this family. On pedigree analysis and sequencing of their mitochondrial DNA, a novel homoplasmic mutation of the mitochondrial tRNA^{Thr} gene (15894G>A) was identified in these individuals. This mutation correlated with a destabilized conserved base pair in this tRNA acceptor stem. Position 7 is known to be crucial for carrying out effective codon recognition and stability of tRNA. In accordance with the importance of this conserved site, we observed that the predicted structure of this tRNA with the mutation was noticeably remodeled in a molecular dynamics simulation when compared to the isoform of the wild-type. All other mutations observed in the individual's mtDNA were known variants belonging to Asian M7b haplogroup. Thus, this is the first report that provides evidence of the association between a mutation in tRNA and an enhanced risk of maternally-transmissible obesity, offering more insights into obesity and its underlying nature.

P2-178

Obesity is potentially associated with a novel mitochondrial tRNAGly 10029A>G mutation in a Chinese family

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In this study, we conducted a clinical, genetic, and molecular profiling of a Han Chinese family with evident of matrilineally-inherited obesity. Obesity was evident in 2/6 matrilineal relatives in a single generation of this family (of 3 available generations). When the mitochondrial DNA of these individuals was sequenced and a pedigree analysis was performed, we were able to identify a novel homoplasmic mutation of the mitochondrial tRNA^{Gly} gene (10029A>G) in these individuals. This mutation was linked to destabilization of a conserved base pair in the anticodon of this tRNA. This position (position 43) is known to be important for mediating effective codon recognition and tRNA stability. Consistent with the importance of this conserved site, we found that the predicted structure of a tRNA^{Gly} structure bearing a 10029A>G mutation was markedly altered in a molecular dynamics simulation relative to the wild-type isoform. All other mutations identified in the mtDNA of these individuals (3 in total) were known variants associated with Asian haplogroup D4. As such, our report provides novel evidence of a link between a tRNA mutation and an elevated risk of maternally-transmissible obesity risk, offering potentially novel insights into the underlying nature of obesity.

P2-179

Frequency of MC4R Pathway Variants in a Large US Cohort of Pediatric and Adult Patients with Severe Obesity

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Background: The melanocortin-4 receptor (MC4R) pathway is critical for the regulation of energy balance. Variants in a number of genes within this pathway have well-established associations with severe obesity. However, the overall frequency of rare variants in these genes has not been assessed systematically in a clinically relevant population, and it is unknown whether variant frequency differs depending on the age of ascertainment. Genetic testing can improve diagnosis of rare genetic diseases of obesity and identify patients who may benefit from targeted therapeutic intervention.

Methods: We sequenced exons and intron-exon boundaries for 40 obesity-related genes in individuals with severe obesity (<18 years old, ^{397th} percentile BMI for age; ³18 years old, BMI ³40kg/m²)

who participated in the US-based Uncovering Rare Obesity™ diagnostic genetic testing program. This Next Generation Sequencing panel included 11 genes associated with non-syndromic obesity that encode proteins that function in the MC4R pathway (*POMC*, *PCSK1*, *LEPR*, *SRC1*, *SH2B1*, *MC4R*, *MC3R*, *CPE*, *LEP*, *KSR2*, and *SIM1*). Variants were classified as pathogenic/likely pathogenic (P/LP) or as a variant of uncertain significance (VUS) according to ACMG criteria. We additionally included one non-rare variant, *PCSK1* p.N221D, for which published functional and population studies suggests a potential contribution to obesity. Patients with variants in 5 of these genes (*POMC*, *PCSK1*, *LEPR*, *SRC1*, and *SH2B1*) have previously been assessed in a trial using the MC4R agonist setmelanotide and demonstrated meaningful weight loss.

Results: Among the 7826 individuals, 16% were <6, 33% were 6 to 12, 30% were 12 to 18, and 21% were greater than 18 years old. 19% of individuals carried ≥1 rare variant in ≥1 of the 11 studied genes, including 3.6% carrying a P/LP variant and 15.4% carrying a VUS variant. Restricting to the 5 genes with prior demonstrated responsiveness to setmelanotide, the yield was 11% for P/LP or VUS variants. An additional 6.4% carried the *PCSK1* p.N221D variant. No differences in yield were observed by age group.

Conclusions: In our large US-based cohort of individuals with severe early-onset obesity, 25.4% of individuals carry a potentially clinically relevant variant in one or more of 11 MC4R pathway-related genes. Genetic testing of patients with severe obesity may therefore be an important component of understanding the etiology of these patients' phenotypes. No differences in yield were observed across age groups, indicating that genetic testing for obesity-related genes is appropriate in both pediatric and adult patients with severe obesity.

P2-180

Impact of the COVID-19 pandemic and related lockdown measures on lifestyle behaviours and quality of life in children and adolescents with severe obesity

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Introduction: Lockdown measures following the COVID-19 pandemic are shown to have greatly affected lifestyle behaviours and health-related quality of life (HRQoL) of children. The impact on children with severe obesity has not yet been described. Aim of this study was to investigate the impact of COVID-19 lockdown on

eating behaviours, physical activity (PA), screen time, and HRQoL of children (including adolescents) with severe obesity.

Methods: Questionnaires and semi-structured telephone interviews were used in this mixed-methods study performed during the first COVID-19 lockdown in the Netherlands (April 2020). Children, who were treated at our obesity centre, were included. The Dutch Eating Behaviour Questionnaire – Child, Paediatric Quality of Life Inventory, and Dutch Physical Activity Questionnaire were completed by their families pre-pandemic and during lockdown. Changes over time in percentile scores, weekly PA, and screen time were assessed. Qualitative analyses were performed following the Grounded Theory.

Results: Ninety families were approached; 83 families included. Mean age of children was 11.2 years (SD 4.6), 52% were female, mean BMI SD score was +3.8 (SD 1.0).

Outcome during lockdown	Mean (SD)	Δ	p-value
Restrained eating score	63.4 (33.8)	+3.2	0.39
Emotional eating score	67.2 (32.9)	+9.2	0.11
External eating score	68.5 (28.4)	+0.3	0.57
Weekly PA	7.2 (7.6) hr	-1.9 hr	0.02
Weekly screen time	18.0 (11.7) hr	-0.2 hr	0.65
PedsQL total score	65.4 (18.6)	+3.0	0.51

Weekly PA decreased, but emotional, restrained, external eating, HRQoL and screen time did not change on group level (Table). In 51% of the population, mean weekly PA decreased to ≤2 hours/week. Increased emotional eating during lockdown was observed mostly in older children, whereas increased external eating was observed mostly in younger children. Children with high emotional and external eating during lockdown or pre-existent psychosocial problems had the lowest HRQoL ($p<0.01$). An increased demand for food was frequently observed ($n=21$), mostly children aged <10 years (19/21), and was attributed to loss of daily structure or perceived stress. Families who reported unchanged ($n=15$) or improved eating behaviours ($n=11$) attributed this to already existing strict eating schemes.

Conclusion: We show differential responses to COVID-19 lockdown measures in children with severe obesity, with unfavourable changes in PA on group level and in eating styles and HRQoL in substantial minorities. Children with pre-existent psychosocial problems or pre-pandemic high external or emotional eating were most at risk. These children should be targeted to minimize short- and long-term negative physical and mental health consequences.

P2-181

Longitudinal association of the anti-inflammatory serum marker GDF-15 with serum IgA and IgG in apparently healthy children

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Introduction: Both the innate and adaptive immune responses are deregulated in individuals with obesity and are a key driver of its associated metabolic alterations. Although the anti-inflammatory growth differentiation factor 15 (GDF-15) is a candidate protein against obesity, its mechanisms regulating the immune responses are not fully understood.

Methods: We examined whether serum GDF-15 was related to serum levels of immunoglobulins (a component of the adaptive immune system) in a cohort of healthy children recruited at the primary health care centers of Girona, in Northeastern Spain (204 Caucasian children, 101 girls and 103 boys). Children were assessed longitudinally at baseline (8.5 ± 1.8 years) and follow-up (13.0 ± 1.9 years).

Results: GDF-15 positively associated with IgA and IgG levels and the IgA*IgG product in apparently healthy children at both baseline and follow-up. The associations were more pronounced in heavier children (those with BMI-SDS above the median) as well as in children with higher accumulation of renal fat (those with renal fat-to-height ratio above the median), in whom they remained significant after correcting for possible confounding variables. Serum GDF-15 levels accounted for up to 16% of the variance of IgG levels and 14% of the variance of IgA*IgG product at followup.

Conclusion: The longitudinal associations of the anti-inflammatory GDF-15 with IgA, IgG and the IgA*IgG product in children with higher BMI or higher renal fat accumulation suggest a role of GDF-15 in human obesity through the regulation of the adaptive immune system.

P2-182

Describing the Natural History of Clinical, Biochemical and Radiological outcomes of children with Familial Partial Lipodystrophy type 2 (FPLD2) attending a National Service for Severe Insulin Resistance: a Retrospective Cohort Study

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Background: FPLD2 results from autosomal dominant mutations in the LMNA gene. The physical appearance develops through adolescence where subcutaneous fat deposits of the limbs, trunk, buttocks and legs do not develop resulting in a muscular appearance. The metabolic phenotype includes elevations in triglyceride concentrations and hepatosteatosis with resultant insulin resistance. Co-morbidities that may manifest during young adulthood include early-onset diabetes, coronary artery disease and hypertrophic cardiomyopathy, with resultant reduction in life expectancy. The most effective management is the adoption of a lifelong low fat diet to minimise ectopic fat accumulation. Conventional therapies for hypertriglyceridaemia and diabetes have limited efficacy. Recombinant leptin can be beneficial and has recently been approved for use in patients with FPLD2 who have diabetes and elevated triglycerides.

Genetic testing permits the diagnosis of FPLD2 in the offspring of index cases before they would present clinically. Current guidance is that they should follow a healthy low fat diet, with annual screening for co-morbidities, however the natural history of FPLD2 throughout childhood is not well understood. We report outcomes from a cohort of children with FPLD2 under the care of the UK National Centre for severe insulin resistance in Cambridge, United Kingdom. Patients are offered an annual appointment for clinician and dietetic review with screening for co-morbidities.

Methods: Following institutional approval, a retrospective case note review of 12 [5M] children with FPLD2 was undertaken. Relationships between dependent variables (HbA1c, triglycerides, fasting insulin, fasting glucose and ALT) across time were explored using a multivariate model, adjusted for age and gender.

Results: Age median [range] at first appointment was 9.8[6.0-14.6]yrs with no gender difference. Age at most recent follow up was 16.3 [9.1-21.3]yrs with 4.2[1.0-6.0]yrs follow up. 3 patients (all female) developed diabetes between 12 and 19yrs. 1 female has hypertrophic cardiomyopathy and 4 [1M] developed mild hepatic steatosis by a median age of 14[12-15]yrs. 3 patients [1M] reported mental health problems related to lipodystrophy.

There were no relationships between biochemical results and age.

Conclusion: In this small cohort of children, despite dietetic input, we found evidence of co-morbidities after the age of 12 years, more commonly in females, consistent with described outcomes for adults. The absence of relationships with biochemical screening tests and age likely reflects the small numbers in this cohort.

We propose that, whilst clinical review and dietetic advice and support are of benefit for children with FPLD2, undertaking formal screening for co-morbidities before the age of 10 years is unlikely to be of benefit, however clinical input from an MDT including dietician, psychologist and clinician should be offered from diagnosis.

P2-183

Evaluation of the BigO system in a clinical setting in Greece

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Background: Obesity in childhood and adolescence represents one of the most important public health problems. Over the last decade, the widespread use of personal digital technologies, such as smart mobiles and accelerometers, create new possibilities for collecting behavioral data objectively.

Objective: To evaluate the body mass index (BMI) trajectory after at least one month's use of the BigO system.

Methodology: The study was carried out as part of the four-year European project BigO (<http://bigoprogram.eu>, Horizon2020, No. 727688). Overweight and obese children and adolescents aged 9-18 years participated in the study following approval by the local Committee on the Ethics of Human Research. Written informed consent was obtained by parents/guardians in all cases. The data collection system included the BigO technology platform, which interfaces with a Smartphone and Smartwatch, and records data objectively (using inertial sensors and GPS) for each patient. Participants used the BigO system for 4 weeks in order to take photographs of the food they consumed, as well as food advertisements, and wore the watch for specific periods during the week (at least 2 weekdays, 1 weekend and 3 nights).

Results: The study population consisted of 857 children and adolescents (448 males, 409 females; mean age $\pm$ SD: 12.630 $\pm$ 2.466) who used the BigO system for at least one month. Subjects were classified as having obesity (n=665, 77.6%), overweight (n=187, 21.8%) or normal BMI (n=5, 0.6%) according to WHO cut-off points. At initial evaluation, the percentage of subjects with obesity was 77.6%, overweight 21.8% and normal BMI 0.6%. A higher number of boys had obesity compared with girls (54.1% vs. 45.9%), while a higher number of girls had overweight compared with boys (54.0% vs. 46.0%). Following at least one month's use of the BigO system, the proportion of obese subjects decreased by 3% (77.6% vs. 75.3%, p=0.002), while the proportion of overweight and normal-BMI subjects increased by 5% and 216%, respectively (21.8% vs. 22.9%, 0.6% vs. 1.9%, p=0.002). Similar changes were observed in both boys and girls. In general, the use of the BigO system for at least one month resulted in a decrease of BMI by 1.1% (28.2 kg/m² vs. 27.9 kg/m², p<0.001) in all subjects.

Conclusions: These novel tools and interventions record the behavior of overweight and obese children and adolescents objectively. Therefore, they may be useful at designing new public health policies in order to address the epidemic of childhood obesity effectively.

P2-184

Assessment of DRD2 dopamine receptor gene rs6277 in pediatric obesity: a case-control study

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Introduction: Obesity is a multifactorial disease resulting from an interplay between genetics and the environment. Metabolic, nutritional, psychosocial, and lifestyle factors participate, promoting various degrees of overweight or obesity. Pediatric obesity increases after infancy and is higher in early adulthood, showing a heritability of up to 85%. Genetic variants associated with BMI in children can exert their effects by affecting eating behavior, as is the case with single nucleotide polymorphisms (SNP) of the DRD2 gene. Patients who have the risk variation are more likely to have binge eating and hedonic disorders. The present study aimed to evaluate the allele and genotypic frequencies of the SNP rs6277 of the DRD2 gene in a pediatric population with obesity and their eutrophic controls.

Methodology: The case-control study enrolled 218 pediatric patients aged 5 to 16 years, 118 obese, and 100 eutrophics. In addition to the clinical evaluation, all participants underwent biochemical tests to measure the levels of fasting lipids, blood glucose, and insulin to calculate HOMA IR. DNA samples were extracted and genotyped by the real-time polymerase chain reaction method (real-time PCR).

Results: The risk allele (G) and the homozygous GG genotype were present in 57.6% and 36.4% of obese individuals and 54% and 29% of eutrophic individuals. Although the chi-square test was not significant for the distribution of the DRD2 polymorphism rs6277 genotypes among eutrophic and obese subjects, the Z-score for proportions of two populations was significant (0.00001; CI = 0, 05), indicating a tendency of the homozygous genotype for the risk allele (GG) to focus on the sample of the obese population.

The comparison of the allelic and genotypic distribution carried out between the Metabolically Sick (OMD) and Obese Metabolically Healthy (WHO) subgroups were significantly different for the distribution of the genotypes ($X^2 = 5.860$ and $p = 0.053$), with a predominance of the GG genotype among the OMD. The Odds Ratio was estimated for two or more cardiovascular factors between the groups, which resulted in an OR of 2.65 (CI = 1.016 to 3.682; $p = 0.031$) when the genotypes contained the risk allele.

Conclusion: The allelic and genotypic distribution proved to be significantly different from the distribution of the genotypes, with a predominance of GG among the metabolically ill obese. The A allele can be correlated with a protective effect in eutrophic individuals, despite its variation.

Keywords: pediatric obesity; DRD2 gene; polymorphisms; genotyping.

P2-185

A Comprehensive, Multidisciplinary, Personalized, Lifestyle Intervention Program is Associated with Increased Leukocyte Telomere Length in Children and Adolescents with Overweight and Obesity

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Background/Aim: Leucocyte telomere length (LTL) is a robust marker of biological aging and is associated with obesity and cardiometabolic risk factors even in childhood and adolescence. The aim of the present study was to assess the effect of a structured, comprehensive, multidisciplinary, personalized, lifestyle intervention program of healthy diet and physical exercise on LTL in children and adolescents with overweight and obese.

Materials and Methods: Five hundred (n=508) children and adolescents (239 males, 269 females; 282 prepubertal, 226 pubertal), aged 10.14 ± 0.13 years were recruited to participate in the study. Participants were classified as obese (n=267, 52.6%), overweight (n=174, 34.2%) or of normal BMI (n=67, 13.2%) according to the IOTF cut-off points and were studied prospectively for one year. All subjects followed a structured, comprehensive, multidisciplinary, personalized, lifestyle intervention program of healthy

diet and physical exercise, with frequent clinical and laboratory evaluation. LTL was measured using quantitative real-time PCR and telomeric restriction fragments (TRF) at the beginning of the study and following 12 months of intervention. In addition, success of the intervention was assessed by employing two criteria: i) The change (improvement) of IOTF category, and ii) The change of BMI z-score by 0.6. Secondary measures were metabolic and hormonal parameters that are known to change in obesity.

Results: Following 12 months of intervention, there was a significant decrease of BMI z-score (1.72 ± 0.06 ; $P < 0.01$). In 193 subjects (47.42%) the IOTF category improved, while in 175 subjects (42.99%) the BMI z-score decreased by 0.6. In all subjects, LTL increased significantly after 1 year of the lifestyle interventions (LTL_{baseline}: 1.35 ± 0.01 , LTL_{12 months}: 1.41 ± 0.01 , $P < 0.01$), irrespective of gender, pubertal status or BMI. Waist circumference was the best negative predictor of LTL at initial assessment. The implementation of the lifestyle interventions also resulted in a significant improvement in clinical (BMI, BMI z-score and waist to height ratio) and body composition indices of obesity, inflammatory markers, hepatic enzymes, HbA1C, QUICKI index, and lipid profile in all participants.

Conclusion: Our findings suggest that a comprehensive, multidisciplinary, personalized, lifestyle intervention program is associated with increased LTL in children and adolescents with overweight and obesity. Furthermore, the increase in LTL may be associated with a favorable metabolic profile and decreased morbidity later in life.

P2-186

Diagnostic accuracy of Tri-Ponderal mass index (kg/m³) for identifying glucose intolerance in obese children and adolescents

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Introduction: The identification of obese patients with increased susceptibility and risk for glucose intolerance and type 2 diabetes requires an oral glucose tolerance test (OGTT). Reference values for Body mass index (BMI) and Tri-Ponderal mass index (TMI) according to age and sex of healthy children in Spain without malnutrition or obesity have recently been published (*). TMI values remain very uniform in both boys and girls from the age of 8 to 18 years, therefore a single cut-off point is optimal to identify overweight (TMI ≥ 13.8 and ≤ 15.2) and obesity (TMI ≥ 15.3).

Objectives: to determine the prevalence of glucose intolerance and Type 2 diabetes in a cohort of obese children and adolescents and to establish the predictive value of the Tri-Ponderal mass index (TMI) and other anthropometric parameters to identify these comorbidities.

Patients and Methods: Cross-sectional study of 239 obese patients (125 males) aged 8 to 18 years (12.5 ± 2.3). 45.9% of which have grade 3 obesity. ROC curves were used to find the best cut-off point for: TMI (kg/m³), BMI (kg/m²), BMI z-score value (zsBMI)

	ROC Area	Sensitivity	Specificity	Correctly classified	Cut -off point (Youden)	Best Cut off point (AUC)
BMI	0.630	59.9	70.5	69.4	32.6	32.6
zsBMI	0.612	59.0	66.3	65.6	5.8	+ 5.8
TMI	0.582	31.8	88.4	83.2	23.1	21.5
ICT	0.557	40.0	80.1	76.5	0.66	0.63

and waist-to-height ratio (WHtR) to identify patients with glucose intolerance or type 2 diabetes according to American Diabetes Association criteria.

Results: The prevalence of glucose intolerance and type 2 diabetes in this cohort is 9% (10 males and 12 females) and 0% respectively, with no differences observed in relation to sex and age.

Conclusion: The diagnostic accuracy of IMT for identifying obese children and adolescents aged 8 to 18 years with impaired glucose tolerance is superior to the other anthropometric parameters evaluated and allows correct classification of 83.2% of patients. Obese patients with IMT > 21.5 should be considered for OGTT.

P2-187

Effect of Semaglutide on body weight in obese children with craniopharyngioma: a preliminary report

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Background: Pituitary insufficiency and severe obesity are common sequelae of craniopharyngioma and its treatment. Once weekly glucagon-like Peptide 1 (GLP1) analog's semaglutide has recently shown efficacy in adults with common obesity.

Objective: We evaluated the efficacy and safety of Semaglutide, a once-weekly GLP-1 analog, in 6 children with craniopharyngioma and morbid obesity.

Subjects and Methods: This retrospective study included 6 children, (1 girl, 5 boys) followed at Angers University Hospital, with a history of craniopharyngioma. All suffered from severe obesity (BMI Z-score > 3 or rapid increase in BMI despite appropriate hormone replacement and lifestyle intervention). Children received subcutaneous semaglutide once a week, with a starting dose of 0.25mg/week, monthly increased to 0,5 mg then 1 mg/week, maintained at 1 mg/week for 6 months, and then increased to the maximally tolerated dose (not exceeding 2 mg). The parents and children received oral information regarding what is known about GLP-1 analogs and Semaglutide in obesity treatment, the main undesirable effects, the uncertainty about the efficacy and safety in craniopharyngioma, the out of marketing authorization of semaglutide in childhood obesity. Semaglutide treatment was indicated in the ALD protocol of the national health insurance, and cranial MRI were performed every 3 months at the onset of the treatment. All parents and children agreed to the treatment.

Results: Mean age was 15 ± 3.1 years, time from craniopharyngioma diagnosis was 7.9 ± 5.4 years, mean BMI was 2.47 ± 0.38 Z score, and mean weight increase the previous year was 15.7 ± 7.3 kg. Five subjects received rhGH, 6 levothyroxin, 6 hydrocortisone, 5 sex steroid or recombinant hCG and recombinant FSH, and 6 DDAVP. After a mean duration of semaglutide of 7.3 ± 5.8 months, a mean last dose of 1.1 ± 0.2 mg/week, the mean excess weight loss (EWL) was 28 ± 28 % (0-70%). Three children had moderate adverse events such as belching, abdominal pain, and diarrheas and 1 participant had a suicidal attempt.

Conclusion: Semaglutide treatment showed encouraging results regarding the loss of weight in children with craniopharyngioma induced obesity. Further randomized studies are necessary, but preliminary results are usually necessary before performing such large studies.

P2-188

Development of a predictive normogram to assess the risk of liver steatosis in childhood obesity

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Background: Liver steatosis (LS) results from ectopic fat deposition and can be present in obesity even at early ages. Similar to insulin resistance, the onset of LS does not seem to depend exclusively upon the severity of obesity and shows a large interindividual variability.

Objective: Our objective was to develop a predictive normogram for LS in children and adolescents with obesity based on their demographic, anthropometric, body composition and metabolic features.

Patients and Methods: Presence of LS (ultrasonography) was studied in 50 children and 100 adolescents with obesity (BMI-SDS: $+4.10 \pm 1.37$; 50% Caucasians/50% Latinos; 50% males/50% females in each group). The variables that were significant in a

preliminary univariate analysis including demographic (sex, ethnicity), body fat content and distribution (whole-body DXA-scan, abdominal MRI) and metabolic parameters (uric acid, lipid profile, glucose and insulin, fasting and throughout the OGTT) served as independent variables for multivariate analysis (binary logistic regression using forward conditional method; dependent variable: LS). The discriminatory power of the model was evaluated using receiver-operator characteristics (ROC) curves.

Results: Prevalence of LS was 21.3% (n=32), higher in Latinos (χ^2 : 8.69; $p < 0.01$) both in children (33.3% vs. 16.0%) and adolescents (31.4% vs. 8.0%). Univariate analysis showed that the excess of body fat (BMI-SDS, body-fat%-SDS or fat/lean mass ratio by DXA) did not reach statistical significance, whereas abdominal fat distribution did [trunk/lower-limb and abdominal visceral/subcutaneous fat ratios (both $p < 0.05$)]. Significant influences of HOMA, WBISI and insulin at 120' in the OGTT (glucose metabolism) and triglycerides and HDL (fat metabolism) were also found. In the whole cohort (n=150), the Hosmer-Lemeshow model showed a discriminatory power of 0.7931 for LS prediction considering ethnicity, sex and HOMA as independent variables. However, when children and adolescents were analyzed separately, this model was not useful in prepubertal children whilst its discriminatory power increased in adolescents (0.8349), establishing a numerical risk score for LS in adolescents with obesity based upon their sex, ethnicity and HOMA value potentially applicable in the clinical setting. A similar model was also possible considering the abdominal visceral/subcutaneous fat ratio.

Conclusion: Ethnicity, sex, insulin resistance (as estimated by HOMA) and visceral fat accumulation, but not the severity of obesity, are the major determinants of the risk to develop LS in childhood obesity. Such risk can be estimated through a numerical predictive normogram in adolescents, but not in prepubertal children.

P2-189

Prospective evaluation of liver stiffness in obese children: the role of shear wave elastography

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Objectives: The increased incidence of childhood obesity and related non-alcoholic fatty liver disease (NAFLD) has determined the need to identify a non-invasive technique to diagnose and monitor NAFLD. Two-dimensional shear wave elastography (2D-SWE) has emerged as a reliable, non-invasive, tool to evaluate liver tissue elasticity in clinical practice. Aims of this study were to longitudinally evaluate 2D-SWE changes in relation to weight loss, metabolic profile and body composition modifications and to

investigate the correlation between 2D-SWE variation and clinical and biochemical indices of cardio-metabolic risk in obese children.

Methods: Thirty-three children underwent anthropometric (height, weight, BMI, waist circumference) and bioimpedentiometric (fat mass; free fat mass; total body water) evaluations, fasting biochemical assessments (glucose, insulin, total cholesterol, HDL, LDL, triglycerides, transaminases, oral glucose tolerance test), ultrasound and SWE evaluations (Mindray Resona 7 US machine equipped with a broadband SC5-1U convex probe), at baseline (V0) and after a 12-months follow-up (V12). Homeostasis model assessment of insulin resistance (HOMA-IR) and β -cell function (HOMA- β), Matsuda-index, triglycerides/HDL-ratio, total cholesterol/HDL-ratio, Areas Under the Curves for glucose (AUCg) and insulin (AUCi) and their ratio were assessed.

Standardized diet and exercise programs have been prescribed to all patients. Variation of all parameters was evaluated in intra- and inter-group comparison analysis in children who had not lost weight (Group A) and those who had lost weight (Group B) at V12.

Results: A significant reduction of mean 2D-SWE value was demonstrated both in the entire cohort ($p = 0.002$) and in Group B children ($p = 0.004$). Intra-group comparison analysis between V0 and V12 documented a significant decrease of BMI, BMI SDS and a significant improvement of metabolic profile, documented by the reduction of insulin, glucose, HOMA-IR, HbA1c, triglycerides, triglycerides/HDL-ratio, transaminases, and by an increase of Matsuda-index and HDL, in children of Group B but not in those of Group A. Inter-group comparison analysis of clinical and biochemical parameters, showed significant differences for BMI, BMI SDS, insulin, HOMA-IR, HOMA-B, triglycerides, triglycerides/HDL-ratio, total cholesterol/HDL-ratio, transaminases between Group A and Group B children after 12-months follow-up.

Conclusions: These results suggested an association between weight loss, metabolic profile improvement and 2D-SWE value reduction. SWE could play a significant role in the non-invasive assessment of NAFLD in children and adolescents with obesity.

P2-190

Evaluation of the nutritional behavior of small and large for gestational age children

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Background: In recent years a special interest of researchers is focused on questions related to the early stages of the formation of food behavior (FB), considering their close connection with socially significant problems of the present - obesity, metabolic syndrome, cardiovascular pathology, etc.

Aims: To assess the characteristics of the children's nutritional behavior, taking into account the level of physical development at birth.

Methods: A research of 122 parents was conducted using the Child Eating Behavior Questionnaire (CEBQ) (Wardle, 2001). The questionnaire was filled out by the mother and additionally contained information on the anthropometric indicators of the child and parents. The average age of the mothers at the time of questioning was 30.0 (28.0; 33.0) years. The study included healthy full-term babies aged 13 to 36 months of life. According to the weight at birth children were divided into 3 groups of observation: group 1 – LGA (n=52, BW 4315.3±263.7 g, length 55.6±1.4 cm), group 2 – SGA (n=34, BW 2459.4±202.6 g, length 47.3±2.5 cm), group 3 – AGA (n=36, BW 3345.0±225.8 g, length 52.1±1.6 cm). The umbilical cord leptin was 11.1 [4.7; 32.7], 3.4 [1.2; 4.9], 5.0 [2.3; 9.01] ng/ml, respectively ($p_{1-3}=0.001$, $p_{1-2}=0.024$).

Results: In children group 1 BW was 13.8 (12.1; 15.0) kg, z-score BW 1.2 (0.8; 1.7). Similar values in infants group 2 were 11.0 (10.1; 12.5) kg, -0.6 (-1.3; 0.6). In group 3 median BW was 12.4 (11.7; 14.0) kg, z-score BW 0.7 (0.0; 1.2). Comparative analysis of mean values according to the scales of the CEBQ showed statistically significant differences ($p=0.008$) in the age of 1 to 3 years for DD for children group 2 (2.30(1.70;4.00)) with children group 3(1.85(1.70;2.30)). In infants group 2, a negative correlation between BW ($r_s=-0.361$, $p=0.036$) and z-score BW ($r_s=-0.366$, $p=0.033$) with EF was found. In group 1 mother's weight and BMI had an effect on SE ($r_s=-0.351$, $p=0.011$; $r_s=-0.346$, $p=0.012$), positive correlation between the level of cord blood leptin and FR was revealed ($r_s=0.312$, $p=0.04$). The correlation between FR and EOE was stronger among infants group 1 in comparison with other children ($r_1=0.695$, $r_2=0.612$, $r_3=0.415$, $p<0.05$).

Conclusions: Specific features of FB formation among LGA and SGA children have been established. Analysis and timely correction of eating behavior and the diet of children should be carried out from the infancy.

P2-191

Resting energy expenditure and body composition in children and adolescents with severe obesity due to (suspected) medical causes: comparison between different subtypes of obesity

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Background: Paediatric obesity is a multifactorial disease characterized by an imbalance between energy intake and expenditure. In rare cases, obesity is caused by underlying medical disorders arising from disruptions in the leptin-melanocortin pathway, which regulates satiety and energy expenditure.

Aim: To investigate resting energy expenditure (REE) in relation to body composition in children and adolescents with severe obesity with (suspected) medical causes.

Methods: For this prospective observational study, we included patients who underwent an extensive diagnostic workup in our academic paediatric obesity centre. This included genetic testing, assessment of hypothalamic and medication-induced causes of obesity, REE measurement by indirect calorimetry (QUARK RMR) and body composition by air displacement plethysmography (BODPOD). The ratio between measured REE (mREE) in kcal/day and predicted REE (Schofield formula) is expressed as REE%, with lowered mREE defined as REE% ≤90%. Additionally, the ratio between mREE and fat-free-mass (FFM) was calculated. Associations of mREE/FFM with age and BMI SDS were investigated.

Results: In total, n=285 patients with severe obesity were included, of which in 65 (23%) an underlying medical cause was identified (Table). Mean age was 10.7 ± 4.4 years, 60% were female, mean BMI SDS was 3.7 ± 1.1. REE characteristics are presented in the Table. Across all patients, mREE was positively associated

	All patients (n=285)	Non-syndromic genetic obesity (n=28)	Syndromic genetic obesity (n=27)	Hypothalamic obesity (n=6)	Medication- induced obesity (n=4)	Idiopathic obesity (n=220)
mREE kcal/day	1706 (499)	1860 (655)	1475 (358)	1523 (285)	1517 (229)	1645 (523)
REE%	100.1 (13.6)	104.5 (14.6)	98.5 (9.0)	91.6 (17.6)	91.1 (20.3)	99.9 (13.7)
Lowered mREE	60 (21%)	4 (14%)	5 (19%)	2 (33%)	1 (25%)	48 (22%)
mREE/FFM kcal/ day/kg	46.8 (10.8)	45.9 (10.2)	50.8 (14.8)	42.0 (7.1)	-	46.5 (10.4)

Data presented as mean (SD) or count (%).

to FFM ($r = 0.87$, $p < 0.001$), whereas mREE/FFM was negatively associated with age ($r = -0.65$, $p < 0.001$), but not BMI SDS ($r = -0.00$, $p = 0.98$).

Conclusions: We present the REE characteristics of a large cohort of patients with severe obesity due to (suspected) medical causes, which on group level were similar in children with an underlying medical cause and with idiopathic severe obesity. In a substantial number of patients, a lowered REE was found. This knowledge can aid in developing patient-tailored treatment approaches, e.g. personalized dietary plans and/or pharmacologic treatment affecting central energy expenditure regulation such as glucagon-like peptide-1 receptor agonists and dexamphetamine.

P2-192

Exercise-induced expression of myokines in adolescents with simple obesity

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Myokines - biologically active proteins produces and secretes by skeletal muscles in response to physical activity (PA). They play a role in lipid and glucose metabolism, myogenesis and osteogenesis, thermogenesis activity. Exercise-induced expression of myokines in adolescents with simple obesity insufficiently studied.

Objective: to determine which intensity and duration of PA maximally changes the level of myokines (interleukin-6 (IL-6), myostatin, decorin, irisin).

Materials and Methods: 26 children (10 male/16 female), age 15 [13;16] years, SDS BMI: +2.91 [2.24;3.29] were divided into two groups: I (n=13) was performed PA (walking on a treadmill under heart rate control) duration 30 and 60 minutes at the same intensity (less than 3 metabolic equivalents (MET)) and II (n=13) was performed PA of different intensity: low (LPA) — less than 3 MET and moderate (MPA) — 3-6 MET at the same duration of 45 minutes. Myokines in blood were measured before and after PA.

Results: The groups were matched by age, sex, Tanner stages and basal levels of myokines. IL-6 concentrations were 0.205 [0.141; 0.236] and 0.256 [0.162; 0.344] pg/ml, myostatin 22.19 [18.65; 23.06] and 23.94 [21.53; 25.85] ng/ml, decorin 3.89 [3.036; 4.469] and 4.332 [4.043; 4.743] ng/ml, irisin 33.32 [22.516; 36.348] and 31.896 [22.27; 34.8] mkg/ml.

After 30 minutes of PA IL-6 level was increased by 68.3% ($p < 0.05$). PA for a 60 minutes produce lifting the levels of IL-6, myostatin by 68.3%, 28.8%, but irisin was decreased by 26.7% ($p < 0.05$ for all).

After LPA the levels of IL-6, myostatin, decorin were increased by 132%, 16.7%, 17.1%, irisin was decreased by 16% ($p < 0.05$ for all). MPA produce elevation the level of IL-6, myostatin, decorin by 151.6%, 30.9%, 34.3%, then irisin was reduced by 21.3% ($p < 0.05$ for all).

Conclusion: The results demonstrate the effect of PA on myokine secretion in adolescents with obesity. MPA induced an increase in the levels of IL-6, myostatin, decorin, while PA within 60 minutes led to a significant decrease serum levels of irisin.

P2-193

Early decline in Sertoli cell function during puberty in overweight and obese boys: a cross-sectional study

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Context: Alterations in semen characteristics and Sertoli and Leydig cell function have been described in obese male adults. Whether these alterations occur before adulthood has not been fully evaluated.

Objective and Design: Cross sectional study from 2010 to 2018 describing gonadal function in overweight-obese (ow/ob) boys through childhood and adolescence.

Setting: Monocentric study in the Pediatric Endocrinology Unit of Angers University Hospital.

Patients, Intervention, and Main Outcome Measures: 351 obese and overweight boys aged 5 to 19 years underwent physical examination, dual-energy X-ray absorptiometry for body composition, OGTT on insulin and glucose, and measurements of FSH, LH, anti-Müllerian hormone (AMH), inhibin B, testosterone, and estradiol. Hormonal levels were compared to normative data obtained from 652 lean healthy boys of similar age or Tanner stage.

Results: The increase in median inhibin B and testosterone levels during puberty was significantly lower in ow/ob compared to lean boys (i) from age > 12 years and thereafter for inhibin B, and (ii) from age > 14 years and thereafter for testosterone. At Tanner stages 4 and 5, 26%, 31%, and 18% of inhibin B, testosterone, and AMH values, respectively, were below the 5th percentile in ow/ob subjects ($p < 0.01$). In multiple regression analyses, estradiol and total bone mineral density Z-score were negative predictors of inhibin B, fat mass percentage was a negative predictor of testosterone, and insulin was a negative predictor of AMH.

Conclusion: An early decline in Sertoli cell function preceding that in Leydig cell function was observed during puberty in the ow/ob boys.

P2-194

Vitamin D deficiency in obese children

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Objective: determination of changes in metabolic status and vitamin D concentrations in obese children.

Methods: We examined 221 children in the University Hospital (Minsk) from 2019 to 2021 yrs. Their anthropometric parameters (height, weight, body mass index (BMI)) were determined. Blood levels of vitamin D, insulin were determined.

All children were divided into 2 groups: group 1 children with morbid obesity (MO) - 159 patients (98 boys(B)/61 girls(G)) (BMI more than 99th percentile for sex and age) (BMI 33.04 ± 4.67 kg/m², age 13.17 ± 2.42 years); group 2 - 62 patients (B/G=31/31) with alimentary obesity (AO) (BMI-95-99th percentile for sex and age) (BMI 27.60 ± 2.06 kg/m², age 13.43 ± 2.27 years). The control group (C) consisted of 60 patients (B/G=30/30) with normal body weight (BMI 19.86 ± 2.24 kg/m², age 13.32 ± 2.30 years).

Results: In boys and girls with obesity higher concentrations of insulin were detected relative to the control group (AO (G 16.36 (9.90–19.20) μ U/ml; B 17.07 (8.40–20.00) μ U/ml) and MO (G 21.06 (12.60–24.50) μ U/ml; B 20.79 (12.75–25.40) μ U/ml); C (G 8.35 (5.90–11.30) μ U/ml; B 9.83 (7.90–11.40) μ U/ml) ($G U_{AO-K}=228.00$; $p=0.0001$; $U_{MO-K}=276.00$; $p=0.0001$; B $U_{AO-K}=493.50$; $p=0.0001$; $U_{MO-K}=641.00$; $p=0.0001$)).

Insulin resistance index level (HOMA-IR) in patients with O (G 3.23 (1.97–3.94); B 3.49 (1.75–4.27)) and MO (G 4.14 (2.37–5.32); B 4.31 (2.55–5.46)) was higher than in the control (G 1.60 (0.99–2.18); B 1.89 (1.53–2.30)) ($G U_{AO-K}=219.00$; $p=0.0001$; $U_{MO-K}=304.00$; $p=0.0001$; B $U_{AO-K}=1050.50$; $p=0.0001$; $U_{MO-K}=592.50$; $p=0.0001$).

In patient of the study group a significant decrease in the level of vitamin D (G AO 25.90 (22.53–30.58) vs 39.36 (32.00–45.94) ng/ml; $U=67.00$; $p=0.0001$; G MO 20.18 (15.22–25.60) vs 39.36 (32.00–45.94) ng/ml; $U=36.50$; $p=0.0001$; B AO 27.57 (24.03–31.78) vs 36.12 (30.77–41.69) ng/ml; $U=161.50$; $p=0.0001$; B MO 23.01 (17.94–28.89) vs 36.12 (30.77–41.69) ng/ml; $U=327.00$; $p=0.0001$).

Conclusion: Children with obesity have a significant decrease in the concentration of vitamin D.

P2-195

Assessment of Hyperphagia in Patients with Monogenic Obesity

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Introduction: Besides an excessive, early-childhood weight gain, hyperphagia is the key symptom in patients with monogenic obesity. However, the assessment of hyperphagia is still challenging. Here, we applied the hyperphagia questionnaire developed for patients with Prader-Willi-Syndrome (PWS) to assess the severity of hyperphagia in patients with monogenic obesity.

Methods: Pediatric patients with biallelic pathogenic leptin receptor (LEPR) variants, heterozygous pathogenic melanocortin-4 receptor (MC4R) variants and 16p11.2 microdeletion including deletion of Src homology 2B1 (SH2B1) were recruited from our outpatient clinic. The 13-item hyperphagia questionnaire from Dykens et al. (2007), developed and validated to assess hyperphagia in patients with PWS was completed by their parents. All items were summarized in a total hyperphagia score and its subscores hyperphagic behaviour, hyperphagic drive and hyperphagic severity.

Results: Twenty children with monogenic obesity (mean age 9.67 ± 6.10 , mean BMI SDS 3.90 ± 0.91) were included in the analysis, thereof 8 patients with LEPR variants, 7 patients with MC4R variants, and 5 patients with 16p11.2 microdeletions. There were no group differences except for a significant higher BMI SDS in patients with LEPR variants (4.70 ± 0.79) compared to patients with MC4R variants (3.36 ± 0.73 , $p=0.004$) and 16p11.2 deletions (3.39 ± 0.38 , $p=0.015$).

The hyperphagia questionnaire showed a significant group difference only in the total hyperphagia score ($p=0.025$). A post hoc analysis revealed significantly higher total hyperphagia scores in patients with LEPR (32.0 ± 9.32 , $p=0.019$) and MC4R variants (31.4 ± 5.44 , $p=0.018$) compared to patients with 16p11.2 deletions (21.4 ± 5.46). Furthermore, patients with 16p11.2 deletions had hyperphagia scores similar to previous published obese controls. Regardless of genetic variant, there was a moderate negative correlation between patients age and the scores total hyperphagia ($r=-0.456$, $p=0.043$) and hyperphagic behavior ($r=-0.516$, $p=0.020$).

Conclusion: The hyperphagia scores indicate that the severity of hyperphagia is comparable in patients with biallelic LEPR and heterozygous MC4R variants. Consistent with parental narratives, patients with 16p11.2 deletions show hyperphagia scores indicative of less severe hyperphagia than patients with LEPR or MC4R variants. In addition, the inverse relationship between age and total hyperphagia score and between age and hyperphagia behavior subscore suggests that the severity of hyperphagia declines with age, with the highest scores in infancy and preschool age. Overall, the hyperphagia questionnaire for patients with PWS is a useful tool to assess the severity of hyperphagia in patients with monogenic obesity.

Machine Learning Quest for Predictive Markers of Lifestyle Modification Outcomes in Pediatric Obesity Treatment

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Context: The traditional approach to childhood obesity management is lifestyle modification/LSM. Nevertheless, the response rate is variable and difficult to predict.

Aim: A systematic search for markers to predict outcomes of simple LSM in pediatric obesity management.

Patients/Methods: Out of 240 children with obesity (BMI>97%), recruited to a prospective 'multi-OMICS' study granted by ESPE Research Unit, 159 subjects (age 8-17 yrs, median 12.8 yrs; 45% females) finished twelve-months of LSM obesity management at three clinical centers in three counties. Their baseline (V0) phenotype was precisely described with more than 180 clinical and laboratory features grouped as markers of general description, body composition/BC, family and patient's history, lifestyle/LS and socioeconomic status/SES, insulin resistance/IR, liver diseases/LD, metabolic syndrome/MetS, steroid metabolome and gut microbiome. Additional 150 features were measured at V3/V6/V12 months. Machine learning technique/CART as implemented in 'rpart' R-package was applied to build decision trees to automatically identify the combination of markers and their cut-offs with the strongest correlation to a "success" of LSM, defined as a decrease in z-score BMIV12-V0.

Results: 118 out of 159 (74.2%) participants were classified as responders to LSM. When built on the IR & LD features, a decision tree pointed to a strongest role of the following parameters: acanthosis nigricans/AN, resistin levels, glucose 120', NAFLD^{USG} and insulin/glucose ratio. The AN feature was significantly associated with the response to LSM (OR 2.75; p=0.0106), where the lack/presence of AN predicted success in 84%/65% cases, respectively. When the lack of AN was observed simultaneously with resistin value <16 ng/ml the response rate grew to 91% (OR 9.05; p=0.0026), while the presence of AN with glucose 120'≥136 mg/dl predicted 93% of the successful outcomes (OR 8.51; p=0.0281). On

the other extreme, high insulin/glucose ratio ≥0.34 (with the presence of AN together with NAFLD^{USG}, and with glucose 120'<136 mg/dl), decreased the success rate to 23% (OR 0.20; p=0.0452). Out of SES&LS features at V0, a small (<6.6hrs) number of sleep hours on schooldays /high frequency of sweet beverages were found to be associated with the lowest chance for success (OR 0.15/0.34, p=0.0023/0.013, respectively).

Conclusions: Insulin resistance features, history of inappropriate sleep or beverages consumption before intervention are significantly associated with failure of LSM in childhood obesity. Pending the validation on an independent cohort, our findings suggest the predictive role of these markers.

Triponderal mass index for the categorisation of childhood obesity on the basis of 58.364 observations of 7.792 patients

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Introduction: childhood obesity constitutes a relevant problem of public health. Body mass index (BMI) is the most used anthropometric parameter for its definition: >2 z-score deviation (SD) according to age and sex for reference charts. Recent studies have proposed triponderal mass index (TMI) to identify metabolic risk by obesity. TMI presents the advantage to be a constant value simplifying the calculations.

Aims: determine the usefulness of TMI as an identifier of childhood obesity (0-18 years).

Methods: demographic (age, sex) and anthropometric data (weight, size) of 58.354 clinical observations of 7.792 boys and girls, 0-18 years old, of the Pediatric-Endocrine Department of a Tertiary Hospital were evaluated. BMI (kg/m²), SD value for age and sex and TMI (kg/m³) were calculated. Sensitivity, specificity, VPP and VPN for the values of TMI according to the values BMI-SD z score (<2, 2-3, 3-4, 4-5, >5 SD) for sex were calculated. Two groups of age (<8 years and 8-18 years) were defined. UAC curve was used to determine the optimum cut-off point that maximizes the sensitivity and specificity of TMI in relation to the BMI z-score value.

Results: of 58.354 observations, 45.57% correspond to the <8 years group (42.62% boys, 57.40% girls) and 54.44% to the 8-18 years group (48.61% girls, 51.38% boys). In 8-18 years group a positive linear relation (r >0,95) was obtained between the BMI z score- value and TMI. For the < 8 years we did not observe this relation (r < 0,4). In children 8-18 years old, TMI point that correlates better with BMI-SD values was: 17.08, 18.90, 19.94, 21.36 for BMI(SD)<=2, 2<BMI(SD)<=3, 3<BMI(SD)<=4, BMI (SD)>4 for boys and 16.87, 18.48, 19.64, 21.18 for girls respectively. The AUC curve and the confidence interval for each TMI value are shown in attached table.

Niños 8-18 años				Niñas 8-18 años			
IMC (SD)	IMT	Área	95% IC	IMC (SD)	IMT	Área	95% IC
<=2	17.08	0.9026	0.8953-0.9098	<=2	16.87	0.8965	0.8900-0.9030
2-3	18.90	0.8029	0.7882-0.8177	2-3	18.48	0.8130	0.8004-0.8225
3-4	19.94	0.7757	0.7540-0.7974	3-4	19.64	0.7877	0.7699-0.8055
4-5	21.36	0.7479	0.7141-0.7816	4-5	21.18	0.8090	0.7842-0.8338
>=5	21.36	0.8854	0.8603-0.9104	>=5	21.18	0.8895	0.8705-0.9085

Conclusions:

- TMI presents a strong linear correlation with BMI-SD values in children 8-18 years old
- TMI allows to describe the obesity degree easier.
- In children <8 years the relation between both variables does not seem to be so useful

P2-198

Successful weight loss and resolution of hepatic fibrosis in a girl with severe obesity

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Introduction: Childhood obesity is continuing to increase worldwide resulting in a rise in the number of individuals with complications secondary to obesity. Non-alcoholic fatty liver disease (NAFLD) is seen in both adult and paediatric populations and if not treated appropriately is potentially life-threatening, as it may progress to advanced fibrosis, cirrhosis or hepatocellular carcinoma. NAFLD has now become the most common indication for liver transplant in adults.

Case Report: We report a thirteen-year-old female who initially presented to the primary care at the age of ten years with abdominal pain. She was noted to have a high body mass index (BMI) of 28.8kg/m² (+2.97 SDS) and a weight of 69.2 kg (+4.58 SDS). Biochemistry showed deranged liver function tests and a liver ultrasound identified extensive fatty deposition in the liver. The liver biopsy confirmed advanced fibrosis (NAFLD activity score of 7/8 and a chronicity fibrosis score of 3/4). Autoimmune and infection causes were excluded. The patient was managed with lifestyle intervention, but unfortunately this was unsuccessful. She was referred to the multidisciplinary team (MDT) weight management clinic at the age of thirteen years with a weight of 110.5kg (+6.05 SDS) and BMI of 36.1kg/m² (+3.18 SDS). Following a three-month period of an intense MDT programme, which included two-weekly reviews and Liraglutide (glucagon-like peptide-1 agonist) treatment, the patient demonstrated 9.7% weight loss. Her weight at the end of three months was 99.8kg (+4.83 SDS) and BMI was 32.9kg/m² (+2.81 SDS). A repeat liver ultrasound revealed some echogenicity suggestive of fatty changes, but the hepatomegaly and inflammation had resolved. The liver function tests have fully normalised following the treatment course (Table 1).

Conclusion: We report successful resolution of steatohepatitis and 9.7% weight loss in an adolescent female with significant

obesity following a 3-month course of Liraglutide treatment along with intense MDT support.

Table 1: Liver function test results following weight loss

Liver function tests	Aged 10 years	Aged 13 years pre-treatment	3-months post- treatment
Bilirubin			
Normal range: 0-15 umol/L	5	8	10
Aspartate Amino Transferase (AST)			
Normal range: 12-41 iu/L	88	43	23
Alanine Aminotransferase (ALT)			
Normal range: 8-36 iu/L	177	82	35
Gamma Glutamyl Transpeptidase (GGT)			
Normal range: 0-50 iu/L	73	31	31

P2-199

Association of Thyroid-Stimulating Hormone and Free Thyroxine Concentrations with Cardiometabolic Risk Factors in Euthyroid Obese Children and Adolescents with Metabolic Syndrome

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Background: Obesity in childhood and adolescence represents a major public health problem of our century and the leading cause

of premature cardiovascular disease (CVD). A moderate elevation of thyroid-stimulating hormone (TSH) concentrations is frequently observed in obese children.

Aim: The aim of our study was to evaluate the association of TSH and free thyroxine (FT4) concentrations with the clustering of cardiometabolic risk factors in obese euthyroid children and adolescents with Metabolic Syndrome (MS) compared with their counterparts without MS.

Methods: One thousand four hundred (n=1400) obese children and adolescents attending our 'Out-patient Clinic for the Prevention and Management of Overweight and Obesity in Childhood and Adolescents' were evaluated in order to determine those fulfilling the International Diabetes Federation (IDF) criteria for MS. The study was approved by the local Committee on the Ethics of Human Research. All participants underwent clinical examination and standard anthropometric measurements were obtained by a single trained observer. A fasting blood sample for baseline biochemical and endocrinologic investigations was obtained at 08:00h, and was followed by an oral glucose tolerance test.

Results: Seventy eight (n=78) children and adolescents [mean age $\pm$ SD: 13.1 $\pm$ 1.9 years; 46 males (59.0%) and 32 females (41.0%); 13 prepubertal (16.7%), 65 pubertal (83.3%), BMI 35.6 $\pm$ 4.6, SBP(mmHg) 126.8 $\pm$ 12.2, DBP(mmHg) 75.2 $\pm$ 1.1] were identified as having MS compared with fifty four (n= 54) obese children and adolescents without MS [mean age $\pm$ SD: 12.0 $\pm$ 2.1 years; 33 males (61.1%) and 21 females (38.9%); 16 prepubertal (29.6%), 38 pubertal (70.4%), BMI 32.3 $\pm$ 3.8, SBP(mmHg) 115.6 $\pm$ 9.8, DBP(mmHg) 68.1 $\pm$ 1.2]. In the MS group, the variables FT4 and waist circumference appeared to have a statistically significant negative correlation ($r=-0.246$, p -value=0.031) after adjustment for possible confounders. Similar negative correlation was found between FT4 and BMI ($r=-0.225$, p -value=0.048) whereas in non MS group, a negative correlation was found between FT4 and insulin ($r=-0.393$, p -value=0.004). Simultaneously, comparable correlations adapted to age, sex and BMI were performed in both populations between TSH, FT4 and cardiometabolic risk factors and repeatedly FT4 had a negative correlation with insulin ($r=-0.176$, p -value=0.048). No significant correlation was found between TSH and other cardiometabolic risk factors. These results were comparable for the two patient groups with or without MS, indicating that the prevalence of MS didn't affect to a greater extent the variables.

Conclusions: Our findings demonstrate that lower FT4, even within the reference ranges, may be related to increased cardiometabolic risk factors in obese children and adolescents with or without MS.

P2-200

Impact of weight loss on gonadic function in overweight and obese boys

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Introduction: In obese boys, alteration of Sertoli and Leydig cell functions have been described, but potential reversibility of these alterations after weight loss during childhood has not been fully evaluated.

Objective: Evaluate the impact of weight loss on gonadic function in obese boys.

Setting: Monocentric study in the Pediatric Endocrinology Unit of Angers University Hospital and its follow-up and rehabilitation care.

Methods: Thirty-four obese boys aged 10 to 18 participated between 2012 and 2020 to a 12-weeks therapeutic educational program. At baseline and at week 12, all underwent physical examination, DEXA for body composition, and measurements of FSH, LH, AMH, inhibin B, testosterone, estradiol, fasting insulin, and glucose.

Results: Weight, Body Mass Index (BMI), percentage of fat mass, fasting insulin, and Homeostasis model assessment of insulin resistance (HOMA-IR) decreased significantly at week 12 ($p<.01$). Median testosterone levels increased significantly after weight loss ($p=.001$), and this increase correlates with the amount of fat mass loss ($r=-0.39$, $p<.05$). Median inhibin B, AMH, FSH, LH and estradiol levels were not statistically different after weight loss.

Conclusion: Alteration of Leydig cell function may be reversible after weight loss in obese children, while no change was found in Sertoli cell function. Increase in testosterone levels may be linked to fat mass loss.

P2-201

Weight status and body composition of children and adolescents during the COVID-19 pandemic

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Background: The COVID-19 pandemic has tremendous effects on lifestyle that could potentially cause health-related problems. Therefore, extreme preventive measures were taken, including the closure of schools and after school activities. This dramatic

alteration in daily routine could lead to adverse consequence of increasing obesity. In this study we aimed to investigate the change in weight status and body composition parameters of children and adolescents during the pandemic.

Methods: This real-life, observational study was conducted in the Pediatric Endocrine Unit in a tertiary medical center. Our unit has implemented the analysis of body composition by means of bioelectrical impedance analysis (BIA, Tanita MC-780MA, GMON Professional Software) as part of routine assessment of patients referred for endocrine consultation. The BIA database was searched for children and adolescents (age 5-18 years) with the sole diagnosis of 'observation of growth' and/or 'observation of puberty' whose body composition parameters were measured during the COVID-19 pandemic (from May 15, 2020 until December 15, 2020). Included were subjects for whom pre-COVID-19 BIA measurements were available. Height, body mass index (BMI) and muscle-to-fat ratio (MFR) z-scores were calculated.

Results: 220 pediatric subjects (109 boys; mean current age 11.8 $\pm$ 3.3 years; 37 with underweight, 123 with normal weight, and 60 with overweight/obesity) were included in the analysis. During the pandemic the median [IQR] BMI z-scores significantly increased in subjects with underweight (from -2.07[-2.34, -1.88] to -1.73[-2.35, -1.35], $P < 0.001$) and normal weight (from -0.38[-0.95, 0.27] to -0.24[-0.87, 0.37], $P = 0.035$), while it did not change in subjects with overweight/obesity (from 1.74[1.40, 2.03] to 1.70[1.36, 1.97], $P = 0.412$). MFR z-scores significantly increased in subjects with underweight ($P = 0.05$) and normal weight ($P = 0.008$), but not in subjects with overweight/obesity ($P = 0.169$). There were significant associations in BMI z-scores ($r=0.961$, $P < 0.001$) and MFR z-scores ($r=0.854$, $P < 0.001$) before and during the pandemic.

Conclusions: Our findings are encouraging, since improvement in weight status and body composition parameters during the COVID-19 pandemic was observed in subjects with underweight and normal weight, and stability was observed in subjects with overweight/obesity.

P2-202

The challenges faced in the management of Congenital Generalized Lipodystrophy

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Background: Congenital Generalized Lipodystrophy (CGL) is a rare autosomal recessive disease. The prevalence has been reported to be 1 in 10million with around 500 cases worldwide. The absence of functional adipocytes results in storage of lipids in other tissues, including muscle & liver. The diagnosis of CGL is based on clinical data; however, there is phenotypic heterogeneity. Metreleptin injections cause decreased appetite & is beneficial in lowering triglycerides (TG), liver enzymes, & better glycemic control. Unfortunately, it is not available in Egypt.

We hereby report 2 cases diagnosed with CGL, and the challenges faced in their management in the absence of metreleptin.

Case 1: A 13-year-old girl born to non-consanguineous parents. Her parents noticed facial dysmorphism & loss of subcutaneous fat. At age 8 years, she had recurrent attacks of abdominal pain & her U/S showed bilateral ovarian cyst torsion.

At age 9 years, she was diagnosed clinically with CGL (hepatomegaly, acanthosis nigricans, acromegaly features & muscular appearance). Her TG, fasting blood sugar, & liver functions were normal. After skipping follow up for 2 years, xanthomas were observed on the upper & lower limbs with severe hyperTG. She was also diagnosed with DM with HbA1c 13% & high C-peptide. She was discharged on dietary advice, insulin, metformin, omega 3, fenofibrates & statins.

At age 12 years, she complained of severe abdominal pain with shooting lipase & admitted with acute pancreatitis due to hyperTG. She continued to have recurrent attacks of pancreatitis-even though antilipidemic treatment was maximized. Her last HbA1C is 9.6% on insulin requirement 5 U/Kg/day & she never had DKA.

Case 2: A 12-year-old girl born SGA to consanguineous parents. She was diagnosed with CGL at the age of 4 months with typical facial features, hepatomegaly, hirsutism, hyperTG, & elevated liver enzymes. Her liver biopsy showed moderate macrovesicular steatosis & cirrhosis. She was given fenofibrates.

At 4.5 years, she had advanced bone age, height +2.6SD, & developed precocious puberty. She complained of polyuria, polydipsia at 7 years & was diagnosed with DM (HOMA-IR 8.1%, HbA1c 8.4%), & started metformin. Her last HbA1c is 6.9% on only metformin 2000 mg/day & has normal TG level. She has never had attacks of pancreatitis or DKA. However, she has liver cirrhosis & is on liver support.

Conclusions: CGL is a rare & severe disease that can manifest with DM at any age. Patients can be diagnosed clinically as their phenotypic characteristics are unique; however, different presentations and severity exist. Without metreleptin, challenges are faced & treatment should be individualized.

P2-203

Anthropometric and clinical situation in two groups of young adults born Small for Gestational Age (a group with catch-up and another without catch-up and treated with Growth Hormone)

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Introduction: Children with Small for Gestational Age (SGA) are known to have lower neurocognitive development and an increased in cardiovascular risk in adulthood. 10% of SGA don't usually do the catch-up and if they meet criteria they have indication to follow Growth Hormone (GH) treatment.

Objectives: To establish the difference between SGA diagnosed children who did or did not catch-up (treated with GH), in terms of: newborn anthropometry (weight at birth (WB) and Length at

birth (LB), Final Height (FH) relative to their Target Height (TH): (FH-TH), Body Mass Index (BMI), lipid profile, metabolism of carbohydrate, blood pressure (BP) and academic level valued as studies conducted.

Materials and Methods: Data are collected from a sample of 61 adults born PEG (treated and not treated with GH). Informed consent was obtained by phone, as well as clinical-analytical data that were contrasted with The Clinical History. Those who were premature, multiple parity and those with syndromes were excluded.

NOT CACHT-UP GROUP: 30 adults (15 female). Age (mean: 22.8 years); range: 18-30 y. At the birth: WB (sds); mean: -2 sds; range: -3.8- (-0.4); LB (SDS); mean: -2.37 (-0.55 to -4.44). Final height (cm) in female, mean: 153 (r: 148-163.5) and males: 167 (r: 160-170.5). The FH-TH (sds): -0.57 (r: -2.05-1). The actual BMI is 19.8 (r: 15.2-25). Only a patient has overweight. The 48.4% have University studies.

CACHT-UP GROUP: 31 adults (15 female). Age (mean: 27.5 years); range: 23-32 y. At the birth: WB (sds); mean: -3 sds; range: -4.5- (-1.6); LB (SDS); mean: -3.2 (r: -4.7 to -1.99). Final height (cm) in female, mean: 160.8 (r: 152-174) and males: 169.7 (r: 160-189.0). The FH-TH (sds): -0.31 (r: -2.7-1.54). The actual BMI is 23.6 (r: 17.2-31.1). Three adults have obesity and six have overweight. The 25% have abnormal lipid profile or abnormal BP. The 38% have University studies. Anthropometric data at birth are significant smaller in catch-up group ($p < 0.001$). The mean final height is significant higher in Catch-up group ($p < 0.001$). No difference in FH-TH. The BMI is significant higher in Catch-up group ($p < 0.001$).

Conclusions:

Anthropometry at birth is lower in those who recovered size, but the final size is larger.

- Both groups reach similar academic levels
- There are no differences between the two groups in FH-TH.
- BMI is higher in those who did catch-up and they presents more cardiovascular risk.

P2-204

Changes in objectively measured physical activity after 2-year lifestyle intervention in pediatric patients with abdominal obesity

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Introduction: it has been widely demonstrated that high physical activity (PA) levels prevent obesity development. The practice of moderate, regular PA reduces abdominal obesity, hypertension, insulin resistance, dyslipidemia and improves risk factors for obesity-related comorbidities (e.g. diabetes or cardiovascular diseases) independently of weight loss. However, in the childhood population, where sedentary behavior has increased in recent decades, few studies have assessed the effect of lifestyle interventions on

changes in PA, measured by accelerometry in pediatric patients with abdominal obesity.

Methods: one hundred and two children and adolescents with abdominal obesity (7-16 years old) were enrolled in a lifestyle intervention program for two years. Participants were encouraged to accumulate extra 200 min/week of PA. PA was assessed by accelerometry. Available data of objectively measured PA was obtained from 38 participants at the end of intervention.

Results: participants (mean age 11 years; 61% female) achieved a significant reduction in anthropometric (percentage of fat mass -3.99 ± 5.76 ; $p < 0.001$) and biochemical parameters (total cholesterol -15.12 ± 21.41 , $p < 0.001$; LDL-cholesterol -12.27 ± 16.18 , $p < 0.001$; triglycerides -26.81 ± 39.63 ; leptin -6.95 ± 14.03 , $p = 0.023$) after the 2-year lifestyle intervention. In addition, a significant decrease in light PA levels (-87 min/day, $p < 0.001$) was observed. In multiple regression analysis changes in light PA levels were positively associated with changes in leptin levels ($R^2 = 0.321$, $p = 0.012$).

Conclusion: participants significantly improved anthropometric and biochemical parameters. In addition, favorable changes in PA levels could affect leptin levels after 2-year lifestyle intervention in pediatric patients with abdominal obesity.

P2-205

Assessment of cardiometabolic risk factor clustering in obese children and adolescents with metabolic syndrome

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Background: Obesity in childhood and adolescence has reached epidemic proportions. Endothelial dysfunction, as a consequence of dyslipidemia, hypertension, insulin resistance and inflammation, imposes a substantial risk for the development of metabolic syndrome (MS) in childhood and compromises the health of the pediatric population by promoting premature development of atherosclerotic cardiovascular disease.

Aim: To investigate the cardiovascular risk in obese children and adolescents with MS compared with their obese counterparts without MS.

Patients and Methods: Eighty eight ($n = 88$) obese children and adolescents [mean age $\pm$ SD: 13.1 ± 1.9 years; 53 males (60.2%) and 35 females (39.8%); 14 prepubertal (15.9%) and 74 pubertal (84.1%)] with MS and sixty ($n = 60$) obese children and adolescents without MS [12.2 ± 2.1 years; 37 males (61.7%) and 23 females (38.3%); 18 prepubertal (30%) and 42 pubertal (70%)] were studied prospectively for one year. All participants received personalized

advice on diet and exercise, while 26 (29.5%) participants in the MS group and 13 (21.7%) participants in the control group also received metformin. Biochemical and endocrinologic investigations, oral glucose tolerance test, echocardiography, ultrasonography of the carotid arteries and liver were performed at the beginning and at the end of study.

Results: Systolic and diastolic blood pressure was significantly higher in children with MS (127.9 ± 13.1 and 76.7 ± 11.3 mmHg, respectively) than those without MS (116.6 ± 10.5 and 68.2 ± 9.2 mmHg, $P < 0.001$). At the beginning of the study (t_0), subjects with MS had significantly lower HDL [39.1 ± 1.2 vs. 45.2 ± 1.2 mg/dL, $p < 0.001$], and higher triglycerides (125.1 ± 1.6 vs. 86.5 ± 1.5 mg/dL, $p < 0.001$) and insulin (30.4 ± 1.6 vs. 20.7 ± 1.4 μ IU/mL, $p < 0.001$) concentrations compared with the control group. The carotid intima-media thickness (cIMT) at t_0 was 0.8 ± 1.1 mm in the MS group and 0.7 ± 1.1 mm in the non MS group, respectively (normal range: 0.49 ± 0.03 mm), whereas after 1 year of intervention cIMT_{t₁₂} improved significantly only in children with MS (0.5 ± 0.2 mm, $p < 0.05$). Furthermore, patients with MS and ≥ 3 risk factors had significantly higher cIMT compared to those with 2 or less risk factors. Interventricular septal end diastole and systole were significantly higher in patients with MS (8.4 ± 1.7 mm and 9.0 ± 1.3 mm, respectively) than the control group (7.8 ± 1.2 mm and 8.2 ± 1.3 mm, $p < 0.05$). Hepatic steatosis was identified in 69 (78%) of the participants with MS and in 34 (56.7%) obese without MS.

Conclusions: Our findings demonstrate increased cardiovascular risk in children and adolescents with MS, as well as an improvement in certain cardiovascular parameters following intervention.

P2-206

HOMA-IR in obese children with BMI ≥ 2.5 SDS, but not < 2.5 SDS, differ significantly from normal weight children

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Objective: Compare HOMA-IR between obese and normal weight children.

Methods: 292 children (156 females), BMI (≥ 0 SD), Tanner stage 1/ >2 : 163/129, divided in four groups (Group 1: $0SD < BMI < 2SD$, Group 2: $2SD \leq BMI < 2.25SD$, Group 3: $2.25SD \leq BMI < 2.5SD$, Group 4: $BMI \geq 2.5SD$) were analyzed retrospectively from the medical records. Age, sex, fasting blood glucose and insulin as well as the homeostasis model assessment of insulin resistance (HOMA-IR) [(fasting glucose-mmol/L $\times$ fasting insulin mIU/l)/22.5] were recorded and insulin resistance was defined as $HOMA-IR \geq 3.4$. One-Way and Two-Way Analysis of variance (ANOVA), $p < 0.05$, were calculated among groups using the SPSS statistics program.

Results: Mean age was 9.5 yrs (SD, 3.07), BMI: 2.28 (SD, 0.59), HOMA-IR: 3.88 (SD, 3.6), fasting glucose: 87.3 (SD, 8.3) mg/dl, fasting insulin: 17.9 (SD, 16) mIU/Lt. Clinical and laboratory characteristics are summarized in table 1. HOMA-IR was significantly higher in group 4 only as opposed to group 1 ($p: 0.02$) but not group 2 or 3. Prepubertal boys in groups 2, 3, 4 and overall had higher HOMA-IR as opposed to girls (4.1/3.5, boys/girls), but in puberty this finding was reversed (3.6/4.4 boys/girls). However, there was no statistically significant difference among groups in relation to sex or puberty.

Conclusion: Obese children with BMI ≥ 2.5 SDS, but not BMI < 2.5 SDS, present significantly higher HOMA-IR as opposed to normal weight children, irrespectively of sex or Tanner stage.

Table 1. Clinical and laboratory characteristics, Mean (SD).

	Group 1 (n=55)	Group 2 (n=78)	Group 3 (n=70)	Group 4 (n=89)	p
Age (yrs)	10.9 (2.4)	9.7 (2.2)	9.5 (2.8)	7.6 (3.6)	*
Sex (boys/girls)	20/35	37/41	32/38	47/42	
Tanner stage I/II-IV	20/35	47/31	36/34	60/29	*
BMI z-score	1.7 (0.27)	2.1 (0.06)	2.4 (0.08)	2.9 (0.65)	*
HOMA IR	3.1 (1.0)	3.6 (3.0)	3.9 (2.7)	4.6 (5.1)	
< 3.4	69%	62%	52%	52%	*
≥ 3.4	31%	38%	48%	48%	
Fasting Glucose (mg/dl)	89(8.6)	87 (8.3)	87 (7.8)	86 (8.2)	*
Fasting Insulin (mU/l)	14 (8)	17 (14)	18 (11)	21 (23)	*

P2-207**Restriction of physical activity is the main cause of childhood obesity during the COVID-19 pandemic – reflections from a study conducted in 3 clinical centers in southern Poland**

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Background: The aim of this study was to analyze the impact of the COVID-19 pandemic lockdown on behaviors and subsequent changes in BMI in children from southern Poland.

Methods: The study included 206 participants (104 females and 102 males) with a complete analysis of 177 (96 females and 81 males) with a mean age of 12.8 ± 2.6 years admitted to three pediatric endocrinology clinics (Rzeszów, Kraków, and Katowice) between June and September 2020. The study used an original questionnaire regarding eating habits, physical activity, screen time, and sleep before and during the lockdown. Anthropometric measurements were performed under clinical settings twice (before the pandemic in January-March 2020, and in June-September 2020).

Results: During the lockdown, BMI z-scores increased over the whole group, especially in obese children (0.073 ± 0.18). The amount of children who declared light and vigorous physical activity of more than 60 minutes per day declined from 41.2% and 18.6% to 31.1% and 6.2% ($p=0.03$ and $p<0.001$) respectively; sleep times over 8 hours increased (46.9% vs. 60.4% $p=0.007$); screen times over 5 hours daily increased (14.7% to 46.9%, $p<0.001$). Eating habits did not change significantly.

Conclusions: The main factor leading to childhood obesity during the pandemic is limitation of physical activity. During the COVID-19 pandemic, forward-thinking strategies must be developed to prevent childhood obesity.

P2-208**OSAS in childhood obesity is a more frequent and earlier complication than expected**

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Introduction: Childhood obesity is associated with several complications, involving many systems. The prevalence of

respiratory problems, such as obstructive sleep apnea syndrome (OSAS), is higher in obese children and adolescents. In fact, OSAS affects 13–59% of obese children and the severity is strongly associated with weight excess. Although overnight pulse oximetry (PO) can be used for diagnosing OSAS, a complete night polysomnography (PSG), which records peripheral oxygen saturation, heart rate, respiratory airflow and effort during sleep providing information about the sleep stages, is the gold standard for Sleep Disorders of Breathing (SDB) diagnosis.

Aim: An observational study to evaluate differences in SDB between obese and non-obese children and adolescents referred snoring. Patients and methods: 77 subjects, aged between 2 months and 17 years were enrolled. All the subjects underwent a PO and a complete night PSG, and all the parameters for apnea/hypopnea and quality of sleep were analyzed. Parents of all the subjects enrolled filled out OSAS18 questionnaire for evaluation of the quality of life. For obese subjects, metabolic parameters were collected. Results and discussion: 22 obese (14M) and 45 Non-obese subjects (33M) were recruited, with a mean age of 10.5 ± 2.8 and 4.8 ± 2.5 respectively ($P<0.0001$). All the obese children resulted affected by OSAS. At PO: obese children have lower both Oxyhemoglobin Desaturation Index (ODI), $p=0.02$, and McGill oximetry scoring system (MOS), $p=0.002$, as expression of more prolonged desaturations in obese subjects compared to the shorter, but deeper, and organized in cluster desaturations of non-obese children with OSAS. At PSG: Obese children presented a higher apnea/hypopnea index (AHI), $p=0.03$, revealing more severe OSAS. Obstructive-AHI (index of peripheral apnea) was not different in the 2 groups, confirming that obese subjects had both prolonged obstructive apneas and alterations in the drive trigger for breathing. No differences in neither sleep efficacy nor %REM phase (in our experience, as non-obese children with OSAS were much younger, they were more habitual and less adaptive to fall asleep in a different setting such as the hospital).

Conclusions: OSAS is a frequent and early complication in obese children with snoring. OSAS is more severe in young children with obesity, as documented by PSG (more sensible than PO). The type of desaturations are both obstructive and central. In a hospital setting, no differences were found in sleep quality between obese and non-obese subjects, maybe because of the different age of the 2 groups.

A novel homozygous variant of the leptin receptor (LEPR) gene causing familial early-onset severe obesity in two siblings

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Introduction: The leptin-melanocortin pathway is a well-studied pivotal player of body weight regulation and energy homeostasis. Pathogenic mutations of the genes involved in this pathway may result in early-onset severe obesity (ESO).

Case Report: We hereby report the case of a 14-year-old girl who was referred to our pediatric outpatient clinic for the evaluation of ESO. Her parents were non-obese first cousins born in Morocco. At the time of consultation, the two brothers of the proband were healthy and had normal BMI, while the 8-year-old sister presented with ESO.

The proband's birth weight was 3000 grams (-1.1 SDS, WHO). After the first month of life, she progressively became hyperphagic and rapidly developed severe obesity, with her height SDS being always within the reference ranges for age. Despite dietary and lifestyle interventions, her BMI progressively raised from 36.4 Kg/m² (+7.98 SDS) at the age of 3 years to 60.86 Kg/m² (+4.63 SDS) when she was 16 years old. Over time she developed obesity-related complications: impaired glucose tolerance, liver steatosis and obstructive sleep apnea syndrome.

Endocrine testing and genetic counseling ruled out hypothyroidism, hypercortisolism and Prader-Willi syndrome. The extreme severity and early onset of the clinical picture in both proband and her sister, the patchy distribution of obesity among the proband's relatives and the absence of syndromic features prompted to perform a next generation sequencing (NGS).

A novel homozygous *c.1603+3A>T* variant involving the leptin receptor (*LEPR*) gene was demonstrated in both the proband and her sister. Parents were found to be heterozygous carriers, while both brothers were variant-negative.

The proband and her sister have been enrolled in a clinical trial treatment with a melanocortin-4 receptor (MC4R)-agonist, a promising weight loss drug for patients presenting with *LEPR* resistance.

Discussion: Monogenic obesity resulting from mutations in the *LEPR* gene has been described for the first time two decades ago. The inheritance pattern and the genotype-phenotype association support the hypothesis of a pathogenic role of the novel *c.1603+3A>T* variant hereby described.

Conclusions: In conclusion, hyperphagia, patchy familial involvement and consanguineous parents should promptly rise the suspicion of monogenic obesity. Functional analysis may confirm the pathogenicity of *c.1603+3A>T* variant. The therapeutic effectiveness of a novel MC4R-agonist will be tested in the proband and her sister, as they have been enrolled in a clinical trial for the treatment of patients with ESO due to inactivating *LEPR* gene mutations.

Sleep quality and metabolic syndrome in pediatric patients with abdominal obesity

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Aim: to evaluate sleep quality by accelerometry and its association with anthropometry and biochemical parameters in children and adolescents after a multidisciplinary intervention

Subjects, Materials and Methods: One hundred and twenty-two children and adolescents with abdominal obesity, aged 7 to 16 years, were included in a multidisciplinary intervention study to lose weight. Abdominal obesity was diagnosed using the waist circumference (>p90). The intervention included an intensive phase during 2 months. Participants were divided in two groups: intervention and control. Intervention group was treated with hypocaloric Mediterranean diet and the control group with the standard recommendations from Community Nutrition Spanish Society, 2007. Both groups were advised to increase in 200 minutes per week their moderate-vigorous physical activity. Sleep was assessed by accelerometry (Actigraph GT3X) at the onset, after intensive phase, at 12 and 24 months of follow-up. Sleep parameters analysed were: number of awakenings and sleep latency, total sleep time, time in bed, awakenings duration and wake after sleep onset (WASO). Anthropometric parameters measured were: weight, height, body mass index, waist, hip and neck circumferences, fat mass and fat-free mass. Biochemical parameters determined were: insulin, leptin, cholesterol and triglycerides. Statistical analysis was done using STATA 12.0.

Results: sleep parameters improved in both groups throughout the follow-up and the improvement was higher and statistically significant in the intervention group. We observed the following statistically significant associations: latency and efficiency, number of awakenings and awakenings duration, efficiency with all the sleep parameters, number of awakenings and efficiency, awakenings duration and WASO, time in bed and both total sleep time and WASO. At 2 years follow-up, we observed a higher reduction in both insulin and leptin and a higher significant improvement in all the anthropometric parameters in the intervention group. At 2 years follow-up, we observed the following statistically significant associations: triglycerides reduction and time in bed, fat mass decrease and number of awakenings reduction, awakenings duration reduction and LDL-cholesterol decrease, latency improvement and insulin reduction.

Conclusion: the significant anthropometric, biochemical and sleep parameters changes observed after intervention remain throughout the follow-up of the patients, and is accompanied by an improvement in their sleep quality, and a decrease in their cardiometabolic risk metabolic.

P2-211

The lockdown effects on a pediatric obese population in the COVID-19 era

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Background: The social consequences of COVID-19 pandemic are universally known. In particular, the pediatric population is dealing with a radical lifestyle change. For some risk categories, such as overweight and obese children, the impact of home confinement has been greater than for others. Not only have the increased sedentary life, the wrong diet and social distancing stopped the chance of losing weight, but also worsened the general life conditions.

Methods: Data show the differences between 40 obese and overweight pediatric patients of our Clinic in Messina (Italy). We evaluated weight, height, BMI and other biochemical parameters, such as total cholesterol, HDL, LDL, triglyceride, transaminases, glycemia and insulinemia. After the lockdown, we contacted all patients in order to get some information about diet, physical activity and sedentary lifestyle changes in correlation to the level of their parents' instruction. Additionally, we evaluated 20 children twice from a clinical and laboratory perspective.

Results: The study showed an increase of daily meals during COVID-19 lockdown (3.2 ± 0.4 vs 5 ± 1 , $P < 0.001$). In particular, children whose parents have primary school diploma ate a greater significant number of meals during the lockdown, compared to the others who have parents with secondary school diploma ($P = 0.0019$). In addition, the 95% of patients did low physical activity during the lockdown and the 97.5% spent more time in sedentary activity. Even if BMI's values don't show significant differences, they have increased after the lockdown. We didn't find any correlation between biochemical parameters before and after the lockdown.

Conclusion: The lockdown has had bad consequences on good style of life's maintenance in overweight and obese children. The absence of a significant correlation between the worsening of biochemical parameters and the lockdown doesn't allow to exclude any long-term consequences. It's safe to assume that, if the hours spent in sedentary activity and the number of meals do not diminish there will probably be repercussions on the biochemical parameters.

P2-212

The Relationship between Acanthosis Nigricans and Vitamin D Levels in Obese Children

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Aim: Acanthosis nigricans (AN) is the most important skin complication of obesity. In our study, the relationship of acanthosis nigricans and vitamin D levels was evaluated in children.

Methods: Obese children aged between 6 and 18 years old, who were examined in the pediatric endocrinology outpatient clinic, were included. The patients' anthropometric measurements and laboratory results and vitamin D levels were recorded.

Results: Eighty nine obese children were evaluated. The mean age of the cases was 11.51 ± 3.04 years old. Of the cases, 58.4% were female ($n=52$) 41.6% ($n=37$) were male, 59.6% of them were pubertal ($n=53$) while 40.6 of them were prepubertal ($n=36$). In 60.9 % of cases ($n=53$) AN was determined. In the cases, Low vitamin D level was found in 83.1% ($n=74$) of cases. Obese children with AN have lower levels of vitamin D (11.59 ± 4.33 ; 14.83 ± 7.52 $p=0.013$) and significantly higher insulin levels and HOMA-IR $p=0.005$, $p=0.001$). Obese children who have low vitamin D levels have higher HOMA-IR (5.43 ± 2.20 ; 4.04 ± 1.72 $p=0.035$).

Conclusions: In our study, a relationship between acanthosis nigricans and vitamin D levels were detected. Acanthosis nigricans is a skin sign that can be easily detected by clinician. It is an important and easy-to-detect dermatosis that helps determine patients at risk of metabolic complications and related with low vitamin D levels in obese children.

P2-213

Influence of birth weight on cardiovascular risk factors in obese children and adolescents

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Background: Birth weight (BW) is associated with the development of obesity, insulin resistance and type-2 diabetes in adulthood. The results of studies on the correlation between BW and the severity of obesity and cardiovascular risk factors (CVRF) among obese children are contradictory. The objective of our study was to evaluate the association between birth weight and the presence of CVRF in genetically homogeneous group of obese children and adolescents.

Subject and Methods: 789 obese children and adolescents of Sardinian descent (median age 9.54 years (2.6-17.7); 359 males), all born from uneventful pregnancies, were included in the study. Anthropometric markers (body mass index (BMI), height, waist

circumference (WC)), pubertal stage, systolic and diastolic blood pressure (SP, DP), lipids profile (HDL and triglycerides), fasting plasma glucose (GLU), and insulin were assessed. The HOMA index was calculated as insulin resistance index. Patients were divided according to BW into 5 groups (GP0, BW<2500 g, n=37; GP1, BW≥2500-<3000 g, n=144; GP2, BW ≥3000-<3500 g, n=320; GP3, BW≥3500-<4000g, n=226; GP4, BW ≥4000 g, n=62).

Results: The 5 groups were matched for age, BMI-SDS, and male/female and prepubertal/pubertal ratio. Median insulin and HOMA were higher in GP0 than in the other groups ($p=0.02$ and $p=0.03$, respectively). Median HDL was lower in GP1 than in GP2 and GP4 ($p=0.02$), similar results were obtained when only subjects born full term ($n=706$) were considered. The other CVRF were similar in the 5 groups.

We separately analyzed 586 subjects belonging to G1, G2, and G3 born with BW appropriate for gestational age (AGA). CVRF were similar among the 3 groups (GP1 $n=70$, GP2 $n=293$, GP3 $n=201$). Similarly, CVRF were similar among the 525 AGA full term subjects (GP1 $n=57$, GP2 $n=277$, GP3 $n=184$).

Conclusions: In our cohort of obese children and adolescents, low BW was associated with higher values of serum insulin and HOMA in the entire cohort and in the full term subjects, regardless of age, gender and pubertal stage. In the cohort of AGA and full term AGA subjects, BW is not associated with the BMI and the CVRF analyzed. These findings have important clinical implications for the follow-up of obese children.

P2-214

A study on the Complications associated with Severe Obesity in Children and Young People

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Introduction: The complications of obesity are well recognised and documented in the adult population. There is little data available that reports the complications of childhood obesity seen in clinical practice. The aim of our study is to investigate the different types of complications seen in children and young people (CYP) with obesity.

Methods: 125 CYP aged 0-18 years who had a body mass index (BMI) standard deviation score (SDS) of two or more above the mean were included. Data was collected retrospectively, and the complications identified in each patient analysed.

Results: The mean age of the CYP was 10.9 years ($SD\pm 3.62$, range: 2-18). 81 patients were female and 44 were male. The average BMI was 32.9kg/m^2 ($SD\pm 6.6$, range: 22.7-58.3) and average BMI SDS was $+3.5$ ($SD\pm 1.1$, range: $+2.06$ - $+7.85$). 47% of patients had 2 or more complications secondary to obesity, and a further 33% had at least one complication related to obesity. Dyslipidaemia was the most common complication and was seen in 25% of the individuals. This was followed by hypertension and mental health issues (18% each). Mental health issues included depression, anxiety and self-harm. 31% of patients had risk factors for type 2 diabetes mellitus (T2DM) [family history, acanthosis nigricans and/or insulin resistance]. Of those who had an oral glucose tolerance test (OGTT), 11.4% of the CYP were diagnosed with

pre-diabetes and 9% with T2DM. 21% of patients were diagnosed or had symptoms of obstructive sleep apnoea and 11% had mobility issues. Abnormal puberty was seen in 10% and 18% of individuals were diagnosed or had symptoms of polycystic ovary syndrome. Other complications include raised intracranial pressure, slipped upper femoral epiphysis, skin infections, non-alcoholic fatty liver disease, liver fibrosis, gynaecomastia and nocturnal enuresis.

Conclusion: Overall, 80% of our cohort had at least one complication secondary to their obesity. As these complications have potential to seriously impact the quality of life of these individuals in addition to long term morbidity and mortality, it is important to identify and manage these complications at an early stage along with a co-ordinated effort aimed at weight loss to mitigate the complications and co-morbidities.

P2-215

The Effectiveness of Indigenous Knowledge-Based Lifestyle Interventions in Preventing Obesity and Type 2 Diabetes Mellitus in Indigenous Children in Canada

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Background and Objective: Indigenous children in Canada have higher rates of obesity and type 2 diabetes mellitus (T2DM) and diabetes-related complications when compared to non-Indigenous children. Indigenous knowledge-based view of health encompasses a holistic approach with physical, mental, emotional, and spiritual health dimensions. This view of health will likely impact their engagement in interventions targeting obesity and T2DM. This systematic review and meta-analysis aimed to assess the impact of Indigenous Knowledge-based lifestyle interventions to prevent obesity and T2DM in Indigenous children in Canada.

Methods: We conducted literature searches across multiple databases up to May 2020. Changes in Body Mass Index (BMI) z-score and the diagnosis of T2DM were the primary outcomes. Adiposity, metabolic, and lifestyle determinants of health were set as the secondary outcomes. We used the chi-square test of homogeneity and inconsistency index (I^2) to evaluate the heterogeneity

of the meta-analysis results. GRADE was used to assess the quality of evidence.

Results: Four non-randomized controlled trials (non-RCTs) and six uncontrolled studies were included. Two non-RCT's with peer-led components (intervention: n=169; control: n=161) met the eligibility criteria for the meta-analysis, revealing a reduction in BMI z-score (-0.10, 95% CI: -0.16,-0.04) and waist circumference (WC) (-2.10, 95% CI: -3.69,-0.50) with the interventions. One uncontrolled study (n=133) found no change in BMI z-score and an increase in WC with the intervention. However, another uncontrolled study (n=35) reported an increase in BMI z-score (p-value 0.001) and WC (p-value <0.001) with the intervention. The GRADE assessment revealed low heterogeneity and a very low quality of evidence due to lack of randomization and small sample sizes. There were no reports of diabetes-related prevention programs.

Conclusions: Peer-led Indigenous Knowledge-based lifestyle interventions for pediatric obesity may lead to improved BMI z-score and WC. Obesity and type 2 diabetes prevention programs should engage in community-based participatory action to enhance partnerships with communities and strengthen implementation. Future studies should assess the impact of Indigenous Knowledge-based lifestyle interventions on preventing T2DM and improving glucose homeostasis.

P2-216

The effects of dextroamphetamine treatment in children with hypothalamic obesity

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Introduction: Children with hypothalamic dysfunction, e.g. due to a genetic or acquired cause such as suprasellar tumours, often suffer from hyperphagia and/or decreased resting energy expenditure (REE). This process induces uncontrollable weight gain, resulting in severe hypothalamic obesity (HO). No effective treatment is available yet for HO. Amphetamines are psychostimulants

that are known for their appetite reducing and REE stimulating side effects. Here, we present the effects of dextroamphetamine treatment in children and adolescents with acquired, genetic, or congenital HO.

Methods: A retrospective cohort evaluation was performed at 2 endocrine paediatric clinics. Patients with progressive therapy-resistant HO, either due to an acquired, genetic, or congenital cause, and off-label treatment with dextroamphetamines were included. Treatment was initiated at once or twice daily 5 mg. This could be weekly increased with 5 mg/day to a maximum of 0.5 mg/kg/day, depending on the patient's wellbeing or side effects. At start and during follow-up, BMI standard deviation scores (BMI SDS), REE (% of predicted), changes in (hyperphagic) behaviour, and side effects were assessed.

Results: Nineteen patients were treated with dextroamphetamines. Their mean age was 12.3 years $\pm$ 4.0 and mean treatment duration was 19.5 months $\pm$ 12.9. Fourteen children (acquired in n=10, genetic in n=3, congenital in n=1) responded to therapy, either with weight loss (n=11) or BMI SDS stabilization (n=3), with a mean Δ BMI SDS of -0.6 ± 0.8 . The predicted REE increased with $9.7\% \pm 10.6$ in the responder subgroup (n = 11). Three children (acquired in n=2, genetic in n=1) gained weight (mean Δ BMI SDS $+0.5 \pm 0.1$). In two children, the effects of dextroamphetamines could not be evaluated due to early treatment termination because of hypertension or a concurrent intensive supportive lifestyle treatment at a rehabilitation clinic. Thirteen out of 19 children reported improvement of hyperphagia, energy level, and/or behaviour. Reported side effects were hypertension, difficulties falling asleep, and negative behaviour changes. At last moment of follow-up, treatment was continued in ten children with an acquired HO and two children with a genetic HO.

Conclusion: In children and adolescents with progressive therapy-resistant HO, due to an acquired, genetic, or congenital cause, treatment with dextroamphetamine may be beneficial and result in either weight loss or weight stabilization. Moreover, it reduces subjectively reported hyperphagia and improve energy level and/or behaviour. Future studies are needed to support these results.

P2-217

Nutritional status in premature infants born small by gestational age in the first 5 years of life

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There is not enough reasoned data on the dynamics of body weight indices in premature infants born small by gestational age (SGA).

Aim: To study the nutritional status in premature babies born small by gestational age, in the first 5 years of life.

Materials and Methods: The prospective study included pre-term infant with SGA (n = 100) and prematurity corresponding to gestational age - AGA (n = 69) with their division taking into account gestational age: 32-36 weeks and 22-31 weeks. Assessment of body mass and body mass index (BMI, kg / m²) was carried out in the first 2 years of life, taking into account the corrected age. Frequency of dynamic observation: 2 times during the first year

of life, then once a year. The data are presented as a median and interquartile range with an assessment of the significance of differences according to the Mann-Whitney test. The calculation of standard deviations (SD) of body mass and SD body mass index was carried out using the «Anthro» program (WHO).

Results: Body weight indicators at birth in premature babies born small by gestational age were consistently lower ($p < 0.01$) than in premature babies corresponding to gestational age: at 32-36 weeks gestation - 650 [610; 932] g, -1.7 [-1.91; -1.38] SD.

Moderately and late preterm with SGA reached body weight indices of preterm with AGA by age 4 years: 15.1 [13.2; 16.3] kg, -0.7 [-1.7; 0.1] SD. No body weight deficit was registered during the observation period. Overweight (SD BMI from +1.0 to +2.0 SD) was noted during the 5-year follow-up period in 21.2-27.3% of the surveyed, which did not significantly differ from the frequency indicators in the group of premature AGA (25, 0-30.0%, $p > 0.05$). Very preterm SGA did not reach the body mass indicators of AGA children: intergroup differences persisted throughout the observation period. At the age of 5 years, the body weight of very premature infants with SGA corresponded to 15.0 [14.8; 15.5] kg, in comparison with premature AGA - 16.5 [15.0; 18.4] kg. Quite often, very preterm SGA had a body weight deficit: at 6 months - 72.2% (in the case of AGA - 27.3%, $p < 0.05$), at subsequent ages - from 11.1% to 16.7% (in the case of AGA - 7.7-13.6%, $p > 0.05$).

Fetal growth retardation has an adverse effect on the subsequent physical development of premature babies, especially very preterm.

P2-218

Impact of overweight and obesity in pediatrics. Metabolic syndrome and its components

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The current lifestyle, with a diet increasingly removed from the Mediterranean diet, together with the habitual sedentary lifestyle, is associated with many of the so-called non-communicable diseases, such as the metabolic syndrome. Every day these pathologies are more frequent in pediatrics, so this study has tried to establish the prevalence of metabolic syndrome and its components in overweight and obese children and assess its impact. **METHODS** A descriptive study has been carried out, collecting both demographic and clinical data, as well as analytical and ultrasound data of all patients who have attended outpatient pediatric endocrinology consultations with a diagnosis of overweight and obesity between 6 and 14 years of age for 1 year (year 2019); and analyzing the data using Excel. The components of the definition of the metabolic syndrome have been evaluated, among others. **RESULTS** A total of 59 patients were found to be overweight or obese, of which 9 were excluded from the study because they were under 6 years of age. Among the 50 remaining patients, there were no sex differences (50% male, 50% female) and the mean age was 10.4 years. 66% were obese and 37% overweight. 60% were Caucasian, followed by South Americans (28%) and Africans (12%). 50% had a

family history of metabolic syndrome or one of its components. The majority (60%) ate in the school cafeteria and did physical exercise regularly (61.1%). Blood pressure was measured in 50% of the patients, with 16% of them presenting arterial hypertension (HT). 100% analysis, 10% oral glucose overload (SOG) and abdominal ultrasound were performed in 38% of the patients. In the attached table we see the analytical and ultrasound results. The analytical values requested in the first visit are included. 2 patients met criteria for metabolic syndrome (5.6%). **TOTAL ALTERED DATA%** Glucose ($> 100\text{mg} / \text{dl}$) 1 48 2.1 Insulin ($> 15\text{mcU} / \text{ml}$) 13 28 46.4 Glycosylated Hb ($< 5.9\%$) 2 40 5 Total cholesterol ($> 200\text{mg} / \text{dl}$) **CONCLUSION** One of the main causes of mortality in the Western world are cardiovascular diseases, with non-communicable diseases such as obesity, hypertension, insulin resistance or diabetes mellitus and hypercholesterolemia being the main risk factors for suffering them. A high percentage of these pathologies was observed among the pediatric patients studied, with several of our patients meeting criteria for metabolic syndrome. It is a growing problem in our midst, which will probably continue to grow if we do nothing to contain it.

P2-219

What do lipids tell us about the pandemic?

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The pandemic has changed habits in families around the world. Eating habits and physical activity were directly impacted by social distance. The first year of the pandemic left its mark on children's health.

The purpose of this analysis was to evaluate the relationship between the first year of the pandemic and the serum lipid profile in children who underwent lab tests in a private laboratory in Curitiba-PR.

Methods: Observational and retrospective, serum levels of triglycerides (TG), total cholesterol (TC) and HDL cholesterol (HDL-c) were assessed in 36,658 patients aged 0 to 19 years old, in the period from April/2019 to March/2020 (pre-pandemic) and April/2020 to March/2021 (pandemic), which may have performed a complete or partial lipid profile, once or in more than one opportunity during these 24 months, totaling 148,927 tests.

The population sample has 54.8% girls and 45.2% boys, distributed in two age groups, from 0 to 9 years old (block 1) and from 10 to 19 years old (block 2) for the purposes of normal reference values.

TC values $< 170\text{mg/dL}$, HDL $> 45\text{mg/dL}$ and TG $< 85\text{mg/dL}$ (group1) or $< 100\text{mg/dL}$ (group 2) were considered normal.

Results: There was a reduction of 14.41% in the number of lipids measurements performed in the pre-pandemic x pandemic period.

The percentage of altered tests was higher in the pandemic sample, corresponding to 33.26% against 28.52% in the pre-pandemic.

Assessing TC and TG, highlighting its greater link with eating habits, we observed that in the first period there were 32.33% of measurements above the reference range and now they are 36.91%.

Regarding HDL-c, relating it to physical activity, data indicates 20.89% below 45 mg/dL in the 2019-2020, evolving to 25.96% in 2020-2021.

Conclusion: Lipids are telling us a worrying story.

We have some biases that cannot be ignored and that are part of the clinical history of each child. We do not have clinical data for this assessment.

From the perspective of laboratory measurements, there was an increasing rate of dyslipidemia in the pediatric population evaluated and a worsening of the HDL-c profile, suggesting a measurable impact of the reduction in physical activity during the pandemic period.

Further analysis is needed to legitimize this trend as a fact as well as for the solid structuring of the cause-effect relationship.

P2-220

Characteristics of eating behavior in children with type 1 diabetes and obesity

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Objective: to evaluate the characteristics of eating behavior in children with type 1 diabetes mellitus and various forms of obesity.

Methods: We examined 80 children in the University Hospital (Minsk) in 2021.

All Children were Divided into 2 Groups: group 1 30 children (18 boys (B) (BMI 31.68 ± 4.57 kg/m², age 13.23 ± 2.01 years) and 12 girls (G) (BMI 30.30 ± 4.65 kg/m², age 13.43 ± 2.49 years)) with different forms of obesity (alimentary (AO), morbid (MO)); group 2 - and 50 children (27 boys (B) (BMI 23.68 ± 2.17 kg/m², age 13.56 ± 2.11 years) and 23 girls (G) (BMI 23.30 ± 2.15 kg/m², age 13.28 ± 2.04 years)) with type 1 diabetes (T1D).

Their anthropometric parameters (height, weight, body mass index (BMI)) were determined. Biochemical blood tests were performed (total protein, glycated hemoglobin, alkaline phosphatase, triglycerides, cholesterol, total calcium, potassium, sodium, creatinine, urea, glucose). The analysis of food diaries is carried out. The frequency of the use of keto diets by adolescents was estimated.

Results: According to the analysis of food diaries, there was a decrease in the consumption of starchy vegetables by obese children compared to their peers with diabetes. In the group of children with obesity, cellular vegetables were included in the diet less often than in their peers with diabetes. There was a significantly lower consumption of fish by children. The consumption of cereals and pasta by obese children exceeded those of children with diabetes. According to the evaluation of food diaries, an increase in the consumption of foods with a high glycemic index (GI) in obese children compared to children with diabetes was revealed. The examined patients consumed a large number of confectionery products. The inclusion of confectionery products in the diet of children is considered as one of the risk factors for the formation of obesity. Excessive consumption of easily digestible carbohydrates leads to a sharp postprandial increase in blood glucose and insulin levels. Our study revealed that obese children were significantly more likely to consume high - GI foods (confectionery) and less

likely to consume low-and medium-GI foods (cereals, starchy vegetables, fiber vegetables).

Conclusions: In children with obesity and diabetes, errors in nutrition were noted. The keto diet is contraindicated in children with carbohydrate disorders, it can not only decompress the underlying disease, but also adversely affect the function of many significant systems.

P2-221

"Sleep Properly, Reduce Intake, and Get Stepping" (SPRINGS): a multidisciplinary approach to managing paediatric morbid obesity with severe obstructive sleep apnoea

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Introduction: Paediatric morbid obesity (BMI >99.6th centile for age) causes severe obstructive sleep apnoea (OSA) requiring respiratory support. Patient prognosis is poor and requires urgent intervention. Four patients with morbid obesity and severe OSA were admitted for multidisciplinary team (MDT) intensive weight management and continuous positive airway pressure (CPAP) initiation.

Methods: The patients (3 male, 1 female; ages 9-16 years) had BMIs >99.6th centile (>3 SDS). Two had developmental delay. One patient was taking metformin prior to admission, another taking orlistat was also commenced on liraglutide.

During an inpatient admission (between 10-33 days), all patients/families received specialist input from obesity and respiratory MDTs including clinical nurse specialists, dietetics, and a psychologist. All patients had overnight sleep studies performed due to clinical concerns of OSA. The choice of study was determined by availability and patient tolerance, including in some a cardio-respiratory study. All patients started a calorie-restricted diet and personalised exercise plans were provided to all except one patient with global developmental delay, with target goals set by the MDT and families in collaboration.

Results: All patients had severe obstructive sleep apnoea (median oxygen desaturation index (ODI): 36.5 events/hour; range: 34-98) and suboptimal minimum oxygen saturations (median: 73.5%; range 39-80%). When measured, maximum CO₂ was between 6-10.5kPa. All were successfully initiated on overnight CPAP in hospital. Sleep parameters rapidly improved in all following overnight CPAP initiation; including a reduction in ODI (median ODI: 13.9 events/hour; range: 9.7-14.3) and reduction in median minimum oxygen saturations (median: 80.5%; range: 77-85%). All patients have continued overnight CPAP.

Weight loss and BMI-SDS improvement during the admission continued up to 12-months following discharge (Table 1).

Table 1. Change in weight and z-scores at discharge and subsequently

		Patient			
		A	B	C	D
Admission weight (kg)		184.5	86	155.8	83.4
BMI-SDS		4.36	4.48	3.83	3.80
Weight loss (kg)	At Discharge	-4.9	-8.4	-7.6	-3.4
	3 months	-14.5	-14.7	-20.4	-10.7
	6 months	-29.5	-20.0	-29.6	-14.4
	12 months	-45.3	-23.0		
	At Discharge	-0.05	-0.15	-0.13	-0.13
BMI-SDS change	3 months	-0.14	-0.36	-0.41	-0.44
	6 months	-0.34	-0.54	-0.71	-0.70
	12 months	-0.62	-0.88		

Discussion: The mechanisms for weight loss may be due to a range of factors, including a lifestyle shift following an intensive MDT intervention, improved sleep quality through CPAP enhancing weight loss and medication for weight reduction. This approach may benefit a range of patients with morbid obesity and severe OSA.

P2-222

Design of a Phase 2, Double-Blind, Placebo-Controlled Trial of Setmelanotide in Patients with Genetic Variants in the Melanocortin-4 Receptor Pathway

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Background: Rare genetic causes of obesity include variants in genes within the melanocortin-4 receptor (MC4R) pathway, a principal regulator of energy balance. Weight and hunger reductions following treatment with the MC4R agonist setmelanotide have been demonstrated in patients with obesity due to variants in multiple genes, including *POMC*, *LEPR*, *SRC1*, and *SH2B1*. We describe a trial design of setmelanotide in patients with additional specific gene variants based on an evidence-based framework that suggested relevance to the MC4R pathway.

Methods: This Phase 2, double-blind, placebo-controlled, 2-stage study will enroll ~500 patients in Stage 1 to achieve ~130 qualified patients in Stage 2. Patients aged 6 to 65 years with pathogenic, likely pathogenic, or uncertain significance genetic variants based on American College of Medical Genetics criteria in

a preselected set (n=31) of MC4R pathway genes, including *LEP*, *SIM1*, *MRAP2*, and *KSR2*, and body mass index (BMI) ≥ 40 kg/m² or BMI ≥ 97 th percentile according to age (for those aged ≥ 18 or <18 years, respectively) and sex are eligible. Exclusion criteria include recent intensive diet or exercise resulting in $>3\%$ weight loss, bariatric surgery within 6 months of enrollment, significant features or diagnosis of syndromic obesity, glycated hemoglobin $>10.0\%$, and glomerular filtration rate <60 mL/min. Patients or caregivers will self-administer subcutaneous setmelanotide. For patients aged ≥ 12 years, daily dosages will be 2 mg for 14 days, then 3 mg thereafter; for patients aged 6 to <12 years, daily dosages will be 1 mg for 7 days, 2 mg for 7 days, and 3 mg thereafter. Patients achieving $\geq 5\%$ weight loss from baseline or ≥ 0.1 -point reduction from baseline in BMI Z score (for those aged ≥ 18 or <18 years, respectively) at the end of Stage 1 (16-week open-label run-in) will be eligible to enter Stage 2 (randomized withdrawal period). Eligible patients will be randomized 2:1 to continue daily setmelanotide or receive matching placebo for 24 weeks. The primary endpoint is the proportion of patients achieving $\geq 10\%$ weight loss or ≥ 0.3 -point reduction from baseline in BMI Z score (for those aged ≥ 18 or <18 years, respectively) from baseline at Week 40. Secondary endpoints are initial response to open-label setmelanotide and changes in body weight, waist circumference, hunger, and quality of life. Exploratory endpoints are change in metabolic parameters and treatment responses stratified by genes. Safety will be assessed by severity and frequency of adverse events. The first patient will be enrolled before the end of 2021.

P2-223

Absence of dyslipidemia in obese children with BMI ≥ 2.5 SDS and similar lipidemic profile to those with BMI <2.5 SDS or normal weight

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Objective: Compare triglycerides, total cholesterol, HDL and LDL levels between obese and normal weight children.

Methods: 547 children (286 females) with BMI (≥ 0 SD) were divided in four groups (Group 1: $0\text{SD} < \text{BMI} < 2\text{SD}$, Group 2: $2\text{SD} \leq \text{BMI} < 2.25\text{SD}$, Group 3: $2.25\text{SD} \leq \text{BMI} < 2.5\text{SD}$, Group 4: $\text{BMI} \geq 2.5\text{SD}$) and analyzed retrospectively from the medical records. Age, sex, BMI z-score, triglycerides, total cholesterol, HDL and LDL (mg/dl) levels were recorded. One-Way Analysis of variance (ANOVA) and χ^2 test ($p < 0.05$) were calculated among groups using the SPSS statistics programme.

Results: Mean age was 9.5yrs (SD, 3.07), BMI: 2.28(SD, 0.59), Total cholesterol: 166.9 (SD, 32.7), triglycerides: 81.5 (SD, 46.2), HDL: 52.3 (SD, 13.0), LDL: 99.5 (SD, 27.3). Clinical and laboratory characteristics are summarized in table 1. There was neither statistically significant difference in the sex distribution nor statistically

Table 1. Clinical and laboratory characteristics, Mean (SD).

	Group 1 (n=157)	Group 2 (n=130)	Group 3 (n=124)	Group 4 (n=136)	p
Age (yrs)	10.9 (2.4)	9.7 (2.2)	9.5 (2.8)	7.6 (3.6)	*
Sex (males/females)	67/90	63/ 67	60 / 64	71/65	NS
Tanner 1/>2	43%/57%	65%/35%	64%/36%	76%/24%	**
BMI z-score	1.7 (0.27)	2.1 (0.06)	2.4 (0.08)	2.9 (0.65)	*
Total cholesterol (mg/dl)	164.5 (34.1)	171 (35)	160.7 (28.9)	169.5 (31.7)	
<200	86%	79%	89%	86%	NS
>=200	14%	21%	11%	14%	
Triglycerides (mg/dl)	75.9 (39.4)	85.8 (44.3)	81.7 (59.1)	83.6 (41.3)	
<100	82%	73%	76%	76%	NS
>=100	18%	27%	24%	24%	
HDL (mg/dl)	53.6 (13.4)	52.5 (12)	52.3 (12.8)	50.4 (13.6)	
>40	91%	89%	81%	87%	NS
<40	9%	11%	19%	13%	
LDL (mg/dl)	100 (26)	101.8 (30)	93.2 (24.5)		
				102.5 (27.9)	
<130	88%	82%	94%	82%	NS
				18%	
>130	12%	18%	6%		

*One-Way Analysis of variance (ANOVA), $p < 0.05$.

**x2 test , $p < 0.05$.

significant difference in the lipidemic profile among the four groups. Obese children were more often prepubertal as opposed to normal weight children ($p < 0.05$).

Conclusions: Obese children with BMI ≥ 2.5 SDS do not present dyslipidemia and have similar lipidemic profile to those with BMI < 2.5 SDS or normal weight children.

P2-224

Inflammation associated to body composition in European prepubertal children: Results from the IDEFICS study

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Background: Obesity is characterised by excessive fat accumulation coursing with a chronic mild inflammatory state, with adipose tissue (AT) being the main site of increased systemic cytokine production. Increased adiposity early in life is the main risk factor for cardiometabolic disorders later in life, with the abnormal accumulation of lipids in AT leading to the production of pro-inflammatory cytokines. Inflammatory process that involves metabolic and cardiovascular diseases has been reported in children and adolescents tracking into adulthood.

Objective: To evaluate the association between TNF- α , IP-10, IL-6, IL-15, IL-8, IL-1ra, leptin or adiponectin with adiposity in prepubertal children.

Methods: 3459 children between 2 and 9 years old participated in the IDEFICS study. The relationship between fat (BMI, skinfolds thickness (SF) as marker of subcutaneous fat and waist circumference (WC) as a surrogate marker of abdominal adiposity and plasma concentrations of TNF- α , IL-6, IL-15, IL-8, IL-1ra, leptin or adiponectin was studied.

Linear regression analysis adjusted for age, sex, center and ISCED level was applied.

Results: Leptin levels were associated with z-BMI ($B = 5.749$ 95%CI 5.481, 6.017), sum of z-SF ($B = 5.671$ 95%CI 5.406, 5.936) and z-WC ($B = 5.689$ 95%CI 5.416, 5.961). Adiponectin levels were associated with z-BMI ($B = 2.941$ 95%CI 2.533, 3.350), z-SF ($B = 2.948$ 95%CI 2.530, 3.336) and z-WC ($B = 2.935$ 95%CI 3.335). TNF levels were associated with z-BMI ($B = 0.865$ 95%CI 0.733, 0.997), z-SF ($B = 0.864$ 95%CI 0.729, 0.999) and z.WC ($B = 0.869$ 95%CI 0.743, 1.004). IP-10 levels were associated with BMI ($B = 5.423$ 95%CI 5.190, 5.657), SF ($B = 5.426$ 95%CI 5.192, 5.660) and z-WC ($B = 5.689$ 95%CI 5.416, 5.961). IL-8 correlated with z-BMI ($B = 1.082$ 95%CI 0.886, 1.276), z-SF ($B = 1.082$ 95%CI 0.882, 1.281) and z-WC ($B = 1.077$ 95%CI 0.877, 1.277). IL-6 correlated with z-BMI ($B = -1.346$ 95%CI -1.642, -1.050), z-SF ($B = -1.357$ 95%CI -1.660, -1.054) and z-WC ($B = -1.327$ 95%CI -1.629, -1.024). IL-1ra levels were associated with z-BMI ($B = 6.849$ 95%CI 6.628, 7.071), z-SF ($B = 6.831$ 95%CI 6.606, 7.057) and z-WC ($B = 6.872$ 95%CI 6.646, 7.098).

Discussion: Detection of inflammation associated with changes in body composition from the early stages of life could be key in

order to prevent further degree of overweight or obesity and its comorbidities. This helps to better understand the mechanisms involved in the aetiology of obesity as well as to establish primary prevention interventions and identify potential targets against this pathology.

P2-225

A case report of sitosterolemia and the early differential diagnosis

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Objective: To explore the clinical manifestations and early identification of sitosterolemia.

Methods: To summarize the clinical characteristics of the case and review literatures of sitosterolemia.

Result: The child was an 11-year-old boy. The main complaint was that subcutaneous yellow nodules were found more than 1 years with blood cholesterol increased for 4 months. Two months ago, the patient came to the dermatology clinic. Subcutaneous nodule biopsy of the buttocks showed xanthomas. Family history: nothing special. Physical examination: BP: 99/57mmHg, BMI 14.2kg / m² (P5). Scattered xanthomas were found which are yellow-brown, soft, round or oval, clear border with the diameter 0.3cm to 1.0cm on knee joints, buttocks and elbow joints with no tenderness, ulceration, rash or bleeding. Laboratory test: TC 9mmol / L, TG 0.67mmol / L, LDL-c 8.60mmol / L. Liver function were normal. OGTT, thyroid function and 8AM cortisol were normal. Blood MS / MS and urine GCMS were normal. Liver, heart color ultrasound were normal. Brain MRI and MRA were normal. Genetic testing showed a compound heterozygous mutation of the ABCG5 gene. The mutation c.751C> T is derived from the mother, while the mutation c.1528C> G is derived from the father. So the diagnosis was confirmed. Treatment includes two aspects: one is diet control, and the other is medicine Diet Control: Both cholesterol and plant sterols in the diet need to be strictly controlled. Plant sterol-rich foods include vegetable oils, wheat germ, nuts, seeds, and avocados. However, it is not possible to have a completely plant sterols-free diet because they are present in almost every plant food and a low plant sterol diet can only reduce plasma sterol levels by about 30%. Therefore ezetimibe (5mg qd) was described to the patient. After 9 months of treatment, the child's xanthomas gradually subsided and TC decrease to 5.17mmol/L, and LDL-c decreased to 3.45mmol/L without any side effect.

Conclusion: The clinical manifestation of sitosterolemia was mainly xanthomas. From this point, it is sometimes difficult to identify from other disease. However, when dyslipidemia is not particularly high, xanthomas have already appeared which may imply the diagnosis of sitosterolemia. Once familial hypercholesterolemia occurs, low-density lipoprotein will be very high; Cerberontenacious xanthomatosis generally shows xanthomas, but blood lipids is not high; Wolman disease: this disease is rare in children. It is caused by an abnormal lysosomal acid lipase gene (LIPA) mutation with recessive inheritance. All of the above maybe give us some clinic clues to make a differential diagnosis.

P2-226

Thyroid function in youth with metabolic syndrome

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Introduction: Widespread obesity, as well as dystyroidism, dictates the investigation of possible thyroid dysfunction in young people with metabolic syndrome (MS).

Aim: Study of thyroid status in young people with metabolic syndrome.

Materials and Methods: The study involved 46 patients (25 boys and 21 girls) with MS at the age of 18 ± 3.1 years. The inclusion criteria were an increase in body mass index (BMI) more than 30.0 kg / m², simultaneously recorded insulin resistance, dyslipidemia, arterial hypertension, and disorders of carbohydrate metabolism. In all subjects, the HOMA-IR insulin resistance index was higher than 2.77, there was an increase in triglycerides, atherogenic dyslipidemia. All patients underwent ultrasound examination of the thyroid gland, thyroid stimulating hormone (TSH), free thyroxine (fT4), free triiodothyronine (fT3), antibodies to thyroglobulin (AbTG) and antibodies to thyroperoxidase (AbTPO) were determined. The control group consisted of 22 obese patients without metabolic symptoms. Statistical significance was determined by the STATISTICS system for Windows.

Results: In 1/3 of the surveyed, a tendency to increase in size was noted, and in 2/3 to a significant ($p < 0.05$) increase in the volume and echogenicity of the thyroid gland. A direct relationship was found between the size of the thyroid gland and BMI. 52% of patients showed a significant ($p < 0.05$) increase in TSH and normal fT4, half of them had a significant increase in AbTPO and an insignificant increase in AbTG. An insignificant decrease in the concentration of fT4 and fT3 and a slightly increased concentration of TSH were recorded in 20% of the subjects. There was a significant increase in AbTPO in 30% of patients. Half of the patients had a significant increase in AbTG. A positive correlation was found between the concentration of TSH and BMI, the index of insulin resistance HOMA-IR and the index of atherogenicity. In 12% of young people with MS, there is a significant ($p < 0.05$) increase in TSH in combination with a significant decrease ($p < 0.05$) fT4 and a significant increase in AbTPO, which indicates autoimmune thyroiditis with hypothyroidism.

Conclusion: A significant increase in TSH was found in 52% of patients with MS. Autoimmune thyroiditis with hypothyroidism was registered in 12% of young people with Metabolic Syndrome. Insufficiency of the thyroid gland, especially in combination with the stimulation of antibody production, may be one of the mechanisms for the development and progression of MS in young people. Further research is needed on this issue.

Global survey study of awareness, care and treatment of adolescents living with obesity, their caregivers and healthcare professionals: ACTION Teens

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Background: Obesity rates in children and adolescents have increased dramatically across the globe, and the lifelong impact of obesity is more severe when onset begins at ≤ 20 years of age. However, the experiences, challenges and needs of adolescents living with obesity (ALwO), their caregivers, and the healthcare providers (HCPs) who treat them are poorly understood. ACTION Teens, the first study of its kind, aims to improve the lives of ALwO by generating evidence to drive awareness around the needs of ALwO and caregivers, and to identify areas of misalignment between ALwO, caregivers and HCPs.

Methods: ACTION Teens is a quantitative survey-based study currently collecting data in ten countries (Australia, Colombia, Italy, Korea, Mexico, Saudi Arabia, Spain, Taiwan, Turkey and United Kingdom). The study includes ALwO and their caregivers, as well as HCPs with direct, recent experience of clinical obesity management in adolescents. The survey, designed with guidance from an international steering committee consisting of HCPs and subject matter experts, focuses on several aspects of obesity care. Questions consider attitudes and perceptions about obesity and its impact; weight loss attempts, and motivations and barriers to losing weight; patterns of weight loss conversations; ALwO and caregiver interactions with HCPs about obesity; sources of information used to learn about obesity and weight management;

sociodemographics of participants; and overall health and well-being of ALwO. The study is targeting 6,150 ALwO, 6,150 caregivers, and 2,300 HCPs with separate, though overlapping, surveys. Sample sizes were selected to reflect the size of the population of ALwO in each country. To maximise the inclusion of 'matched pairs' of an ALwO and their specific caregiver, permission will be sought from qualifying caregivers for the relevant child to be involved. The study has been designed to address several specific needs of the ALwO population. Age-specific definitions of obesity were used, most frequently a BMI ≥ 95 th percentile for age and sex, per locally appropriate definitions. Assessment of pubertal stage would have been desirable to evaluate its impact on survey outcomes, but this would not be achievable without inclusion of potentially culturally inappropriate questions. Therefore, a proxy of age subgroups was considered appropriate by the steering committee. Among HCPs, objective rather than subjective criteria to identify advanced formal obesity training were used to reduce false positives.

Results: Study results will be reported in 2022.

Conclusions: ACTION Teens will provide critical global insights to improve awareness of management, treatment and support for ALwO.

Lifestyle habits, consumption of non-nutritive sweeteners and obesity in students and young adults' population in Latvia

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Background: Since 1975 the prevalence of obesity has tripled. As one of the habits of a healthy lifestyle is to reduce the fast sugars in our meals, the supply of non-nutritive sweeteners in the food supply has increased by offering sweeter meals without extra calorie intake.

Objectives: To explore the characteristics of students and young adults' lifestyle habits and consumption of non-nutritive sweeteners and their relation to overweight and obesity.

Materials and Methods: A cross-sectional population study was carried out in three different schools and on social media with 997 respondents aged 8-30, divided into three age subgroups 8-13 y, 14-17y, 19-30y. A voluntary anonymous questionnaire about their anthropometric data, lifestyle habits, eating and physical activities habits was conducted. Data was statistically analyzed by Microsoft Excel 2010, SPSS version 19.0 and RStudio IDE 1.3.

Results: 16.6 % of respondents were overweight or obese (BMI > 85 th perc.) Age group 19-30y had more overweight respondents 21.4% ($p=0.02$).

Only 36.9% of adults do physical activities at the level that WHO recommends for prevention of noncommunicable diseases. Men are more physical active than women $p=0.03$. There was no significant difference in physical activities among overweight and normal weight respondents, except age group 8-13y students with normal weight take more sport activities ($p=0.0103$).

74.2% of young adults has screen time more than 3 hours per day, young adults have more screen time than students (12% vs. 3.2% more than 8 hours per day ($p < 2 \times 10^{-16}$)).

67.3% of respondents eat less fruits and vegetables than WHO recommended 5 portions per day (Normal weight = 64.3%, Overweight = 75%)

27.7% of respondents add extra sugar to tea or coffee, only 3.3% of respondents add non-nutritive sweeteners in daily use. 12.5% of respondents use natural sweetener stevia.

51.20 % of respondents drink at least 250ml of sweetened beverages per day (men more than women $p = 0.00187$). Overweight adults drink more sweetened beverages than those with normal weight ($p = 0.0194$). Most popular sweetened beverage is fruit juice (40% drink once per month, men > women, $p = 0.02$). Overweight people compared to normal weight drink more *Coca Cola Zero* ($p = 0.009$).

Conclusion: Obesity, screen time, lack of physical activities and lack of fruits and vegetables in daily intake increase with age. Young adults and students choose more sugar sweetened meals than non-nutritive sweetened. Being overweight correlates with the consumption of non-nutritive sweeteners, the consumption of fruits and vegetables as well as the level of physical activities.

P2-229

Influence of the basal metabolic profile on the evolution of the pediatric patient with obesity

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Objective: To study how basal metabolism influences the somatometric evolution of the child and adolescent population with obesity in a pediatric endocrinology clinic; multichannel impedance study, TANITA BF 430.

Results: 100 randomly selected patients from a database with 1400 records were studied. Most of the patients who come to these consultations for obesity are girls, between 8 and 11 years old. The group of boys at the beginning of follow-up showed a higher basal metabolism and more similar than the group of girls. Girls had a higher fat mass content compared to boys at the beginning of follow-up. At one year of follow-up, both groups achieved a decrease in the percentage of fat mass, being double in boys compared to girls. After three years of the study, it was observed that 54% of the boys achieved a reduction in their MG compared to 36% of the girls. Overall, weight reduction is not achieved in this pediatric population; what we do observe is a decrease in fat content in the medium term 1-3 years. The reduction of this fat mass could be a protective factor against cardiovascular diseases in adults. Given the same adherence to nutritional programs, we think that the rate of physical exercise influences this reduction. It was also observed that the most relevant data in the evolution of obesity in these patients is the basal metabolism that they present at the beginning of follow-up.

Discussion: Childhood obesity is a problem of increasing importance in our society. Knowing its characteristics would allow

different strategies to be taken for a better treatment and diagnosis of these cases. Thus, it would be possible to increase the requirements and the basal metabolism of the patient would increase, favoring the loss of fat mass. We only look at the weight variable, a bias could be committed by not perceiving that there has been a decrease in fat content at the cost of an increase in muscle mass.

Conclusion: We are committed to the existence of a multichannel impedance meter in each of the pediatric endocrine consultations as it is a non-invasive test, easy to use and that can provide a lot of information about the evolution of these patients. Since we believe that focusing efforts on those children who have a worse basal metabolism could contribute to improving the efficiency and effectiveness of the scarce health resources that we have.

Fetal, Neonatal Endocrinology and Metabolism (to Include Hypoglycaemia)

P2-230

The utility of continuous glucose monitoring systems in the management of children with persistent hypoglycaemia

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Background: Glucose monitoring is vital in children with persistent hypoglycaemia to reduce the risk of adverse neuro-behavioural outcomes¹. Continuous glucose monitoring (CGM) systems provide real-time glucose levels however; information on its usefulness in monitoring glucose levels in this cohort is limited^{2,3}.

Objective: To ascertain the effectiveness of CGM and to evaluate parents' experience of using CGM for monitoring glucose levels in children with hypoglycaemia who do not have diabetes.

Methods: Retrospective analysis of sensor glucose (SG) values from Dexcom G4 CGM with paired finger-prick blood glucose (BG) values was performed to determine the accuracy of CGM. The parent experience of CGM was assessed using a questionnaire.

Results: SG data from 40 children (median age 6 months) with persistent hypoglycaemia (60% Hyperinsulinism) were analysed. The mean difference between 5,650 paired BG and SG values was 0.28mmol/L. There was a positive correlation between the two methods ($r = 0.79$). The sensitivity and specificity of CGM to identify severe hypoglycaemia (BG < 3.0 mmol/L) were 54.3% (95% CI: 39.0% to 69.1%) and 97.4% (95% CI: 96.9% to 97.8%) respectively. The positive predictive value for detecting severe hypoglycaemia was 16.0% (95% CI: 10.6% to 22.7%) while the negative predictive value was 99.6% (95% CI: 99.3% to 99.7%). Parents ($n = 11$) reported less anxiety ($n = 9$), better sleep at night ($n = 7$) and preferred to use CGM for monitoring ($n = 9$).

Conclusion: Although the high number of false positive readings precludes the routine use of CGM in the evaluation of hypoglycaemia, it avoids unnecessary BG testing during normoglycaemia. It is an acceptable tool to parents for monitoring their children who are at risk of hypoglycaemia. Newer CGM systems with improved accuracy at lower glucose levels have the potential to further improve monitoring.

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Key Words: Hypoglycaemia, continuous glucose monitoring, hyperinsulinism

P2-231

Hyperinsulinaemic hypoglycaemia as a MEHMO syndrome component: a case report

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Introduction: MEHMO syndrome (mental retardation, epileptic seizures, hypogenitalism, microcephaly, and obesity) is a rare X-linked disorder caused by *EIF2S3* gene mutations. This gene encodes a key factor for integrated stress response and initiation of protein synthesis.

Since many hormones are proteins or peptides by nature, some of the reported cases of MEHMO syndrome include endocrine disorders: hypopituitarism (hypogonadism, growth hormone deficiency, hypothyroidism, adrenal insufficiency), diabetes mellitus, and transient hypoglycemia. However, the mechanism of hypoglycaemia in the literature is not indicated.

Here, we present a boy with MEHMO syndrome and hyperinsulinaemic hypoglycaemia.

Case Report: The patient is a second child of non-consanguineous Caucasian family with normal birth weight and length. His 10-year-old brother is healthy. Two male relatives in the mother's family died at young age: at 5 years (cardiac failure, short stature, microcephaly) and at 8 months (pneumonia).

At birth, the proband presented with breathing difficulties but otherwise appeared healthy.

At the age of 6 months, he developed first seizures, had a decline in psychomotor development, and was noted to have microcephaly. The boy was diagnosed with epilepsy and started on anticonvulsants with mild success.

At the age of 21 months, hyperinsulinaemic hypoglycaemia was detected (glucose 2.2 mmol/l, insulin 28 µIU/mL). The patient was started on diazoxide 5 mg/kg/day with a good response. We assumed the child had a congenital disorder of glycosylation based

upon hyperinsulinaemic hypoglycaemia, severe developmental delay, and dysmorphic features (microcephaly, amphora-like face, sloping forehead, high-arched palate, dental diastasis, conical teeth, inverted nipples, and puffy hands and feet). Transferrin isoelectric focusing and genetic tests did not confirm it.

At the age of 3 years, whole genome sequencing revealed c.671T>G mutation in *EIF2S3* gene. Like other patients with MEHMO syndrome, our patient has microcephaly, mental retardation, epileptic seizures, overweight, and dysmorphic features.

At the age of 5 years, diazoxide was weaned off. There were no signs of diabetes mellitus or hypopituitarism (cortisol, ACTH, IGF-1, free T4, and TSH levels are within normal range). He was also found to have hyperammonemia and started on a low protein diet that led to a better seizure management.

Conclusion: To the best of our knowledge, this is the first report of hyperinsulinaemic hypoglycaemia in a patient with MEHMO syndrome. Since *EIF2S3* mutations alter protein production, overproduction of insulin is counterintuitive. Presumably, the mechanism is similar to MODY1 and MODY3, as in these conditions hyperinsulinaemic hypoglycaemia can anticipate diabetes.

P2-232

Methylation of umbilical cord genes associates with gestational weight gain and offspring's cardio-metabolic profile

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Introduction: It is known that excessive gestational weight gain can cause an adverse intrauterine environment and increase the risk of cardio-metabolic diseases in the offspring. Epigenetics could be one of the mechanisms involved in this regulation.

Objective: We aimed to study the DNA methylation profile of umbilical cord tissue that is associated with gestational weight gain (GWG), and its relationship with cardio-metabolic and anthropometric parameters in the offspring at 6 years of age.

Materials and Methods: A methylation array was performed (Infinum®Methylation EPIC BeadChip) in umbilical cord tissue samples of 24 pregnant women with and without gestational obesity. The CpG dinucleotides whose methylation status was associated with GWG were validated in a cohort of 87 mother-newborn pairs by pyrosequencing and gene expression was studied by RT-PCR. A total of 61 newborns were followed up at 6 years of age and their cardio-metabolic and anthropometric parameters were assessed.

Results: The array identified 4451 CG dinucleotides differentially methylated and associated with GWG (all $p < 0.05$), of which 2778 presented gene annotation. Five genes with the greatest biological effects (Odds Ratio close to 1.1 or 0.91) were chosen for validation: *SETD8*, *SLIT3*, *HOXC8*, *RPTOR* and *TMEM214*. Children

with higher methylation of *SETD8* (lysine methyltransferase related to cell metabolism and proliferation) and lower methylation of *SLIT3* (involved in cell proliferation and tissue development) showed a worse cardiometabolic profile at 6 years of age (higher BMI, fat mass, waist circumference and cIMT; all $p < 0.05$). The gene expression levels of *SETD8* and *SLIT3* were opposite to their methylation status and the children with lower and higher expression of *SETD8* and *SLIT3*, respectively, presented differences in their cardiometabolic profile at 6 years old, in a way opposite to the methylation status. Finally, the methylation levels of *HOXC8*, *RPTOR* and *TMEM214* also showed significant associations with different cardio-metabolic parameters, although no relation between methylation and gene expression was observed.

Conclusions: The methylation and gene expression of umbilical cord genes associate with GWG and the cardio-metabolic profile of the offspring at 6 years old. Epigenetic changes in the umbilical cord could explain, at least in part, the relationship between gestational obesity and cardio-metabolic risk in later life.

P2-233

Diazoxide Responsive Congenital Hyperinsulinism

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Introduction: Congenital Hyperinsulinism (CHI) is a common cause of recurrent and persistent hypoglycemia in the neonatal period. Diazoxide is the first line medication used for the management of CHI. We report the clinical profile and the management outcome of a large cohort of patients with diazoxide responsive CHI.

Methodology: A retrospective data collection including antenatal, perinatal and postnatal clinical parameters, laboratory diagnostic data, genetic tests and treatment duration was undertaken on 103 CHI patients managed in a quaternary referral center over a 10 year period.

Results: 90 patients with diazoxide responsive CHI were included in the final analysis. Among these, 78 patients were diagnosed in the neonatal period (mean age of diagnosis 1.36 days [SEM ± 0.4]). Majority of them were boys (69.4%). Nearly 1/3rd of the patients were premature and 1/3rd were born small for gestational age (SGA). Twelve patients presented in the post-neonatal period (after 1 month of life) with CHI and none had history of prematurity, SGA or gestational diabetes mellitus. The mean dose of diazoxide was 4mg/kg/day (± 0.22). Baseline echocardiogram was undertaken in all patients prior to diazoxide initiation. The average duration of the diazoxide therapy was 8.5 $\pm$ 6 months and 81.9% needed treatment for less than 2 years. Children needing treatment for >2 years were found to have high C-peptide ($p = 0.02$) at the time of diagnosis. Genetic mutation was found in 11.1% among the overall study group [11p15.5 methylation defect (1), *HNF4A* (2), *HNF1A* (1), *INSR* (1), *GLUD1* (1), *ABCC8* (4)]. Patients with genetically proven CHI were on diazoxide treatment for more than 2 years. Adverse effects of diazoxide therapy (fluid retention, hyponatremia, hyperkalemia, pulmonary hypertension and hirsutism) were observed in 15.8% of the cohort.

Conclusion: Majority of patients with diazoxide responsive CHI were diagnosed in the neonatal period and were associated with risk factors like prematurity and SGA and tend to require diazoxide treatment for less than one year. Hence, a periodic evaluation of these patients to assess the discontinuation of diazoxide therapy should be undertaken. Patients with genetically proven CHI tend to require longer duration of treatment.

P2-234

Continuous Glucose Monitoring (CGM) Reveals Undertreated Hypoglycemia in Patients with Congenital Hyperinsulinism

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Introduction: Congenital Hyperinsulinism (CHI) is the most frequent cause of severe, persistent hypoglycemia in children. Despite current treatments, patients/caregivers report continued hypoglycemia according to the HI Global Registry 2020 Annual Report. Published literature characterizing hypoglycemia in CHI patients on standard of care (SOC) therapies is lacking.

Objective: To quantify the extent of hypoglycemia in CHI patients on SOC therapies.

Methods: A two-week observational study was conducted in CHI patients ages two years and older, recruited randomly from the Congenital Hyperinsulinism International community, using CGM (Dexcom G4®). Hypoglycemic thresholds in this study were defined as <70 mg/dL (3.9mmol/L), <60mg/dL (3.3 mmol/L), or <50mg/dL (2.8 mmol/L).

Results: Twenty-two patients (M:9, F:13; Age 2-36) with CHI of various genetic causes participated in this study. Fifteen patients were receiving at least one background therapy which included 11 (50%) on diazoxide, 4 (18%) on octreotide, and 7 (32%) managed by other means (continuous enteral dextrose, glucagon, and/or diet). Five patients were also post-pancreatectomy (< 50% to > 95% removal). The mean time in hypoglycemia ($\pm$ SD, % of monitored time) by CGM (< 70mg/dL) for all participants was 1165 (± 164 , 11.6%) and 1101 (± 152 , 10.9%) minutes in weeks 1 and 2, respectively. This included 115 (± 36 , 0.9%) and 91 (± 26 , 1.1%) minutes of severe hypoglycemia (<50 mg/dL). A 2 to 6 year-old subgroup (n=9) experienced a mean hypoglycemia duration of 1445 (± 161 , 14.3%) and 1376 (± 147 , 13.7%) minutes in weeks 1 and 2, respectively with 131 (± 36 , 1.3%) and 146 (± 36 , 1.5%) minutes of severe hypoglycemia. The results equate to an average of over 2.5 hours per day spent in hypoglycemia for all participants and nearly 3.5 hours per day for those 2-6 years old. Notably, patients taking SOC therapies experienced a similar magnitude of hypoglycemia.

Conclusions: Persistent hypoglycemia places patients at risk for adverse clinical outcomes. Current Pediatric Endocrine Society management guidelines recommend maintenance of blood glucose > 70 mg/dL. In this study patients with CHI on available SOC therapies had substantial continued hypoglycemia as revealed by CGM, thereby missing their therapeutic goals. This was especially

true for the younger patients in this study, who are also at the greatest risk of cumulative hypoglycemia. More effective treatments are needed to minimize hypoglycemia to achieve the therapeutic goal of glucose normalization. Going forward, CGM should have an important adjunctive role in the monitoring of CHI patients toward therapeutic goals.

P2-235

A Selective Nonpeptide Somatostatin Receptor 5 (SST5) Agonist Effectively Decreases Insulin Secretion in a KATPHI Mouse Model and in Human HI Islets

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Inactivating mutations of β -cell K_{ATP} channels cause the most common and severe form of congenital hyperinsulinism (HI), a β -cell disorder that results in dysregulated insulin secretion and persistent hypoglycemia. Children with $K_{ATP}HI$ are typically unresponsive to diazoxide, the only FDA-approved drug for HI. Octreotide, an SST2-selective agonist peptide that inhibits insulin secretion, is used as second line therapy, but poor efficacy and SST2-mediated side effects limit its use in infants. Crinetics has had ongoing discovery and development efforts aimed at finding a compound to treat HI that have yielded potent and selective nonpeptide SST5 agonists with sub-nanomolar EC_{50} s in cell-based assays of receptor activation. We characterized the ability of the selective SST5 nonpeptide agonist CRN02481 to suppress insulin secretion and prevent fasting hypoglycemia in the $SUR1^{-/-}$ mouse model of $K_{ATP}HI$. During batch incubation, $SUR1^{-/-}$ mouse islets were stimulated with a physiologic amino acid mixture (4mM) after treatment with CRN02481 (100 nM) or buffer control. CRN02481 significantly decreased baseline (2.4 ± 0.5 vs 1.5 ± 0.2 ng/ μ L) and amino acid-stimulated (4.4 ± 1.1 vs 2.8 ± 1.5 ng/ μ L) insulin secretion. Insulin secretion was also significantly decreased during perfusion with CRN02481 in primary isolated islets from both wildtype (WT) and $SUR1^{-/-}$ mice compared to buffer control. In addition, oral administration of CRN02481 (30 mg/kg) significantly increased fasting glucose and prevented fasting hypoglycemia compared to vehicle treatment (98 ± 18 vs 44 ± 6 mg/dL) in $SUR1^{-/-}$ mice. During a glucose tolerance test, oral administration of CRN02481 significantly increased glucose excursion in both WT and $SUR1^{-/-}$ mice compared to vehicle treatment. CRN02481 also reduced glucose- and tolbutamide-stimulated insulin secretion from islets isolated from human donors. Moreover, CRN02481 significantly decreased insulin secretion compared to control treatment in human islets isolated from two patients with $K_{ATP}HI$ and one patient with Beckwith-Wiedemann Syndrome and HI. Collectively, these data show that the selective SST5 agonist CRN02481 prevents fasting hypoglycemia and effectively suppresses insulin secretion not only in the $K_{ATP}HI$ mouse model, but also in human islets, including those from HI patients. Therefore, compounds

like CRN02481 represent a promising potential novel therapy for children with HI.

P2-236

Placental *FRAT-1* methylation in women with gestational obesity is associated with the body composition in the offspring at 6 years of age

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Background and Aims: Gestational obesity can cause metabolic programming in the offspring. Epigenetic modifications of DNA have been suggested as potential mechanisms underlying this programming. *FRAT-1* is a gene involved in the WNT signaling pathway, which is an important regulator of adipose tissue development. The objective of this work was to study the methylation status of *FRAT-1* in placentas of women with either normal weight or gestational obesity and its association with endocrine-metabolic parameters in the offspring at 6 years of age.

Methodology: A global methylation array (Infinium® Methylation EPIC BeadChip) was made in placental samples from 24 pregnant mothers with normal weight and gestational obesity. Two CpGs in *FRAT-1* were significantly associated with increased maternal weight during gestation (FDR = 2.20×10^{-6} and OR = 0.91; FDR = 2.17×10^{-6} and OR = 0.94). The methylation status of these CpGs in *FRAT-1* was validated by pyrosequencing in a cohort of 64 pregnant women (39 with normal weight and 24 with gestational obesity) and its association with endocrine-metabolic parameters [weight, height, body mass index (BMI) and body composition] in the offspring at 6 years of age was assessed.

Results: *FRAT-1* methylation status was significantly associated with a lower percentage of total fat mass SDS ($r = -0.274$; $p = 0.037$) at 6 years of age. In women with gestational obesity, *FRAT-1* methylation was negatively associated with weight-SDS, BMI-SDS, and visceral fat mass-SDS (r from -0.409 to -0.599 ; all $p < 0.05$). In multivariate analysis, adjusted for confounding variables, the placental methylation status of *FRAT-1* was a predictor of the percentage of fat mass-SDS at 6 years of age ($\beta = -0.263$; $p = 0.041$; $R^2 = 0.140$); as well as of weight-SDS ($\beta = -0.552$; $p = 0.030$; $R^2 = 0.060$), BMI-SDS ($\beta = -0.713$; $p = 0.003$; $R^2 = 0.232$) and visceral fat-SDS ($\beta = -0.452$; $p = 0.042$; $R^2 = 0.319$) in the offspring of mothers with gestational obesity.

Conclusions: Our results suggest that the methylation of the *FRAT-1* may play a role in regulating the body composition of the offspring at 6 years of age. This methylation may explain, at least in part, the metabolic programming in the offspring caused by gestational obesity.

Placenta n-6/n-3 PUFA ratio is associated with visceral adiposity and cardiovascular risk in the offspring at 6 years of age

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Background and Aims: Long chain polyunsaturated fatty acids (LC-PUFA) are essential nutrients for the development of the fetus and are supplied by the mother through the placenta. Omega-6 arachidonic acid (AA) and both omega-3 eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) stand out for their functional roles. Recent studies show that the concentrations of these fatty acids in maternal blood and umbilical cord are associated with adiposity in the offspring. Indeed, prenatal exposure to AA n-6 promotes adipocyte maturation while DHA n-3 is known to inhibit it. Our objective was to study the placental levels of n-6 and n-3 functional LC-PUFA and its association with anthropometric and cardio-metabolic parameters in the offspring at 6 years of age.

Methodology: The n-6 and n-3 PUFA profile was analyzed in 117 placentas from a population cohort of pregnant women-newborn pairs by gas chromatography. Total n-6 and n-3 PUFA content as well as the ratios of LC-PUFA (AA/EPA and AA/DHA) were calculated from the percentages of relative abundance of each PUFA. They were subsequently correlated with anthropometric (weight, height and body mass index) and cardio-metabolic parameters [(total fat mass, visceral fat mass and carotid intima-media thickness (cIMT)) in the offspring at 6 years of age.

Results: Placental concentrations of AA (n-6) and total PUFA n-6 were positively correlated with visceral fat mass ($r = 0.229$, $p = 0.036$ and $r = 0.211$, $p = 0.045$, respectively). DHA (n-3) and total PUFA n-3 were negatively correlated with cIMT ($r = -0.228$, $p = 0.036$ and $r = -0.254$, $p = 0.019$, respectively). The AA/EPA ratio was positively correlated with total fat mass SDS ($r = 0.271$, $p = 0.018$) and visceral fat mass SDS ($r = 0.337$, $p = 0.002$) while the AA/DHA ratio was positively correlated with cIMT ($r = 0.243$, $p = 0.025$). All these associations remained significant in multivariate analysis after adjusting for possible confounding variables (maternal age, gestational weight gain, gestational age, sex, and birth-weight).

Conclusions: A higher ratio of LC-PUFA n-6/n-3 (AA/EPA and AA/DHA) in placenta is associated with higher total and visceral fat and thicker cIMT at 6 years of age. The n-6 and n-3 fatty acids provided by the mother during pregnancy may influence visceral adiposity and cardiovascular risk in the offspring at 6 years of age.

Analysis of Placental Steroidogenesis as a Cause of Recurrent Miscarriage

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Background: Recurrent miscarriage (RM) is traditionally described as three or more consecutive pregnancy losses and remains a challenging condition, affecting 1-3% of couples trying to conceive. Although factors such as uterine abnormalities, maternal hypothyroidism and parental balanced translocations are associated with RM, in most situations the aetiology is unknown. The coexistence of RM and live births in many families suggests a potential association with an underlying recessive, X-linked or imprinted condition. Indeed, placental function and fetal growth and development are intricately linked. The main steroid needed to maintain pregnancy is progesterone. In humans, progesterone synthesis occurs from the maternal corpus luteum in the first 6-8 weeks of gestation at which point the fetally-derived placenta takes over progesterone production ("luteal-placental shift"). The progesterone receptor (*PGR*) is the only classic liganded nuclear receptor without an associated disorder in humans. Furthermore, prematurity is reported in a child with disruption of *CYP11A1* (encoding P450_{scc}) but no bi-allelic loss-of-function variants in *FDX1* or *HSD3B1* have been described.

Aims: We hypothesised that disruption of placental steroidogenesis is associated with recurrent pregnancy loss.

Methods: DNA from 123 couples with RM of unknown aetiology and 22 products of conception (POC) was obtained with ethical approval and consent from the Baby Bio Bank. Custom HaloPlex HS targeted panels were designed to capture 256 genes involved in placental function, novel components of steroidogenesis from transcriptomic analysis, and fetal growth. DNA libraries were prepared, and next-generation sequencing performed using NextSeq platforms. Analysis focused on several inheritance models including rare variants (MAF<0.1) co-segregating in couples (recessive model) as well as imprinted genes, X-linked genes, and non-filtered singleton global gene enrichment analysis. In addition, human placental single-cell RNA sequencing data were analysed to study clustering of factors involved in progesterone and growth pathways (<https://maternal-fetal-interface.cellgeni.sanger.ac.uk>).

Results: Most placental genes involved in progesterone synthesis (e.g., *CYP11A1*, *HSD3B1*, *FDX1*) were strongly localised in the syncytiotrophoblastic cells of the fetal placenta whereas the progesterone receptor was expressed in maternally-derived decidua, as expected. No likely pathogenic variants were found in key components of progesterone synthesis and action that were studied in this RM/POC cohort.

Conclusions: The luteal-placental shift is a key event in progesterone synthesis and the maintenance of pregnancy past the first trimester in humans. However, defects in core components of placental progesterone synthesis and action are not likely to be a common cause of pregnancy loss in couples with a history of recurrent miscarriage.

P2-239

Antenatal Markers Related to Fetal Growth Restriction Can Predict Childhood Systolic Blood Pressure

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Background: Being born small for gestational age (SGA) is linked with higher systolic blood pressure (SBP). Fetuses with growth restriction (FGR) may be either SGA or appropriate size for gestational age at birth. However, it is not known which factors contributing to size at birth influence the relationship with SBP.

Aim: To determine whether antenatal markers of FGR can predict the upper quartile of childhood SBP.

Methods: Brachial SBP was measured for 75 children aged 3-6 years from the Manchester BabyGRO Study, using a Tensiomed® Arteriograph with a child-sized cuff. SBP quartiles were generated. Participants were born to mothers who had attended a specialised clinic, following identification of higher FGR risk based on abnormal maternal serology (pregnancy associated plasma protein-A, beta-human chorionic gonadotrophin, alpha-fetoprotein, Inhibin-A). Antenatal ultrasound data at 23 weeks gestation were obtained. Uterine artery Doppler (UtAD) notching was assigned a rank (0=absent, 1=unilateral, 2=bilateral). Random forest (RF) is a machine learning approach that generates many independent, uncorrelated decision trees based on multiple variables. This was used to determine the relative importance of antenatal variables in prediction of upper quartile of childhood SBP. Variables included in the model were maternal body mass index (BMI), parity, ethnicity (black/white/asian/mixed), maternal SBP and diastolic BP (DBP), maternal serology relating to FGR risk, UtAD pulsatility index, resistance index and notching rank (all measures of uteroplacental blood flow resistance), placental size measurements, 23 week estimated fetal weight (EFW) centile, Δ 23w EFW to birthweight centile and birthweight SDS. A receiver operating characteristic (ROC) curve was generated, providing an area under the curve (AUC). A variable of importance (VIP) score was calculated for each marker that was significant in the model. All analyses were conducted in R (version 3.6).

Results: RF analysis demonstrated antenatal markers relating to FGR risk predict the upper quartile of childhood SBP with an AUC 0.97. The top five ranked variables were maternal DBP, birthweight SDS, parity, notching rank and Δ 23w EFW to birthweight centile.

Conclusion: Maternal and antenatal markers, as well as birthweight SDS are linked with the upper quartile of SBP at 3-6 years. Antenatal markers were within the top five ranked and could help identify those babies at risk of higher SBP in childhood.

P2-240

Hypomethylation of the Prader-Willi imprinting control region associates with postnatal growth and visceral adiposity in healthy children

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Introduction: Children with Prader-Willi syndrome present with short stature and obesity. However, very little is known about the role of this imprinted control region in the general population. This study aims to analyze the methylation status of the PWS imprinting control region (ICR) in placenta and its association with postnatal growth and obesity parameters in healthy children.

Methodology: The methylation percentages of the PWS-ICR were determined by Epytyper™ technology in placentas from 118 healthy newborns included in a cohort of mother-newborn pairs in Girona, a region in Northeastern Spain. Methylation values for the different studied cytosine-guanine nucleotides (CpG) within the PWS-ICR were correlated with anthropometric parameters (weight, height and body composition) in the offspring from birth to 6 years of age.

Results: The methylation status of the PWS-ICR was inversely and independently correlated to weight and height at birth, height during the first month of life, and with height and visceral fat mass at 6 years of age. All inverse associations between PWS-ICR methylation and growth and visceral adiposity parameters were more pronounced in children who had been heavier at birth (those with birthweight above the median; adjusted multivariate models $0.40 > R^2 > 0.30$).

Conclusion: In conclusion, placental PWS-ICR methylation status associates with growth parameters in healthy children from birth to school age as well as with higher visceral adiposity at 6 years of age. As shown for PWS patients, PWS-ICR methylation could similarly be involved in postnatal growth and visceral obesity in healthy infants.

P2-241

Incidence of early neonatal hypoglycemia and some related risk factors in Qatar. A cohort study over two years (2018 and 2019)

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Objective: The objective of this study is to determine the incidence of early neonatal hypoglycemia and to confirm potential risk factors.

Study design: The study was conducted at a tertiary Medical Center in Qatar. between January 2018 and December 2019. First blood glucose concentrations of all infants admitted to the nursery were measured using a “point of care” analyzer (Accu-Chek). We recorded risk factors for hypoglycemia such as birth weight, gestational age, and maternal diabetes. The diagnosis of hypoglycemia cutoffs was 47 mg/dl for full-term (FT) and 40 mg/dl for preterm infants.

Results: Of 16783 and 17000 newborns admitted during 2018 and 2019 respectively and were analyzed.

Year	2018	2019
Newborns	16783	17000
N-Hypoglycemia	691	1073
Length of hospital stay/day	9.6	7.27
IDM	445	712
Not IDM	246	362
Males	363	553
Females	328	522
Incidence of N Hypoglycemia /1000	41.17	63.12
Incidence of IDM/1000	26.51	41.88

P < 0.0001

Discussion: A 1988 multicenter nutritional study by Lucas et al. suggested a blood glucose concentration <47 mg/dL as the critical threshold associated with adverse neurodevelopmental outcomes. Even moderate hypoglycemia is associated with a considerable increase in adverse neurodevelopmental sequelae. Our annual incidence of neonatal hypoglycemia (4.1% and 6.3% in 2018 and 2019 respectively) is considerably low compared to previously reported incidence by Bromiker et al and Harris et al (12.1 % and 12.75% respectively).

Incidence of early neonatal hypoglycemia and some risk factors in Qatar. A cohort study over two years (2018 and 2019).

Conclusions: We showed an increasing trend in the incidence of neonatal hypoglycemic in 2019 versus 2018. IDM constituted 64% and 66% of the total number of N hypoglycemia in 2018 and 2019 respectively.

P2-242

Long-term follow-up in a case with congenital hyperinsulinemic hypoglycemia with a novel p.Ser1389Pro mutation in ABCC8 gene

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Introduction: Hyperinsulinemic hypoglycemia is one of the most common causes of severe and persistent hypoglycemia in neonates and children. Early diagnosis and appropriate treatment prevent brain damage due to recurrent hypoglycemia. Genetic examination often can guide the treatment. The most common affected genes are the ABCC8 and KCNJ11 genes, which encode the SUR1 and Kir6.2 K_{ATP} channels, respectively. Here, a neonate with a novel variant in ABCC8 gene and her genotype-phenotype relationship is presented.

Case: Her genetic analysis was reported as an diazoxide unresponsive missense mutation, due to previous neighbor mutations. Discontinuation of diazoxide treatment was made based on genetic result but she had hypoglycemia again. Hypoglycemia improved when diazoxide was added to therapy. She was followed up as normoglycemic with diazoxide and octreotide until the age of three. When she was three years-old, octreotide treatment was switched to a long-acting release form (LAR) due to family request. Diazoxide was discontinued six months after this treatment. Also, LAR dose requirement decreased over time. Now, she is five year-old and neurodevelopment is appropriate for the age, and the follow-up continues without drug-related side effects. Anthropometric and laboratory findings in the last control are given in **Table-1**.

Table 1. The anthropometric and laboratory results in the last control

Anthropometric		Laboratory	
Height (cm)	107.5	Glucose (mg/dL)	89
Height SDS	-0.62	SGOT/SGPT (U/L)	37/17
Bodyweight (kg)	17.1	IGF-1 (ng/mL)	103 (-0.29 SDS)
Bodyweight SDS	-0.69	IGFBP3 (ng/mL)	3580 (0.4 SDS)
BMI (kg/m ²)	14.8	TSH (mIU/mL)	3.5
BMI SDS	-0.46	fT4 (ng/dL)	1.31

BMI: Body mass index

Discussion-Conclusion: As a result, the genetic examination is important in guiding treatment in patients with HH. However, the genotype-phenotype relationship may not always be clear. After the partial response to diazoxide, LAR treatment was started and

diazoxide was not needed anymore in our case. This situation is thought to be due to the decrease in the severity of the disease with age, or an unknown mechanism of action of LAR treatment on the K_{ATP} channel. It is very important to discuss the cases with HH in terms of guiding clinical follow-up and treatment.

P2-243

Postnatal linear growth and weight gain in infants of non-diabetic mothers (INDM) who were born preterm or near term and had significant neonatal hypoglycemia

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Preterm babies born to non-diabetic mothers (INDM) who experience significant hypoglycemia may have postnatal growth abnormalities.

This study evaluated the growth pattern from birth to the age of 2 years of 40 INDM who were born at or near term with significant hypoglycemia.

Anthropometric measures (z scores) from birth, 2,4,6,12,18 and 2 years were measured in 40 INDM who presented with significant neonatal hypoglycemia (plasma value less than 20-25 mg/dL (1.1-1.4 mmol/L)) that required proper therapy (IV glucose bolus followed by IV glucose infusion) for two days or more. Their anthropometric data were compared to standard growth for normal age and sex-matched infants (WHO growth standards). All preterm babies were started on preterm formula until their WAZ became >-1 SD. (average of 6 months)

Results: Their gestational age (GA) at delivery was 36.4 +/-2 weeks. They had Wt. z score (WAZ) = -2.6 +/-1.8, length Z score (LAZ) = -2 +/-2.3 and Wt. for L. Z score (WLZ) = -2.9 +/-1.9.

At birth 24/40 (60%) had LAZ <-2, 30/40 (75%) had WAZ <-2 and 29/40 (72.5%) had WLZ <-2. They had a progressive gain in WAZ for the first 18 months (from -2.6 to 0). They had a progressive increase in the LAZ for the first 6 months (from -2.1 to -0.46) that was followed by stable LAZ (normal growth velocity) until 2 years of age. By the age of 12 months 4/40 (10%) had LAZ <-2, 4/40 (10%) had WAZ <-2 and only one had WLZ <-2. One infant had WLZ > 2. By the age of 2 years, none had LAZ or WAZ <-2, and only one infant had WLZ <-2. None of those infants had WLZ > 2 (overweight).

Age (mon)	Birth	2	4	6	12	18	24
WAZ	-2.57	-2.10	-1.44	-1.15	-0.40	0	-0.21
WLZ	-2.88	-0.16	-0.45	-0.56	-0.19	0.01	-0.20
LAZ	-2.13	-2.28	-1.55	-0.46	-0.56	-0.50	-0.33

Conclusion: INDMs born preterm or at near term with severe neonatal hypoglycemia had significant short stature and underweight when plotted on WHO growth charts. Feeding preterm formula resulted in a fast postnatal growth pattern with normalization of their linear growth and WAZ during the first year of life. None had overweight at 2 years of age.

P2-244

Genetic Testing Access and Results for Patients with Congenital Hyperinsulinism as Conducted through the CHI and University of Exeter Partnership

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Background and Aims: Congenital hyperinsulinism (HI) is the most frequent cause of severe, persistent hypoglycemia in newborn babies and children. The disease may occur in isolation or can present as part of a syndrome. Routine screening of the known etiological genes (n=>20) identifies a disease-causing mutation in 40-50% of all cases. An accurate and timely genetic diagnosis is clinically important for all individuals as understanding the underlying genetic cause of the HI can guide the clinician in both medical and surgical management.

Congenital Hyperinsulinism International (CHI) is a nonprofit organization dedicated to improving the lives of those living with HI. Since 2018, CHI has provided funding to the University of Exeter to cover the cost of genetic testing for individuals who would otherwise be unable to receive genetic screening. The objective of this study is to report on the results of the genetic testing conducted through this partnership and the benefits to patients worldwide.

Methods: Exeter recruited individuals with clinical diagnosis of HI who were unable to access genetic testing through their own healthcare provider. Exeter performed rapid Sanger sequencing of the KATP channel genes in all individuals. Targeted next-generation sequencing of the remaining known genes was performed in those without a KATP channel mutation if the HI persisted beyond 3 months or additional clinical features suggested syndromic disease.

Results: Between July 2018 and March 2021 CHI funded genetic testing for 526 individuals from 54 countries with medically diagnosed HI. Routine screening identified mutations in 251 out of 526 individuals (47.7%). These mutations were identified in 14 different genes. The most common genetic etiology was KATP channel HI, with *ABCC8* and *KCNJ11* mutations identified in 197 patients (78.4% of solved cases). Of these, 142 individuals had bi-allelic or a dominantly-acting mutation confirming diffuse pancreatic disease. In 55 individuals, a paternally-inherited mutation suggested focal disease which can be cured by lesionectomy.

Discussion: The partnership between CHI and Exeter has enabled 251 individuals with HI to receive an accurate genetic diagnosis. For all of these individuals understanding the underlying genetic cause of the HI has helped to guide medical management by informing on treatment decisions, prognosis and recurrence risk within families. By increasing access to genetic testing, this partnership is improving HI patient care around the world, providing novel insights into mechanisms of insulin secretion, and ensuring there are no barriers for children to receive testing regardless of where they are born.

P2-245**Predictors of short stature in intrauterine growth retardation in a region of north Africa**

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Introduction: The intrauterine growth retardation (IUGR) is defined by weight and / or height below the 10th percentile of reference population curve.

Goal: To determine the predictors of small size at the age of 2 years

Method: Longitudinal prospective study from 2012 to 2016. We followed the growth in height and weight of children born with IUGR at term up to the age of 2 years.

Results: 457 newborns were collected. The IUGR accounted for 3.9% of all births.

12.1% of children have a height delay, the predictive factors identified for short stature at 2 years are maternal height, history of IUGR, height of the child compared to the target height, difference between birth size and target height, weight index and gain in weight and size at 6 months.

Conclusion: In our study, the frequency of stature delay at the age of 2 years is close to the results already published in the world. The predictive factors vary from one study to another, due to the heterogeneity of the IUGR group.

The prevalence of IUGR is unknown in Algeria. The identification of predictive factors of a small size make it possible to carry out an early diagnosis of the delay in height by a regular and targeted follow-up, and thus to improve the quality of the care.

Growth Hormone and IGFs

P2-246**Massive Open Online Learning – accelerating knowledge in digital health in the management of children with growth disorders**

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Background: Over the last decade, and in light of the COVID-19 pandemic, there has been a substantial increase in the use of digital health tools to track growth and manage growth disorders in

children. Paediatric endocrinologists acknowledge the usefulness of these tools in clinical decision making but lack confidence and skills to use them. Atique et al. designed a Massive Open Online Learning Course (MOOC) to increase digital health literacy, and identified a demand for more training to increase skills/capabilities to identify trustworthy and useful health information.¹

Aim: To educate on the management of growth disorders using digital health tools, we developed a MOOC to provide a comprehensive e-learning package.

Methods: The MOOC was designed to explore best practices for utilising digital health tools and data science to manage growth disorders in children and adolescents. Delivered over a 4-week period, with up to 3 hours of education per week, the content is divided into a generic understanding of technology and digital health tools, with a specific focus on the application of technologies for patient support and data-driven tools to support clinicians. It focuses on the principles underpinning the development of digital health tools (proof-of-concept to commercialisation), the process of co-design/creation in the development of digital health tools for children and young people, digital literacy, how to search and critically appraise digital health resources, and how to apply research methods for the evaluation of digital health tools while complying with regulations and privacy. Endocrine-focused learning covers emerging challenges, opportunities and digital health solutions for the management of growth disorders from the perspective of caregivers, patients and healthcare providers. It also focuses on patient-centred translational research exploring the long-term impact of digital health on adherence to therapy and the management of growth disorders, and on studies looking at technology acceptance aspects (e.g. usability, impact on quality of life and implementation strategies). Future opportunities are also explored to develop new technologies in the management of growth disorders.

Conclusion: Given the rapid expansion of digital health, and the drive for improved global connectivity as we enter a post-COVID-19 era, there is a need for the paediatric endocrine community to learn about opportunities to develop and implement digital health tools to manage growth disorders, and to explore opportunities with large international data sets to advance the management of growth disorders.

Reference

Atique S, et al. Annu Int Conf IEEE Eng Med Biol Soc 2016;2016:5636–5639.

P2-247

A girl with concurrent congenital adrenal hyperplasia, isolated growth hormone deficiency type II (IGHD II) and a new mutation in the GH 1 gene – an extremely unusual case

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Background: Classical salt wasting congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21OHD) is a rare disorder, as is isolated growth hormone (GH) deficiency Type II (IGHD II) due to mutation of the growth hormone gene GH1.

Here we describe the unusual case of a girl with concurrent 21OHD and IGHD II and its complex diagnostic work up. A 15.3-year-old girl presented with classical salt wasting CAH due to 21OHD and short stature (height 148.3cm, -2.8 SDS). The diagnosis of CAH had been made in early childhood by hormonal and genetic analyses. Regarding CAH, drug therapy consisted of hydrocortisone and fludrocortisone. Unusual for a patient with CAH, her bone age was delayed by 3 years. There was familial short stature (father's height 158.6 cm, (-3,2 SDS), mother's height 164.4 cm (-0,57 SDS), parental target height 155cm (-2,03 SDS)). IGF-1 level was low (84µg/L, SDS -3.39) while IGFBP-3 was normal (2.95mg/L, -0.54 SDS). A GH stimulation test using arginine test showed an inconspicuous result (GH increase to max. 12,6 ng/mL), so that biochemically the diagnosis of isolated GH deficiency could not be made. Further genetic examinations followed. Abnormalities in the SHOX gene could be excluded, so that a further investigation was carried out by means of next generation sequencing gene panel. A heterozygous variant c.235T>G p.(Cys79Gly) in exon 3 of the GH1 gene was detected which had not been described before. This mutation interrupts the disulfide bridge at position 53 of the mature GH peptide which is important for the correct tertiary structure. After additional genetic analysis of both parents, the same heterozygous variant of the GH1 gene was detected in the father and thus a paternally inherited, autosomal dominant form of IGHD type II was diagnosed.

Conclusion: The combination of CAH and IGHD II has not yet been described. We present a new mutation of GH 1 and speculate that the GH exon 3 mutation c.235T>G of our patient leads to the formation of partially bioinactive GH, as has been described for the mutation Exon 3, c.236G>C by Besson et al. It is important to note, that a normal GH stimulation test does not rule out growth hormone deficiency in any case!

P2-248

Reduction in pappalysin and stanniocalcin levels explain the decrease in IGF-I bioavailability in anorexia nervosa

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Background: Pappalysins (PAPP-A, PAPP-A2) and stanniocalcins (STC-1, STC-2) are novel regulators of the GH-IGF axis, modulating IGF bioavailability through control of cleavage of IGFBPs and release of IGF from the ternary complex. Changes in the peripheral IGF system, including low IGF concentrations independently of GH secretion, have been reported in scenarios of malnutrition such as anorexia nervosa (AN). The role of pappalysins and stanniocalcins in the pathophysiology of this disorder is not fully established.

Objective: Our objective was to determine the changes in the serum levels of the peripheral GH-IGF axis components in a cohort of female adolescents with AN.

Patients and Methods: One hundred and six female adolescents with AN, age 14.93 ± 1.80 years, BMI: -2.13 ± 0.65 SDS, weight loss at diagnosis: 9.06 ± 5.70 kg, and 106 healthy females (age: 14.61 ± 1.42 years, BMI: 0.05 ± 0.85 SDS) were included. At diagnosis, total IGF-I, free IGF-I, IGF-II, IGFBP-2, total and intact IGFBP-3, total and intact IGFBP-4, IGFBP-5, ALS, insulin, PAPP-A, STC-1 and STC-2 were measured by ELISA and PAPP-A2 by CLIA in fasting serum samples.

Results: Patients with AN showed lower concentrations of total and free IGF-I, total IGFBP-3 ($p<0.001$), ALS, insulin ($p<0.01$), PAPP-A2, STC-1 and STC-2 ($p<0.001$) than the controls. Conversely, AN patients presented higher serum levels of IGF-II and IGFBP-2 ($p<0.001$). The free/total IGF-I ratio was decreased ($p<0.05$), whereas the intact/total IGFBP-3 and -4 ratios ($p<0.001$) were increased in patients with AN. No changes were observed in total IGFBP-4, IGFBP-5 or PAPP-A levels.

In patients with AN, standardized BMI was positively correlated with total IGF-I ($p<0.001$), total IGFBP-3 ($p<0.001$) and STC-2 ($p<0.01$), and negatively with IGFBP-2 ($p<0.001$) and the intact/total IGFBP-4 ratio ($p<0.01$). Additionally, weight loss was negatively correlated with STC-2 ($p<0.01$) and PAPP-A2 ($p<0.05$) levels.

Conclusions: The decrease in circulating pappalysin and stanniocalcin levels in patients with anorexia nervosa, would explain, at least in part, the reduction in IGF-I bioavailability, with these changes being influenced by both the nutritional status and changes in body composition.

P2-249**Predictors of short stature in premature infants born small for gestational age**

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Aim: to evaluate the frequency and predictors of short stature in preterm infants born small for gestational age (SGA), by the age of 5 years.

Materials and Methods: We examined 100 premature babies (gestational age of 22-31 weeks – 18, 32-36 weeks – 82), born SGA with the tables Fenton T. R. et al. (2013). Protocol included an assessment of anthropometric indicators and IGF-1 levels in the blood at birth, at the ages of 1 and 5 years. The odds ratio (OR) for verification of risk factors for clinically significant short stature (growth below -2.0 SD relative to chronological age and gender, program Anthro, WHO, 2006) to age 5 years was calculated.

Results: The median body length/height at birth was 40.0 [35.5; 44.0] cm, at the age of 5 years – 104.5 [99.5; 108.5] cm, -1.1 [-2.1; -0.2] SD. The frequency of clinically significant growth retardation by the age of 5 years was at the level of 27.1%, including those born at 22-31 weeks of gestation – 33.3%, 32-36 weeks of gestation – 24.2%. Predictors of poor growth prognosis in premature infants with SGA: gestational age at birth less than 32 weeks (OR 7.3; 95% CI 1.4-38.3), placental insufficiency (OR 7.3; 95% CI 1.4-38.3), SGA (light/short) (OR 5.2; 95% CI 1.1-27.6), severe perinatal nervous system damage – grade 3 cerebral ischemia, intraventricular hemorrhages (OR 5.2; 95% CI 1.1-27.6), clinically significant growth deficit at corrected age 1 year (OR 33.6; 95% CI 3.34-337.0), IGF-1 levels below -1.0 SD at corrected age 1 year (OR 17.1; 95% CI 1.7-172.0) and 5 years (OR 8.9; 95% CI 1.6-49.8).

Conclusions: Growth retardation is a clinically significant problem for premature babies born SGA, and is determined by the influence of a set of factors.

P2-250**Patterns of suboptimal adherence to growth hormone treatment in children living in Italy**

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Background: Monitoring adherence to growth hormone (GH) treatment is important, because poor adherence can lead to suboptimal clinical outcomes. The easypod™ electromechanical injection device in combination with the web-based easypod™ connect platform electronically records and transmits accurate, objective records of the date, time and dose injected of patients receiving GH

with growth disorders, allowing physicians to accurately monitor patients' behavior.

Aim: To study patterns of suboptimal adherence to GH treatment and the effect of age, sex and regimen on treatment adherence in children living in Italy.

Patients and Methods: Data on adherence (mg injected/mg prescribed x 100) from treatment start to 24 months and background characteristics uploaded onto easypod™ connect from January 2007 to June 2019 were included. Inclusion criteria were age 4–18 y and living in Italy. Suboptimal adherence was defined as <85% adherence (>1 missed injection/week). Logistic regression models (suboptimally-adherent vs adherent) were used to study the effect of age at treatment start, sex and regimen on adherence.

Results: Data were available for 677 children for a 0–6-month interval (45% girls, 55% boys; mean age at treatment start 10.7 y; 26% GH Deficiency, 3% Small for Gestational Age, 2% Turner Syndrome, 69% not registered; 56% on a 6-day regimen and 44% on a 7-day regimen), 541 children for 0–12 months, 401 children for 0–18 months and 278 children for 0–24 months. The longer the observation period, the fewer the data available. The proportions of suboptimal adherence were 13%, 19%, 22% and 23% between 0–6, 6–12, 12–18 and 18–24 months, respectively. In total, 34% of all children who were 24 months on treatment were suboptimally adherent in at least one 6-month time interval (0–6, 6–12, 12–18 and 18–24 months): 6% at all four intervals, 6% at three intervals, 8% at two intervals and 14% at one interval. Age at treatment start, sex and regimen had no significant effect on suboptimal adherence.

Conclusions: The easypod™ connect platform with automatic adherence recording and data transmission allows proactive monitoring of adherence. Understanding adherence patterns can be helpful to target children at risk for suboptimal adherence. Further research is needed to apply more advanced statistics, such as machine learning, to predict suboptimal adherence continuously and in real-time. This prediction, together with individual reasons for suboptimal adherence, may contribute to determining when a child needs support and which personalized intervention strategy can be applied to improve adherence.

P2-251**Screening of celiac disease among children with growth hormone deficiency and idiopathic short stature**

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Celiac disease (CD) is an intestinal chronic inflammatory and autoimmune disease that develops as a result of interplay between genetic, immunologic, and environmental factors. Many patients, who are referred for evaluation for short stature, show initially no identifiable abnormalities and labeled as having idiopathic short stature (ISS). Children with growth hormone deficiency may show poor response to growth hormone (GH) replacement therapy. In both conditions, this may be due to the co-existence of CD.

So the aim of the study to determine the prevalence of CD in Egyptian children diagnosed with idiopathic short stature (ISS) and those with GHD who have showed poor response to GH replacement.

Methods: The study was conducted on (60) children with idiopathic short stature, (40) growth hormone deficient children with poor response to a minimum one year of continuous therapy of growth hormone replacement and (40) healthy children as control group. All groups were included irrespective of whether or not they had any other symptom suggestive of CD. Screening is based on tissue transglutaminase immunoglobulin A (TTG Ig A) test. Total Ig A titer has been done to be sure that it was normal.

Results: showed that the overall prevalence of CD based on serology among ISS and GHD is the same and estimated to be 5 %. TTG Ig A titer was significantly higher in the GHD group than the ISS group and higher in both groups than control one. There were 12 cases with levels of total Ig A <20 mg/dL and were referred to perform TTG IgG serological testing but all were confirmed to be negative. All positive cases were referred to perform confirmatory upper endoscopy and histopathological evaluation. Children with ISS were instructed to initiate GFD while those with GHD were instructed to initiate that diet along with continuation of GH replacement therapy.

Conclusion: screening of CD must be done as a routine investigation in children with either ISS or GHD before start of therapy.

P2-252

Pappalysins and stanniocalcins in prenatal and postnatal life

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Background: The human growth pattern varies from intrauterine to extrauterine life, with the GH-IGF axis being immature at birth and IGF-I assuming an important role in promoting postnatal growth. The actions of IGF-I are modulated by its interactions with IGF-BPs, with this interaction being regulated by pappalysins (PAPP-A, PAPP-A2) and stanniocalcins (STC-1, STC-2), and thus modifying the amount of free IGF-I.

Objective: Our aim was to determine the circulating levels of PAPP-A, PAPP-A2, STC-1 and STC-2, together with the changes in the other GH-IGF axis parameters in premature and full-term newborns and healthy young prepubertal children.

Patients and Methods: Full-term newborns (n = 150; gestational age: 39.30 ± 1.10 weeks), 40 pre-term newborns (30.87 ± 3.35 weeks) and 150 healthy prepubertal Spanish children (4.05 ± 1.25 years) were enrolled in the study. All subjects presented normal weight and length/height according to the national references. Samples were obtained from cord blood in newborns and fasting serum samples in children. Total IGF-I, free IGF-I, IGF-II, ALS, insulin, IGF-BP-2, total and intact IGF-BP-3, total and intact IGF-BP-4, IGF-BP-5, PAPP-A, STC-1 and STC-2 were measured by ELISA and PAPP-A2 by CLIA.

Results: Serum concentrations of total IGF-I, IGF-II, total IGF-BP-3 and ALS rose gradually according to gestational age and were significantly higher in children than in newborns. The other parameters, IGF-BP-2, total IGF-BP-4, total IGF-BP-5, STC-1, STC-2, PAPP-A and PAPP-A2, followed an inverse pattern, being elevated during the prenatal period and declining throughout infancy. The free/total IGF-I ratio was higher in newborns, together with lower intact/total IGF-BP-3 and -4 ratios. Additionally, peripheral values of total IGF-BP-4, IGF-BP-5, STC-2, PAPP-A, PAPP-A2 and free/total IGF-I ratio were lower in full-term than in pre-term newborns and decreased progressively with gestational age.

Conclusions: The relationship between the different members of the GH-IGF axis differs substantially from prenatal to early postnatal life, with a remarkable decrease in the bioavailability of IGFs in young children compared to prenatal life, with this possibly being related to the changes in pappalysin levels throughout development. However, the dynamics of this system during fetal life, and how prenatal growth is controlled remain to be elucidated.

P2-253

GROWPATI Study: Growth and puberty description pattern in a well-characterized cohort of patients with growth retardation due to severe primary IGF1 deficiency

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Background: Severe primary insulin-growth factor-1 (IGF1) deficiency (SPIGF1D) is a rare cause of growth delay. The diagnostic criteria include age- and sex-dependent low basal IGF1 concentration (<2.5th percentile), height SDS < -3SDS, absence of growth hormone deficiency and of any secondary causes of growth failure.

Objectives: 1) Report the growth pattern and pubertal status 2) Identify the molecular causes of SPIGF1D 3) Describe the growth response after 1-year recombinant human IGF1 (rhIGF1) treatment in a young patient with ACAN mutation.

Methods: Our group has previously reported a SPIGF1D prevalence of 1.2% among children with growth retardation. This historical cohort was composed by thirty patients (out of 2546) referred to our Department between 2004 and 2009. We have further included 20 patients with SPIFGD. Data were collected concerning growth, puberty, and final height or near adult-final height, if available. Molecular studies are ongoing based on a candidate gene approach or next-generation sequencing gene panel.

Results: Twenty-two patients have already undergone genetic analysis: constitutional bone disease (n=4), hypochondroplasia (n=1), Laron syndrome (n=1), heterozygous *GHR* mutations (n=2), Noonan syndrome (n=1), Silver-Russell syndrome (n=2), heterozygous ACAN mutation (n=1). No pathogenic variants in candidate genes of GH-IG1-bone axis included in the NGS gene panel were identified in 8 patients. Molecular testing is ongoing for 10 more patients (delayed because of Covid-19 epidemic). At inclusion all patients were pubertal stage 1. Mean actual age of patients in the historical and new cohort is 19.3 and 11.3 years respectively. Data are presented for the subgroup of 21 patients from both cohorts. Pubertal onset was normal with a mean age for Tanner stage 2 of 12.5 years for boys (n=11) and 10.2 years for girls (n=10). Two boys (one with SGA and one with idiopathic short stature, ISS) had advanced central puberty, treated by GnRH agonist. We present the case of a 4-year-old girl referred for growth delay; investigations showed SPIGF1D and molecular testing identified an heterozygous mutation in the ACAN gene. She was born SGA and at referral, her height was at -3SD and weight at -2SD. Growth response after 1 year treatment with rhIGF1 is very satisfactory with actual height at -2SD and no adverse effects.

Conclusions: Genetic analysis reflect the heterogeneous spectrum of the disease. rhIGF1 treatment is indicated if criteria for treatment are fulfilled and should not be delayed. Long term follow-up along with molecular studies will provide us more insights in the understanding of SPIGF1D.

P2-254

Clinic, laboratory and prognostic findings of patients who are diagnosed by Kowarski syndrome (biologically inactive growth hormone)

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Objective: The clinical, laboratory and prognostic findings of the patients diagnosed with Kowarski Syndrome (biologically inactive growth hormone) were evaluated between February 2009 and February 2019 in order to contribute to literature.

Materials and Methods: 110 cases diagnosed with Kowarski syndrome between February 2009 and February 2019 were evaluated retrospectively. 97 cases continued to work. 92 cases at least

one year, 62 cases at least two years, 30 cases at least three years, 9 cases at least four years and two cases at least five years were followed. Age at the beginning of medical therapy, body height, body weight, SDS of height, SDS of weight, body surface area, BMI, SDS of BMI, bone age, height age, status of puberty, pituitary MRG, parents' height, midparental height, SDS of midparental height, pre-treatment length growth rate, thyroid function tests, IGF-1 level, responses to the growth hormone stimulation tests, responses to the IGF-1 generation test, GH treatment doses, adverse effects after GH treatment, gaining height and SDS of height were recorded in certain periods with GH treatment. Dose of rhGH was applied between 0.2-0.25 mg/kg/week in our department.

Findings: The average age of the patients was 9.44 ± 3.34 year (48,5% male and 51,5% female). Pre-treatment SDS of height -3.21 ± 1.03 , midparental height 162.51 ± 8.92 , SDS of midparental height -1.04 ± 0.74 , bone age 7.04 ± 3.26 year, height age 6.78 ± 3 year and BMI 15.55 ± 2.42 kg/m², pretreatment length growth rate 3.37 ± 0.92 cm/year were found. Height gaining was 9.04 ± 2.58 cm/year at the end of the first year, 7.3 ± 1.66 cm/year at the end of the second year, 6.48 ± 1.58 cm/year at the end of the third year, 6.96 ± 0.97 cm/year at the end of the fourth year, 5.34 ± 2.58 cm/year at the end of the fifth year of the medical therapy. SDS of height gaining was 0.54 ± 0.48 after the first year, 0.31 ± 0.31 after the second year, 0.28 ± 0.31 after the third year of the medical therapy. Hypothyroidism was detected in 4 patients and scoliosis was detected in 4 patients during the follow-up of patients receiving GH treatment.

Conclusion: Kowarski syndrome has a very good response with low side effects to GH treatment similar to GH deficiency. Therefore, GH treatment should be started in these cases. This study is unique presentation because of the most numbered patients with kowarski syndrome (n=97) is included. The cases treated with the diagnosis of Kowarski syndrome were investigated with multiple parameters over a wide period and data that would contribute to the literature were obtained.

P2-255

Prevalence of insulin-like growth factor 1 (IGF1) deficiency in prepubertal children with isolated short stature (ISS) and their response to GH therapy

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Background/Aims: Primary IGF1 deficiency (IGFD)' is defined by low levels of IGF1 without a concomitant impairment in GH secretion in the absence of secondary cause.

The Aims of This Study: were to evaluate the prevalence of non-GH deficient IGFD in prepubertal children with isolated short stature (SS) and to describe their response to GH therapy.

Methods: This retrospective study included all children with isolated SS seen in our Pediatric Endocrinology Unit from January 2017 to December 2017. Children were included based on the following criteria: i) SS with current height SDS < -2, ii) age > 2 years, and iii) prepubertal status. Exclusion criteria were: i) identified cause of SS and ii) current or past therapy with GH.

IGF1-deficient children were defined as children without GH deficiency and with IGF1 levels below or equal to -1.5 SDS for age and sex.

Results: Among 38 children with isolated SS, 10 (26%) had low IGF1 levels, consistent with a diagnosis of primary IGFD. All were born appropriate for gestational age. When compared with non-IGFD children, IGFD children were shorter ($p = 0.02$) and their parents were shorter ($p = 0.05$) compared to SS with normal IGF1. Bone age and BMI SDS did not differ between the two groups. 40% of SS children with low IGF1 had low BMI SDS (< -1.7). After 1 year of treatment with GH (0.05 mg/kg/d), HtSDS, BMI SDS and bone age did not differ between SS treated with GH versus the non-treated group.

Conclusion: The prevalence of primary IGFD was 26% in children with isolated SS. Concerning the pathophysiology, our study emphasizes that IGFD in some children may be secondary to undernutrition.

P2-256

Thyroid function (TF) in short children with idiopathic short stature (ISS) treated with growth hormone (GH) versus those not treated; a controlled study

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In ISS is a condition with a height is $>2SD$ below the corresponding mean for age, sex, and population. Thyroid abnormalities reported during GH therapy in GH deficient (GHD) children but not well studied in ISS children on GH therapy.

Aim: To investigate effects of GH therapy on TF in a group of euthyroid children with ISS in comparison with ISS group not receiving GH therapy and GHD group on GH therapy.

Materials and Methods: A retrospective study that included 54 prepubertal children with ISS. ISS was diagnosed when the child had short stature (height < -2 SDS) without genetic factors or other physical problems, but the peak GH response was >7 ng/mL. Twenty-four children with ISS were treated with GH for 1 year and 30 did not receive treatment. Twenty-eight children with GHD were treated with GH for the same period used as controls. Anthropometric measurements and IGF-1, thyroid-stimulating hormone (TSH), and free thyroxine (fT4) were analyzed at baseline and after a year in the treated and non-treated groups.

Results: At presentation, none of the children had $fT4 < 10$ pmol/L or $TSH > 5$ mIU/L. After a year of GH therapy, 2 out of 24 (8.3 %) with ISS had $fT4 < 10$ (9.1, 9.2) without an increase in the $TSH > 5$ and 2/28 (7.1%) of the children with GHD had $fT4 < 10$ (9.2 and 9.1) without an increase in $TSH > 5$. None of the non-treated group ($n = 30$) had $fT4 < 10$ or $TSH > 5$. The mean serum concentrations of fT4 and TSH did not differ significantly after the initiation of GH treatment for 1 year of GH treatment. fT4 and TSH didn't differ between the three groups after 1 year of follow-up.

Conclusions: fT4 levels decreased during the first year of GH therapy in 8.3% of ISS children and 7.1% of children with GHD, while TSH levels appeared to be unaffected by GH therapy. Pre-pubertal children with ISS seem to be more predisposed to thyroid function alterations during GH therapy in comparison with those not receiving GH treatment.

P2-257

Investigating the impact of the TuiTek patient support programme, designed to support caregivers of children prescribed recombinant human growth hormone treatment for growth hormone deficiency in Taiwan: A pilot study

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Background: Poor adherence to recombinant human growth hormone (r-hGH) treatment presents a significant barrier to achieving optimal growth outcomes. It is important to identify and address the treatment adherence-related needs of children prescribed r-hGH, and develop new approaches to improve adherence. In this study, we aimed to measure the impact of the TuiTek patient support programme, a multi-component personalised service intervention, on caregivers' knowledge, beliefs and perceptions of GH deficiency (GHD) and adherence to its treatment.

Patients and Methods: The pilot study of the TuiTek patient support programme was conducted among 31 caregivers of

Table. Thyroid function before (1) and after(2) a year of follow up.

Groups	Age1	HtSDS1	BMI SDS	fT41	TSH1	Age2	fT4 2	TSH 2	HtSDS2
ISS On GH	10.3	-2.22	-0.5	13.4	2.47	11.9	12.8	2.78	-1.81
ISS not On GH	10.2	-2.14	-1	148	2.89	11.0	13.1	2.21	-1.95
GHD on GH	9.77	-2.24	-0.5	13.2	3.18	11.1	12.2	3.08	-1.92

children with GHD and receiving r-hGH treatment via the easy-pod™ auto-injector device in Taiwan. Caregivers within the 'high risk' category for belief/perception factors influencing adherence to r-hGH treatment (disease and treatment coherence, emotional burden, self-administration and treatment-related anxiety) were identified via the TuiTek personalisation questionnaire and followed up with bi-weekly telephone calls by a nurse practitioner over a 3-month period. A Wilcoxon signed-rank test was used to compare changes in questionnaire-based scoring patterns between baseline and follow-up.

Results: Between baseline and follow-up, the percentage of caregivers scoring as 'high risk' for emotional burden reduced by 37%; there was also a positive change in confidence of self-administration by 57% and the percentage of caregivers scoring as 'high risk' for treatment-related anxiety was reduced by 52%. At follow-up, all caregivers classified as 'high risk' within the disease and treatment coherence item at baseline had moved into the 'low risk' category. **Table 1** presents an overview of these findings. Statistically significant changes in questionnaire scores between baseline and follow-up for disease and treatment understanding, emotional burden, self-administration and treatment-related anxiety (all $p < 0.05$) were also observed.

Conclusion: These findings indicate that the TuiTek patient support programme can positively address some of the disease and treatment-related barriers amongst caregivers regarding optimal adherence of their children to r-hGH treatment, which has the potential to positively impact on adherence levels and patient clinical outcomes.

P2-258

Incidence of ALS deficiency in patients with growth hormone deficiency at tertiary pediatric endocrinology center

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Acid-labile subunit (ALS) is a glycoprotein, which is produced in the liver in response to growth hormone (GH). The main role of ALS is to form a complex with insulin-like growth factor I (IGF-I)

and IGF binding protein-3 (IGFBP-3) in order to extend their circulating half-life and thus support the action of GH. Although the mechanism and the consequences of ALS deficiency are well studied, ALS-deficient patients are still of research interest because of the unclear incidence of the condition among the short-statured population and the need of specific therapeutic approach to these patients.

Objectives: The aim of this study is to assess the prevalence of ALS deficiency in a cohort of patients with GH deficiency (GHD) followed up in a tertiary University pediatric endocrinology center.

Design: Study participants are 71 children (76 % boys, age range 2-18 years), diagnosed with GHD by 2 standard GH stimulation tests (max GH < 10 ng/ml). Blood serum samples were collected from each patient during the visits at the center, and then were stored frozen at -80° in 0.5 ml aliquots. The analysis was done on a single occasion with standard ALS ELISA kit. The mean age of the children at the time of collection of samples was 11.6 ± 3.3 years, and all patients were on GH therapy.

Results: ALS deficiency screening identified serum ALS levels with range from 2.2 to 60 mg/L, with a mean of 17.4 ± 8.7 mg/L. The mean ALS levels were significantly lower than the published levels from subjects without short stature - 24.2 ± 4.7 mg/L (Baxter, 1990) and 20.3 ± 3.1 mg/L (Juul et. al., 1998), $p < 0.05$ for both, but close to the levels in the referred for GHD patients (6.5 ± 4.8 mg/L). Very low ALS levels (< 4.0 mg/L) were detected in 3 (4.2%) of the patients. The low ALS levels correspond with low SDS_{height} (-2.82 ± 1.21) and low SD_{IGF-1} (-1.43 ± 1.0) before therapy. In one of the 3 patients, the ALS level (2.2 mg/L) was close to those in patients with IGFALS gene mutations (< 1.0 mg/L). The revision of clinical features in this patient showed features than warrant further molecular genetic analysis.

Conclusion: Our results show the prevalence of ALS deficiency in the current GH treated cohort and support the evidence that investigation of ALS levels could be helpful in the differential diagnosis of growth disorders.

Table 1. Overview of caregivers scoring in the 'high risk' category between baseline and follow-up (n=31).

Priority Topic	Baseline		Follow-up		Percentage Change	Achievement of Positive Change*
	n	%	N	%		
Disease and Treatment Coherence	11	35	0	0	100	✓✓✓
Emotional Burden	27	87	17	55	37	✓
Treatment-Related Anxiety	25	81	12	39	52	✓✓
Self-Administration	28	90	12	39	57	✓✓

*✓✓✓ = 100%; ✓✓ = ~50%; ✓ = <50%.

Presentation of IGF-1/IGFBP-3 molar ratio as an effective monitoring index during treatment of growth hormone deficient patients

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Serum levels of insulin-like growth factor-1 (IGF-1) are used universally for monitoring growth hormone (GH) therapy in patients with GH deficiency (GHD). However, the serum levels of IGF-1 are variable, therefore in the last years the serum levels of IGF binding protein-3 (IGFBP-3) and the molar ratio IGF-1/IGFBP-3 were introduced as more effective and stable parameters evaluating the safety and efficacy of GH treatment. Many studies present reference values of IGF-1, IGFBP-3 and evaluation of their ratio (as SD, as logarithm, as specific formula), but currently there is no unified method to compare these parameters.

Objective: The aim of this study is to compare the serum levels of IGF-1, IGFBP-3 and IGF-1/IGFBP-3 ratio with already presented models in order to propose new reliable and easy to use in the everyday practice tool for supporting the assessment of the GH therapy efficacy and safety in GHD patients.

Design: Serum levels of IGF-1 (ng/ml) and IGFBP-3 (ng/ml) were measured in 72 GHD patients (73.6% boys, age range 1-18 years) treated with GH and followed up at a tertiary University pediatric endocrinology center. Blood samples (n=104) were analyzed at different points of the patients' observation (2019-2020) – before starting of therapy (n=7), during the 1st year of treatment (n=26), during the 2nd year (n=15) and after 2 years of treatment (n=56). IGF-1 to IGFBP-3 was calculated as a simple ratio without any prior adjustments.

Results: Before treatment, levels of IGF-1 (mean 118.8 ± 75.8 ng/ml), IGFBP-3 (mean 4100 ± 1776 ng/ml) and IGF-1/IGFBP-3 ratio (mean 0.027 ± 0.009) correlated highly with the values in SD ($r=0.69$, $p<0.05$) and specific formula for calculating molar ratio ($r=0.72$, $p<0.05$). After initiation of GH therapy increase in IGF-1 and IGFBP-3 concentrations was observed (mean 263.9 ± 86.2 ng/ml and 5850 ± 2130 ng/ml) which correlated positively with results from other studies. The IGF-1/IGFBP-3 ratio for the 1st year also increased to 0.042 ± 0.023 , median 0.036 ± 0.027 . Increase of the IGF-1/IGFBP-3 ratios was observed until the second year of treatment, then they remained stable. The ratio did not correlate with age, sex or pubertal status, just with the GH therapy year since start.

Conclusion: The results of this study revealed that the proposed calculation of IGF-1/IGFBP-3 ratio could be used as easily accessible index during GH treatment. Its relation with other parameters of efficacy and safety as well as its behavior in other GH treated conditions remains to be further elucidated.

Current growth hormone therapy practices in Belgium for the treatment of short children born small for gestational age

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Background and Aim: Recombinant growth hormone (GH) is reimbursed for the treatment of short stature (<-2.5 Z-score) in children born small for gestational age (SGA) without postnatal growth, aged ≥ 4 years with a height Z-score >1 below mid-parental height (MPH). We wanted to determine the current GH prescribing practices by pediatric endocrinologists (PE) for SGA related short stature and document the percentages of treated children at risk for a poor adult height outcome.

Patients & Methods: Clinical and auxological data of 159 short children starting a GH therapy in 2017 and 2018 for SGA related short stature were retrieved from BELGROW, a national database held by the Belgian Society for Pediatric Endocrinology and Diabetology (BESPEED), incorporating PE from 15 hospitals. Growth references of Niklasson, 1991 and Intergrowth (when <28.5 weeks gestational age) and those of Roelants, 2004 for weight and height Z-score calculations, respectively at birth and start GH, were used. Older age, height Z-score at start <-3 and the shortest parental height (SPH) Z-score <-2 were defined as predictive parameters of poor adult height outcome.

Results: Clinical data for analysis were available in 146 (72 males) children. In total, 99 files underwent a peer-review organized by the BESPEED. 100 (68%) patients fulfilled strictly all the reimbursement criteria. Not presenting a height Z-score <-2.5 was the most frequent aberration (19%). Patients whose files were peer-reviewed had a higher reimbursement criteria agreement (83% vs 38%), were shorter at start of GH (median (P10; P90) -3.0 (-4.0 ; -2.4) vs -2.7 (-3.5 ; -1.7)) and had more often a prepubertal status (82% vs 64%). Considering the 100 (53 males) patients respecting strictly all reimbursement criteria, median age at start of GH was 7.9 (4.5;13.3) years, median weight Z-score -3.3 (-4.8 ; -1.7), BMI Z-score -1.3 (-3.1 ; 0.3), height Z-score -3.1 (-4.0 ; -2.6) and -2.0 (-3.3 ; 1.3), when corrected for MPH. Respectively 52 (52%) and 27 (27%) had a height Z-score <-3 and a SPH Z-score <-2 , whereas 28 (28%) started treatment after 11 years. Median GH starting dose was 0.036 (0.029 ; 0.046) mg/kg/day.

Conclusions: Currently, GH is prescribed in patients with SGA related short stature in as many girls as boys, but with a quarter starting during adolescence and more than a half having a severe height deficit. Our findings highlight the utility of a peer review system and the need to raise awareness for earlier referral to PE in order to obtain a better adult height outcome.

P2-261

Increased height and IGF1 serum levels in children with non-neurofibromatosis type 1 gliomas

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Introduction: Gliomas are the most common solid tumours during childhood. In children with neurofibromatosis Type 1 (NF1) and optic pathway glioma (OPG), growth hormone excess has been described. However, this phenomenon has not been reported in children with OPG without NF1. We aimed to describe the growth and IGFs/IGFBP3 levels in a large cohort of paediatric patients with non-NF1- associated central nervous system (CNS) tumours.

Methodology: Study Design: We performed a cross-sectional study in a large cohort of patients younger than 18 years of age with CNS tumours, whose growth was evaluated at the Endocrinology Division of the “Hospital de Niños Dr. Ricardo Gutiérrez”. Clinical features, biochemical patterns, growth charts and brain imaging were analyzed. The study was performed according to the Declaration of Helsinki and was approved by the Institutional Review Board.

Subjects: Inclusion Criteria: We included all patients with CNS tumours studied in our division between 6/2012 and 4/2021, with clinical and biochemical growth evaluation.

Exclusion Criteria: Growth hormone deficiency at tumour diagnosis, craniopharyngiomas and other intrasellar tumours, or previously irradiated patients.

Methods: anthropometric data, medical and family history were collected from medical records. Height, weight, IGF1, IGFBP3 were expressed as standard deviation scores (SDS) according to local references and Tanner status. Delta height to midparental height (Δ HMH: patient's height - midparental height) was calculated for each patient and expressed as SDS.

Results: We studied 92 patients, 49 bearing gliomas and 43 with non gliomas (medulloblastomas, ependymomas, papillomas, germinomas, atypical rabdoid teratoid tumours). We found that Δ HMH and IGF1 levels were significantly higher in patients with gliomas vs non gliomas [Δ HMH 0.75 (0.32-1.18) vs -0.13

(-0.48-0.22), $p:0.002$; SDS IGF1 1.10 (0.77-1.51) vs 0.47 (-0.25-0.88) $p:0.02$ Mann Whitney test]. There were no differences in IGF1 levels when patients with gliomas were analyzed by tumour localization, malignancy, and hypothalamic injury. Weight and IGFBP3 levels were similar in patients with gliomas compared to those with others tumours.

Discussion: Patients with non-NF1 gliomas are taller than expected when compared to those with other CNS tumours, according to midparental height. The higher levels of IGF1 observed in these patients should be highlighted since an important group of gliomas are chronic, non- resectable tumours, with the potential to grow.

P2-262

A Survey on Clinician Perceptions of Long-Acting Growth Hormone Analogs

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Background: Daily recombinant human growth hormone (rhGH) has been utilized since 1985 and has been proven to increase height velocity and improve body composition in growth hormone deficiency, various genetic syndromes and chronic kidney disease. Safety and efficacy are well established. Long-acting growth hormone (LAGH) analogs have been developed to improve compliance and patient experience. There are several LAGH preparations in development or early commercial use. A recent meta-analysis which included seven studies comparing LAGH and daily rhGH, found no significant difference in height velocity and height standard deviation scores or a significant difference in incidence of adverse effects.

Methods: This survey was developed on behalf of the ESPE Bone & Growth Plate working group to evaluate current knowledge, perceptions and reservations of paediatricians regarding LAGH analog use. Clinicians were invited by direct email request, society updates and social media post to complete a questionnaire on current practices and future intentions regarding growth hormone prescription.

Results: The majority of the 30 respondents were paediatric endocrinologists (83%). Replies came from Europe (80%), Latin America (10%), Asia (7%) and Middle East (3%). Current practice regarding initiation of daily rhGH treatment, monitoring of efficacy and adverse effects were based on recognized guidelines.

The majority of respondents (90%) have been provided with information on LAGH analogs, usually from conference symposia. Only one responder is currently prescribing LAGH as part of a clinical trial. Based on current knowledge, one third would prescribe LAGH rather than daily treatment but would welcome further information, 43% are undecided while 23% of respondents would not at this time. Reasons to move from daily to long-acting GH analogs include patient compliance (95%), frequency of dosing (83%), pain or distress of child (70%) and safety data (40%). The majority would use the same clinical indications, efficacy and safety parameters that exist for daily treatment. Reservations are based on current knowledge (46%) and pharmacokinetic profile (53%) compared to physiological GH secretion. Cost of LAGH analogs would impact use in 80% of respondents. The majority would prefer increased monitoring (70%) and expect pharmaceutical companies to provide clear dosing guidelines (87%), updated reference ranges for IGF-1/IGF-BP3 (75%) and provision of a surveillance registry (83%).

Conclusion: Introduction of LAGH analogs will require increased information on dosing, comparable cost and provision of surveillance registries to encourage clinician use over daily rhGH therapy.

P2-263

Pituitary gland volume measured by Magnetic Resonance Imaging as diagnostic predictor of persistent Childhood-onset growth hormone deficiency

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Introduction: Pituitary imaging is important for the evaluation of hypothalamo-pituitary axis defects in patients diagnosed with childhood-onset growth hormone deficiency (CO-GHD). Published evidence shows that there is a close relationship between structural changes in the pituitary gland and growth hormone deficiency.

Aim: To evaluate the relationship between clinical, laboratory and magnetic resonance imaging of the pituitary gland in a cohort of CO-GHD patients during the transition period, and to assess the value of pituitary volume as a diagnostic predictor of persistent GHD.

Methods: Retrospective case review of patients diagnosed with CO-GHD referred to our adolescent unit between 2012 and 2020. Adult GHD (AGHD) was defined as a stimulated GH peak < 3 µg/L. Published normative data on pituitary diameters were used to calculate pituitary volumes.

Patients: The study included data from 102 individuals (75 males) diagnosed with CO-GHD (75 patients with Isolated growth hormone deficiency, IGHD; and 27 with multiple pituitary hormone deficiency, MPPHD), who underwent retesting of GH reserve at 18.04 years of age (IQR:17.1-19.1). Patients who had a history of head injuries or radiation exposure were not included. MRI findings were evaluated in 87 individuals.

Results: AGHD was confirmed in 49 individuals with IGHD (66%) and 23 with MPPHD (85%), $p=0.015$. In our cohort PG volume was negatively correlated with MPPHD ($p=0.006$) and persistence of growth hormone deficiency in adulthood ($p=0.024$). Having an anatomically normal pituitary gland (PG), did not decrease the likelihood of being diagnosed with AGHD (Table 1). Multivariate analysis of logistic regression suggested that pituitary volume, CO-MPPHD and IGF1 (SD) off GH therapy are good predictors of AGHD ([SE 88.5 %, SP 27.3%] $p=0.02$).

Table 1.

MRI findings	Non AGHD	AGHD	P value
Pituitary volume (SD)	0.3 ±1.28	-0.47 ±1.36	0.024
Anatomically normal pituitary gland	56.7 %	73.9%	0.089
Abnormal posterior pituitary gland (APP)	20 %	47.8 %	0.009*
Combined Small anterior pituitary gland and abnormal posterior pituitary gland	13.3 %	55 %	0.005*
Septo Optic Dysplasia	11.53 %	21.3 %	0.28
IGF-1 off treatment (SD)	0.73 ±1.31	-0.67 ±2.11	0.001*

Conclusions: Measurement of pituitary gland volume by MRI combined with IGF-1 concentrations off GH treatment, could help clinicians to rationalise the extent of GH axis re-assessment in patients with IGHD/MPPHD at transition.

P2-264

Growth hormone (GH) treatment of children with idiopathic short children (ISS) with normal insulin-like growth factor-1 (IGF-1) versus those with low IGF-I at diagnosis

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ISS is a condition in which the height is more than 2 SD below the corresponding mean height for age, sex and population, in whom no identifiable disorder is present. Some ISS patients may

have varying degrees of IGF-1 deficiency. Recombinant GH treatment has been used by some authors with variable results. Theoretically, low IGF-1 level at presentation may affect their response to GH therapy. The question is: do children with ISS and low IGF-I respond differently to GH therapy than those with normal IGF1 levels?

Aim: The effect of GH therapy (0.035 mg/kg/day) studied on linear growth and weight gain in children with ISS who have low IGF-I (IGF SDS < -1.5)(n=12) versus those who have normal IGF1 at presentation (n=10) who did not receive GH therapy.

Results: At presentation, the HtSDS of the low IGF1 group was statistically lower compared to the normal IGF1 group. The age, BMI, BMISDS, peak GH response to clonidine provocation, and bone age didn't differ between the two groups (Low vs normal IGF-SDS). After a year of GH treatment IGF1 increased significantly in both groups ($p < 0.05$), however, the IGFSDS was still lower in the low IGF1 group. Both groups had significantly increased HtSDS that decreased the difference between their HtSDS and their mid-parental HtSDS. The increase in the HtSDS and daily weight gain was significantly higher in the low IGF1 group. The IGFSDS, BMISDS, HtSDS and difference between HtSDS and mid-parental HtSDS were significantly higher in the treated group.

Conclusions: GH therapy improved linear growth and weight gain in ISS children. This improvement was better in those who had lower IGF1 at presentation compared to those with normal IGF1 levels.

At presentation

After GH therapy

P2-265

Growth response to growth hormone therapy in growth hormone deficient (GHD) children in relation to the distance between their height SDS (HtSDS) and their mid-parental height

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Introduction: Mid-parental height (MPH) is a useful tool in the prediction of final adult height in normal children as well as those on growth hormone (GH) therapy.

Aim of the study to evaluate the growth response to GH therapy in GHD children in relation to their MPH.

Methods: This retrospective study included 22 short prepubertal children with GHD (peak GH < 10 µg/l). They were followed in the Endocrine clinic between the period 2017-2018. Children were classified based on their HtSDS distance from MPHTSDS. Group 1 had HtSDS - MPHTSDS > -1SDS (N=13). Group 2 had HtSDS - MPHTSDS < -1SDS (N=9). Their HtSDS, BMI SDS, weight gain (WG) Growth velocity (GV), and difference from MPHTSDS were measured after a year of GH therapy (0.03 to 0.5 mg/kg/day) to keep their IGFSDS in the normal range (0 - 2 SD).

Result: Children in group had HtSDS = -1.72±0.63 far from their MPHTSDS. Group 2 had HtSDS = -0.22±0.94 far from their MPHTSDS. No statistical difference was noticed in the HtSDS, BMISDS, IGF1SDS or bone age between the two groups at presentation. Group 2 had significantly shorter parents (MPHTSDS = -1.63 +/- 1.1) compared to parents in group 1 (MPHTSDS = -0.63 +/- 0.84) ($p = 0.04$).

After a year of follow-up while on GH therapy, both groups had increased their HtSDS. Their difference from MPHTSDS in group 1 improved by (0.64±0.97) ($P < 0.03$) and in group 2 improved by (0.40±0.28) ($P = 0.01$). The difference in the gain was not statistically significant among the two groups.

Conclusion: Irrespective of the distance between the HtSDS and MPHTSDS, GH deficient children had significant improvement of their HtSDS. In those with shorter parents (group 2), GH therapy improved their HtSDS to above their MPHTSDS (+0.24) in one year. Further controlled long-term studies are needed to investigate this topic.

	Age 1 yr	HtSDS	BMI	BMI SDS	MPHt (cm)	MPHSDS	HtSDS-MPHSDS	IGF-I	IGF1 SDS	Bone age	GH-P
ISS Normal IGF1	10.6	-2.06	16.7	-0.4	166	-0.94	-1.29	247	-0.04	-1.89	12.2
ISS low IGF1	10.3	-2.53	16.4	-0.7	168	-1.14	-1.54	101.4	-2.00	-1.15	14.4
p	0.4	0.02	0.23	0.3	0.32	0.362	0.235	0.004	< 0.001	0.0	0.09

	Age 2	HtSDS 2	BMI 2	BMI SD2	WG g/d	duration mon	Delta BMI	Delta HtSDS	HTSDS2-MPHSDS	D-IGFS
ISS Normal IGF1	11.2	-1.76	17.8	0.0	9.45	14.36	0.16	0.22	-0.90	1
ISS low IGF1	11.8	-1.96	18.1	-0.2	16.7	13.82	0.13	0.41	-1.05	1
p	0.12	0.02	0.29	0.38	0.03	0.06	0.41	0.04	0.09	0.44

	Age	HtSDS1	MPHTSD	HtSDS1-MPHSDS	HtSDS2	HtSDS2-MPHSDS	Delta HtSDS	Delta HtSDS-MPHSDS
Group 1	10.38	-2.35	-0.63	-1.72	-2.06	-1.29	0.35	0.64
	2.63	0.55	0.84	0.63	0.58	0.65	0.56	0.97
*P					0.03	0.03		
Group 2	8.66	-1.85	-1.63	-0.22	-1.53	0.24	0.31	0.40
	4.67	0.68	1.1	0.94	0.90	1.15	0.25	0.28
*P			0.04	0.00	0.01	0.01		

Group 1; HtSDS-MPHSD >-1

Group 2: HtSDS-MPHSD <-1

*<0.05 in the same group

P2-266

Linear growth and response to GH therapy in children with short stature with normal Growth hormone secretion: Comparison between children with delayed versus no delay in the bone age at diagnosis

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Bone age (BA) continues to be a valuable tool in assessing children's growth potential. Children with normal variant short stature can be subdivided into idiopathic short stature (ISS) (with no delay in BA versus chronological age (CA) and constitutional delay (CDG) (with delayed BA versus CA. The response of these two groups to GH therapy remains controversial.

Aim, Patients, and Methods: We studied linear growth, weight gain, skeletal maturation, and GH-IGF-I axis in prepubertal children with ISS in comparison to prepubertal-children with CDG before and after one year of GH therapy.

Results: At the presentation the HtSDS, BMI, BMISDS didn't differ among the groups. The ISS Group was significantly younger than the CDG. The mid-parental height-SDS (MPHtSDS) of the ISS group was significantly lower compared to the CDG group. The difference between the HtSDS of patients from their mid-parental HtSDS (MPHtSDS) was significantly higher in the CDG versus ISS group. Peak GH response to provocation was higher in the ISS group vs the CDG group. The IGFSDS, Free T4, and TSH levels didn't differ among the two groups.

After a year of GH therapy (0.03 -0.05 mg/kg/day), there was a significant increase in the IGFI and IGFSDS in both groups. HtSDS increased significantly in the two groups ($p < 0.05$). The increment in the HtSDS was higher in the CDG versus the ISS whereas the increment in the BMISD was higher in the ISS group vs the CDG group. The difference between the HtSDS and MPHtSDS did not differ between the two groups.

Conclusion: Growth hormone therapy improved linear growth in ISS and CDG children without fast maturation of their bone age. The improvement in HtSDS was better in the CDG group compared to the ISS group after a year of GH therapy.

		Age	HtSDS 1	BMI SDS1	MPH SDS	HtSDS-MPHSDS1	IGF-1 SDS1	BA	GH-P	HtS DS2	BMI SD2	IGF-1 SDS2	WGD	Delta-BMIS-DS	Delta-HtSDS	HTS DS2-MPH SD
ISS	Mean	9.85	-2.16	-0.79	-1.28	-1.07	-0.74	-0.16	15.30	-1.88	-0.31	0.33	12.56	0.42	0.09	-1.00
N=31	SD	2.80	0.50	1.09	0.53	0.72	1.10	0.35	6.71	0.44	1.07	1.29	8.67	0.57	0.35	1.00
CDG	Mean	11.29	-2.27	-0.73	-0.74	-1.53	1.00	-2.03	12.17	-1.95	-0.82	0.62	10.76	-0.03	0.32	-1.10
N=18	SD	2.40	0.64	0.79	0.47	0.49	1.22	0.46	4.57	0.62	0.99	1.27	4.82	0.42	0.29	0.97
P value		0.03	0.26	0.40	0.03	0.01	0.25	<0.001	0.02	0.36	0.08	0.34	0.22	0.01	0.03	0.42

Linear growth and response to GH therapy in children with GHD with normal IGF-I versus those with normal GH secretion associated with low IGFI at presentation

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Introduction: Children with idiopathic short stature have linear growth impairment despite normal or even high levels of GH. In some of these children IGFI level is low (NGH + Low IGFI (IGF-SDS<-1.5). It was observed that some children with GHD (Peak GH < 7 ng/dl after provocation) have normal IGFI levels (GHD +Normal IGFI). The linear growth of these two groups at presentation and their response to GH therapy was not studied well.

Aim: We studied linear growth at presentation and response to a year of GH therapy in children with low IGFI and normal GH secretion (group 1, N= 10) compared to GHD with normal IGF-I (group 2, N = 17).

Results: At presentation, the age, HtSDS, and BMI did not differ significantly among the 2 groups. The difference between the HtSDS of patients from their mid-parental HtSDS (MPHtSDS) was bigger in the IGFI deficient group vs the GHD group (p=0.04).

After an average of 1 year of GH therapy (0.03 -0.05 mg/kg/day), the HtSDS increased significantly in both groups (P<0.01). No significant difference in weight gain per day between the two groups. BMI in group 1 improved after GH therapy, whereas it did not differ in group 2 (P = 0.002 vs 0.1 respectively). There was a significant increase in the IGFSDS in both groups (p<0.05), and the increments of IGFSDS did not differ among them. The difference in HSD from their MPHSD after treatment improved significantly in group 2(P=0.04) but did not differ in group1 (P=0.4).

Conclusion: Our data suggest a comparable good growth response to GH therapy and increment in IGF-1 in GH deficient with normal IGF-1 and in IGF-1 deficient patients with normal GH secretion.

Growth response to growth hormone therapy in short children in relation to their distance from mid-parental heights (MPHt)

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In normal children, mid parental height (MPH) is a useful tool in assessing children's growth and in the prediction of their final adult height. However, this may not be true for short children, especially those with height SD (HtSDS) > - 1SDS compared to their mid-parental height SDS (MPHtSDS). The difference may indicate underlying pathology.

Aim: To assess growth response (change in HtSDS) to GH therapy in short prepubertal children in relation to their MPHtSDS.

Methods: This retrospective study reviewed 42 prepubertal short children with HtSDS <-2. Children classified based on distance from MPHtSDS in two groups. Group1 included children whose HtSDS were 1SDS or more below their MPHSDS (N=25).

Group 2 whose HtSDS less than 1SDS from MPHSDS (N=17). Their BMISDS, IGF1SDS, bone age and growth velocity (GV), and difference from MPHSDS were measured before and after one year. Sixteen children in Group 1 and 11 children in group 2 were treated with growth hormone therapy (0.03- 0.5 mg/kg/d) subcutaneously to keep their IGF1 SD in the normal range (0 to 2 SD).

Result: Children in group 1 had HtSDS - MPHSDS = -1.72±0.52 while in group 2 the difference was -0.33±0.75. (p <0.01). Children in Group 1 were significantly shorter compared to group 2 (HtSDS (-2.35±0.57) vs. (-1.89±0.61) respectively P=0.02). There was no statistical difference in BMISDS, IGF1SDS, or bone age at presentation. After One year of GH therapy the HtSDS of children in the group an increased to -2.01±0.59, (P=0.005), and their difference from MPHSDS improved by (0.67±0.85) P<0.0000. In group 2 the HtSDS increased to -1.66±0.68, (p< 0.01) and their difference from MPHSDS improved by (0.30±0.32) (P=0.01)

Conclusion: This short prepubertal and peripubertal GH therapy had significantly increased their HTSDS and improved the difference between their height and their genetic background (MPHtSDS). Those who had a higher difference compared to MPHTSDS at the beginning had significantly faster correction towards their genetic potential (significant catch up towards the genetic background).

	Age (yr)	Ht SD-1	BMI -1	MPHSD	HSD1- MPHSD	Ht SD-2	BMI -2	HSD2- MPHSD	Delta HSD	Delta BMI	Delta IGF1SD	Wt gain g/day
Group1 N=10	At presentation				After 1 year							
Mean	11.18	-2.47	17.55	-0.82**	-1.76	-2.09	18.7	-1.44	0.38**	1.16*	1.23**	16.89
SD	2.86	0.46	3.7	0.73	0.37	0.4	4.36	0.38	0.38	0.9	1.38	8.3
Group 2 N=17	At presentation				After 1 year							
Mean	9.64	-2.23	17.2	-1.25*	0.87	-1.87	17.9	-0.29	0.36**	0.29	1.36**	11.53
SD	3.67	0.59	3.79	1.16	1.2	0.7	4	1.22	0.44	0.89	0.8	6.16

P-value ** Within the same group, *between two group

	Age	HtSDS1	BMISDS1	HtSDS1-MPHSDS	HtSDS2	BMISDS2	HtSDS2-MPHSDS	Delta HtSDS	Delta HtSDS-MPHSDS
Group 1	10.55	-2.35*	-0.84	-1.72*	-2.01	-0.57	-1.38*	0.33	0.67
	2.85	0.57	0.94	0.52	0.59	1.11	0.52	0.52	0.85
#P					0.005	0.9	0.000		
Group 2	9.48	-1.89	-0.16	-0.33	-1.66	-0.09	-0.04	0.20	0.30
	3.87	0.61	1.17	0.70	0.68	1.13	0.91	0.30	0.32
#P					0.01	0.2	0.01		

*P<0.05 between the two groups

#<0.05 in the same group

P2-269

Immunogenicity of recombinant growth hormone therapy in the children with short stature and consequences on growth-promoting effect

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Background/Aim: Although there are many well-known components that affect the growth response to recombinant growth hormone (rGH), its effect on total height gain is still not fully predictable. A limited number of studies have been reported revealing up-to-date data on the relationship between immunogenicity and growth-promoting effects of rGH. The study aimed to examine the antibody formation against rGH and its consequences on growth-promoting effect in children with short stature.

Materials and Methods: This was a cross-sectional study including 193 children treated with rGH therapy. The participants were classified into three groups, 111 of whom diagnosed with growth hormone deficiency (GHD), 37 idiopathic short stature (ISS), and 45 short stature due to non-endocrine disorders. The number of the participants based on years of treatment was as follows: 24, 34, 46, 39, 21, 29 children; at onset, first, second, third, 4th, and ≥5th years on treatment. The GH antibody (GH-Ab) and total IgE assays were studied from 193 and 97 participants, respectively. The frequency of GH-Ab, and association of rGH immunogenicity with growth response were evaluated in the three groups.

Results: The number of GH-Ab- and total IgE-positive patients were 103 (53.3%) and 25 (25.7%), respectively. The GH-Ab-positive patients were more common in the ISS group (67.5%) (p=0.013). The number of GH-Ab-positive patients was 15 of 24 (62.5%) patients whose test was studied before treatment. The means of first-year height velocity were found to be lower in the GH-Ab-positive than in the GH-Ab-negative patients in the three groups, (GHD; 8.62±2.97cm/year vs. 10.91±3.63cm/year, ISS; 5.63±0.11cm/year vs. 8.30±1.79cm/year, non-endocrine; 7.75±1.26cm/year vs. 10.12±2.26cm/year; p=0.003, p=0.003, and p=0.001, respectively). Similarly, the means of first-year height velocity were found to be lower in IgE-positive patients (7.01±3.25cm/year vs. 8.93±2.16cm/year; p=0.032). The first-year

height velocity was negatively correlated with GH-Ab and total IgE levels in the non-endocrine group, (r=-0.468, p=0.039; r=-0.448, p=0.042, respectively)

Conclusion: This study showed that GH-Ab formation is common in children with short stature, especially those with ISS before and during rGH treatment, and also GH-Ab positivity is associated with lower first-year height velocity. In addition, this indicates that GH-Abs both could play a role in the aetiology of GH-related short stature, and that immunogenicity against rGH could have an impact on first-year height velocity.

P2-270

Unified training materials to improve adherence to GH-treatment

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Background: Since the 1980s, growth hormone (GH) treatment has been administered to children as daily subcutaneous (SC) injections. GH-treatment is extremely costly, and requires a high level of training and education, otherwise there is a risk of a poor response to treatment by the patient. This can lead to a waste of time and money for the family. The key to good adherence and successful treatment is patient understanding of the growth/metabolic problem and the effect of GH.

Effective personnel education is also crucial. Sweden is a large country, spanning 1572 km from north to south. Patient care is divided between six universities and a few small county hospitals. County hospitals have a limited number of patients, and due to this, they have a limited amount of experience. This means that the quality of patient care and the level of education of staff in relation to GH treatment can vary between hospitals. Despite this, longitudinal data on the impact of -standardized education in GH-treatment is lacking.

Aim: To create and implement a standardized program to be used to both educate and train personnel in the proper management

of GH-treatment, as well as educate patients and their families thereby increasing their understanding and thus leading to greater adherence.

Results: The National paediatrics endocrine nursery group have initiated this project to produce “worksheets” that can be used for standardized education in GH-treatment throughout the country. The result of this is a “worksheet” which includes a flow-chart containing questions on both sides of ‘the loop’, dividing the worksheet into two parts. The first part contains fact-bubbles with questions and talking points related to evidence-based knowledge which patients and family have received education on during their visits to the paediatrics clinic. The second part contains the questions that were asked face-to-face with patients during their visits to the clinic. The backside of the “worksheet” contains facts to support the caregiver in the conversation with the patient/family. It is intended that this “worksheet” should be used continuously during any follow-up meetings at the clinic.

Conclusion: Unified training given by the endocrine nursery team from each paediatric clinic throughout the country could improve the adherence and effectiveness of GH-treatment. Implementing the proposed training materials will mean that every patient will receive the same high quality of care and high level of education regardless of where they live in Sweden.

P2-271

Linear growth of prepubertal children born small for gestational age on growth hormone therapy for 3 years

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Introduction: Recombinant growth hormone (GH) is an effective treatment for short children who are born small for gestational age (SGA). Short children born SGA who fail to demonstrate catch-up growth by 2-4 years of age are candidates for GH treatment initiated to achieve catch-up growth to a normal height in early childhood, maintain a normal height gain throughout childhood, and achieve an adult height within the normal target range. However, some children who were SGA present during late childhood with short stature.

Aim and Methods: We evaluated the growth patterns before and after the 3 years of growth hormone treatment for 22 children who presented during late childhood with short stature and were born SGA. No dysmorphic features were observed in this

group of children. They received 0.035 mg of HGH daily and the dose was adjusted to keep IGFSDS > 0 and <2. Growth hormone (GH) treatment (0.035 mg/kg/day) was initiated at the mean age of 7.9±2.2 years. Their bone age was 6.8 +/- 0.9 years at the start of GH therapy (1.1 +/- 0.8 delayed compared to chronological ages).

Results: Height SDS (HtSDS) increased yearly from -3 SDS after the first year to -1.2 SDS after 3 years of treatment. Their BMI SDS after treatment decreased by 0.9 SD versus before treatment. (table). Increased intracranial pressure was recorded in one child which necessitated discontinuation of GH treatment. None of the children had delayed or precocious puberty during GH therapy.

Conclusions: We present 22 short prepubertal children who were born SGA, with no dysmorphic features. Treatment with GH for 3 years had increased growth velocity, and all had entered the normal growth range on their growth charts. No significant side-effects were observed in the majority (21/22) of these children during therapy.

P2-272

Evaluation of the clinical and laboratory parameters and final adult height in patients treated with recombinant human growth hormone

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The aim of this study was to investigate the clinical and laboratory features of patients who received recombinant human growth hormone (rhGH) treatment and to investigate the factors that determine the response to rhGH treatment.

The clinical features of children treated at least one year with rhGH were retrospectively analyzed. Patients were grouped according to diagnosis; isolated GH deficiency (IGHD), multiple pituitary hormone deficiency (MPHD), Turner syndrome, other syndromes, idiopathic short stature.

In total 268 patients (156 boys, 112 girls) with mean age of 11,3 ±3,07 were included in the study. The mean height standard deviation score (SDS) at diagnosis was -2,73±0,76. Most of the patients (86.1%) were isolated GHD. Abnormal MRI were found in 36 (13.4 %) children.

The mean age of diagnosis of patients with MPHD (8.12±4.21) was lower than that of the isolated GHD (11.5±2.8) (p=0.04). Significantly lower levels of serum insulin-like growth factor-1 SDS were determined in the patients with MPHD than isolated GHD (p=0.01). The GH stimulation test peak response was significantly lower in patients with MPHD than all of the other groups.

Age 1-y	BMI SDS1	HtSDS1	Age 2 (y)	HtSDS2	F Age- y	BMI F SDS	HtSDS F	Delta HTSDS	Delta BMI SDS
7.9	-1.02	- 3	9.2	-2.3	11.5	-1.9	-1.2	1.8	-0.89
2.2	1.75	1.1	2.7	1.06	2.4	1.18	1.18	1.1	1.3

1 = before treatment, 2 = after a year of treatment, 3 = after 3 years of treatment

A negative correlation was found between the growth rate in the first year and peak response to GH stimulation test, IGF-1 and IGF-1 SDS. A positive correlation was between growth rate (cm/year) in the first year and target height, weight SDS, body mass index (BMI) and BMI SDS. A negative correlation was found between the change in height SDS in the first year (first year delta height SDS) and height SDS at the beginning of the treatment, peak GH response to L-Dopa GH stimulation test, IGF-1 SDS. In all group, poor response to treatment was 24.3%.

Mean final adult height (FAH) SDS was -1.31 ± 0.78 and final delta height-SDS (the change in height SDS between the beginning and end of treatment) was 1.16 ± 0.51 . FAH was correlated with height SDS at the beginning of treatment, the growth rate in the first year (cm/year) and first year delta height SDS. A positive correlation was found between final delta height SDS and first year delta height SDS ($r=0.40$, $p<0.001$), growth rate (cm/year) in the first year ($r=0.69$, $p<0.001$), difference between chronological age and bone age ($r=0.26$, $p=0.04$). There was a negative correlation between peak GH test response and final delta height SDS ($r=-0.19$, $p=0.04$). As a conclusion, first year delta height SDS and growth rate were the major predictive factors for FAH.

P2-273

The results of treatment with growth hormone in a patient with growth hormone deficiency and type 1 diabetes

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Introduction: Currently, the incidence of diabetes in children is increasing and may coexist with growth hormone deficiency. In diabetic patients, there are many mechanisms which disrupt the growth process and affect the GH/IGF-1 axis. However, with properly controlled diabetes, patients achieve normal height and should be diagnosed for causes of short stature other than diabetes. There are few reports on the safety and effects of the use of recombinant human growth hormone (rHGH) in patients with growth hormone deficiency (GHD) and type 1 diabetes. The purpose of the presentation is to demonstrate the effects of rHGH treatment in a patient with GHD and type 1 diabetes.

Case Study: The girl was diagnosed with diabetes at the age of 15 months and treated with personal insulin pump with good compensation. From the age of 2, the child's growth curve was below the 3rd percentile. At the age of 7 the girl was diagnosed with GHD. Family history revealed that the child's father had been treated with rHGH for GHD. At the age of 7 and 2 months, the girl started rHGH therapy.

Results: After the introduction of treatment, catch-up growth was observed. At the start of rHGH administration, the girl's height was 113.2 cm (<3rd percentile, -2.13 SDS); after one year of treatment it was 121.1 cm (3-10 percentile, -1.71 SDS). Currently, the height of the 13-year-old and 6-month-old child is 155 cm (10-25 percentile; -1.35 SDS). IGF-1 levels were constantly monitored

and kept close to the lower normal range. After rHGH began to be used, the need for insulin increased. Before rHGH therapy, it was approx. 0.6 U/kg of body weight/day, after the start of rHGH therapy, it increased to approx. 1 U/kg of body weight/day; currently it is 0.9 U/kg of body weight/day. No deterioration of the metabolic control of diabetes has been observed. There were no signs of diabetic retinopathy.

Conclusions: In diabetic patients, it is advisable to also look for reasons of short stature other than metabolic imbalance, because children with well-controlled diabetes are not affected by growth disorders. Based on the literature and our own observations, it seems that treating diabetic children with rHGH is safe and beneficial. There is a need to conduct research on larger groups to assess the safety and effects of rHGH therapy in children with type 1 diabetes.

P2-274

Aetiology and different clinical conditions of GHD in children in a region of North Africa

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Background: Growth hormone deficiency (GHD) is defined as a total or partial deficiency in the secretion of growth hormone (GH) by the somatotrophic cells of the anterior pituitary. The exact prevalence of this condition is unknown in Algeria. In Europe and USA, it is estimated between 1/4000 and 1/10000. This variation is explained by clinical polymorphism, the limits of pharmacological stimulation tests for GH stimulation, problems in interpreting the diagnosis threshold value, the poor reproducibility of the tests, and the absence of clinical criteria for certainty.

Aims of Study: The objective of our study is to determine the clinical features and evolution of childhood GHD in our centre.

Methods: It is a retrospective, descriptive study, spanning the period 2010 to 2020; were eligible for the study all GHD patients, several parameters were evaluated, age, sex, size, diagnostic elements, etiology, dose of treatment. We compared the height gain according to the etiology and the dose, pre-pubertal and pubertal, and the severity of the height delay and we analyzed the results of the reassessment.

Results: We collected 123 patients. The mean age was 7 ± 1 year, with a child in the neonatal period, the sex ratio is 1.1. The average height was -3.03 SDS. The diagnosis of GHD was made at a mean age of 8 ± 0.5 years, diagnosis delay was 3 ± 0.6 years. 47% had pathological MRI. GHD was associated with other pituitary deficits at diagnosis in 10%. The mean dose of GH was 0.030 mg / Kg / d, it was greater in partial GHD 0.035 mg / Kg / d vs 0.025 mg / Kg / d in GHD with malformation or associated with other deficits. The mean height gain was 8.9 ± 2.6 cm in the 1st year (> 1 SDS) for patients with malformative or multiple deficit GHD (8.7 ± 2.2 cm vs 5.2 ± 0.8 cm, $P < 0.01$), and patients with started treatment before the age of 5.

An indication for reassessment was asked in 19 patients (23.4%), IGF1 was > -2 SDS in 58% for isolated GHD, versus 21% in GHD with malformation or associated with other deficits ($P < 0.01$)

Conclusion: GH deficiency is a rare pathology, the diagnosis is made on a set of arguments. Our work joins the data in the literature on the criteria of good response to treatment, which are precocity and association with other deficits.

P2-275

Growth hormone therapy in short stature: The variability of responses to treatment after one year. About 41 cases

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Introduction: Growth hormone (GH) therapy has revolutionized the management of patients with short stature. Its common use was first limited to GH deficient children, but now it has been widened to various other clinical conditions. The aim of our study is to compare the response to GH therapy in patients with GH deficiency (GHD), with those with Turner syndrome and patients small-for-gestational age (SGA).

Materials and Methods: We conducted a retrospective study on patients presenting with short stature admitted in the endocrinology department and treated with GH. The results were collected and processed using the SPSS operating software V21.

Results: The prevalence of patients treated with GH was 20,6%. The mean age of patients at diagnosis was 11,4 ± 5 years, and the sex ratio M/F was 1,4.

Indications for GH therapy were mostly represented by GHD in 65,2% of patients, followed by SGA with failure to catch up to the normal height percentiles in 17,4% of patients, then Turner syndrome in 17,4% of patients. The mean starting GH dose was 0.8 mg/day ± 0,2.

In patients with GHD, the mean height before initiating GH therapy was 114 ± 19 cm, and the mean standard deviation (SD) score for height was -4SD ± 1,5SD. After one year of treatment, the mean height was 127 cm ± 14 cm, with a gain of 14 cm, and the mean standard deviation (SD) score for height was -3,4SD ± 1SD.

In patients with SGA, the mean height before initiating GH therapy was 120 cm ± 18 cm, and the mean standard deviation (SD) score for height was -4SD ± 0,8SD. After one year of treatment, the mean height was 131 cm ± 21 cm, with a gain of 11 cm, and the mean standard deviation (SD) score for height was -3,6SD ± 1SD.

In patients with Turner syndrome, the mean height before initiating GH therapy was 114.6 cm ± 9.8 cm, and the mean standard deviation (SD) score for height was -2.8 SD ± 0.91SD. After one year of treatment, the mean height was 120 cm ± 9 cm, and the mean standard deviation (SD) score for height was -2.6 SD ± 1SD.

Discussion and Conclusion: A variability of responses to GH therapy has been noticed in our patients. GH therapy seems to be more effective in patients with GHD in whom the height's gain after one year of treatment was higher than SGA and Turner syndrome. This variability of response might be linked to genetic and individual components which differ from a diagnosis to another.

P2-276

Growth Hormone Resistance; The Iraqi experience

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Abstract

Introduction: Primary growth hormone resistance or growth hormone insensitivity syndrome (Laron syndrome) is an autosomal recessive disorder caused by deletions or mutations in the growth hormone receptor gene or by post receptor defects. Laron is characterized by a clinical appearance of severe growth hormone deficiency with high levels of growth hormone in contrast to low insulin-like growth factor 1 values and in these cases are refractory to both endogenous and exogenous growth hormone treatment with recombinant human insulin-like growth factor-1 (rhIGF-1).

Case Presentation: We describe two Iraqi cases with Laron syndrome:

The first case: A 10-year old female child who presented with postnatal growth failure and hypoglycemic seizures.

The second case: A 5-year old male child who is the son of the cousin of the first case. Presented with postnatal growth failure. Consanguinity, positive for both families as for the patients.

Evaluation of Both Cases: Revealed severe short stature, the classic features of growth hormone deficiency (midfacial hypoplasia, frontal prominence, saddle nose, flat nasal bridge, high pitched voice, dental caries, poor dentition).

Measurements: For the first case; weight 11 kg, height 79 cm both were far below the 3rd centile (-10.6 SDS). Bone age 4 years according to RUS atlas. For the second case, his weight 10 kg, height 72 cm (-7.6 SDS) bone age 4 years.

Investigations: Disclosed high plasma GH levels and low IGF-1 in both cases the rest of investigations were normal.

Conclusion: From the clinical findings in the context of typical phenotype of growth hormone deficiency along with elevated GH level and low IGF-1 confirmed the diagnosis of growth hormone insensitivity syndrome (Laron syndrome). Genetic testing could not be done because of unavailability in our country also specific therapy in the form of recombinant IGF-1 not available.

Growth and Syndromes (to Include Turner Syndrome)

P2-277

Response to growth hormone therapy with high IGF-1-levels and severe insulin resistance in two-cases with SOFT syndrome: A novel homozygous mutation in POC1A

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Introduction: SOFT-syndrome (#MIM 614783) is a rare condition characterized by short stature, onychodysplasia, facial dysmorphism and hypotrichosis caused by *POC1A* gene mutations. Moreover, severe insulin resistance (IR) and metabolic disorders may also accompany. Hereby, we report two-patients with SOFT-syndrome, who had severe short stature and IR, with a novel *POC1A* mutation.

Case Report: Patient 1 (P1), a 16-month old girl and Patient 2 (P2), a 32-month old boy were referred with growth retardation. P1 was born at full-term to consanguineous parents, and P2 was born at 35th gestational week (GW) to unrelated parents. Both of them were born SGA. Their anthropometric measurements and physical examination findings at referral are shown in the Table. Laboratory tests for chronic and metabolic diseases were normal in both patients. In P1, central hypothyroidism was detected, sella MRI was normal; there was no adrenal insufficiency and LT4 (12.5 µg/day) was started. P2 had subclinical central hypothyroidism and no treatment was needed. At follow-up, growth velocities (GV) were low in both patients. Growth hormone (GH) stimulation tests were performed and responses were insufficient. GH treatment was started in P1 and P2 with doses of 42 and 27.5 µg/kg/day, respectively. Both patients required dose adjustments for high IGF-1-levels (mean IGF-1-SDS: 5.7&5.6, respectively). On GH treatment, insulin-levels were also high. OGTT was performed. While P1 had impaired glucose tolerance (2nd-hour-glucose: 163 mg/dL) and severe IR (total-insulin: 2600µU/mL), P2 had only severe IR (total-insulin>2700µU/mL). Additionally, hyperlipidemia was remarkable in P1. While P1 received both of metformin and atorvastatin, P2 received only metformin. As puberty progresses, GV decreased and GH treatment was discontinued at the 4th-year in P1. In P2, the change in height SDS was better than P1, therefore it has been continued in P2. Last clinical findings of patients are detailed in the Table. WES analysis revealed a novel homozygous mutation (p.Leu244Pro) in the *POC1A* gene in both patients.

Conclusion: A novel mutation in the *POC1A* gene was detected by WES analysis, which explained primordial dwarfism, dysmorphic findings and severe IR in both patients. Unlike the literature,

we observed a partial improvement on height SDS in our patients (even in P1, until puberty) were with GH therapy. High IGF-1 levels on GH treatment were also associated with IR. It was also speculated; hyperinsulinemia may also have contributed to the increase in height SDS during the prepubertal period.

P2-278

Effects of growth hormone therapy on serum concentrations of IGF-1 in patients with Turner syndrome: High IGF-1 concentrations despite optimal dose?

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Introduction: Growth hormone (GH) treatment is used to accelerate growth in patients with Turner syndrome (TS). During treatment, evaluation of IGF-1 is strongly recommended for efficacy and safety. Some patients, despite optimum GH doses, have persistent high IGF-1 levels. In this study, we aimed to evaluate the relationship between IGF-1 levels, IGF1R and growth responses of TS patients on GH treatment.

Method: 54 patients with TS (19 classic, 35 mosaic) using GH (45µg/kg/day) were evaluated retrospectively. At the onset, SDS of birth weight (BW), anthropometric measurements, target height, and bone age (BA); and at the first and fourth years of GH-treatment, SDS of anthropometric measurements and IGF-1; and growth velocity (GV) and BA of the patients were noted. According to IGF-1 levels, the patients were divided into 5 groups: patients with IGF-1-SDS in normal ranges on GH treatment constituted Group1; patients whose IGF-1 SDS were increased on treatment and returned to normal with 10-20% dose reduction formed Group2; patients whose IGF-1SDS remained high despite 10-20% dose reduction formed Group3; patients whose IGF-1 SDS returned to normal without any dose change formed Group4; and patients whose IGF-1 SDS remained high without any dose change formed Group5. Comparisons were made between groups covering patients on treatment with normal IGF-1 levels (Group1), and with increased IGF-1 levels (Groups 2,3,4 and 5). *IGF-1R* gene analysis was performed in cases where IGF-1 levels were increased at least once.

Results: The age of treatment onset was slightly higher in Group1 compared to others (p=0.046). No statistical significance was observed in comparison of BW, height-SDS, BA and IGF-1SDS at the onset of treatment between Group1 and Groups 2,3,4,5. While the weight and BMI-SDS were significantly higher in Groups 2-3-4-5 (p=0.03; p=0.04), GV was better in Group 1 (p=0.025). At 1st-year of treatment, weight-SDS (p=0.001), BMI-SDS (p=0.002); and at 4th year of treatment, weight-SDS (p=0.002), and BMI-SDS (p=0.002) were higher in Groups 2-3-4-5. GV in 1st-year (p=0.037)

and 4th-year (p=0.038) were better in Groups 2-3-4-5. No pathogenic variants in *IGF-1R* gene were detected in any of the patients.

Conclusion: The weight and BMI-SDS of patients whose IGF-1 levels were increased at least once were higher than of those patients with normal IGF-1 levels on GH-treatment. Moreover, GV was higher in patients with high IGF-1 SDS than in patients with normal IGF-1 SDS, albeit GH dose decrease in this group. High IGF-1 levels in these patients could not be explained by *IGF-1R* gene mutation.

P2-279

The Effect of Hospital Admission and Nutritional Rehabilitation (NR) on Growth and Metabolic abnormalities in adolescent females with severe Anorexia Nervosa (AN)

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There is a lack of clear evidence-based guidelines for hospital admission of adolescents with anorexia nervosa (AN), resulting in a high degree of variation in practices. Acceptable indications for admission include the following: weight is less than 75% of ideal body weight, temperature < 35.5°C, heart rate < 50 beats/min, systolic BP < 80 mm Hg, and orthostatic change in pulse or in BP.

The Aim of This Study: To evaluate the anthropometric and metabolic changes in adolescent girls with severe AN who required admission (based on the previous criteria) and underwent nutritional rehabilitation.

Patients and Methods: 38 adolescent females with severe AN had been hospitalized with two or more of the previous criteria. Daily supervised nutrition to build up gradually caloric and protein intake and monitoring for weight and metabolic changes were performed by an expert dietitian and adolescent physician.

Results: 20/38 girls had secondary amenorrhea. They were hospitalized for an average of 35 +/- 20 days. During hospitalization, a gradual increase of caloric intake to 2457 +/- 543 was achieved. The weight gain, weight in kg, and BMI increased significantly during nutritional rehabilitation (NR). The circulating levels of FT4 and LH increased significantly. The concentration of prolactin decreased significantly with NR. (table) After 6 months of follow-up, their weight parameters were maintained (Wt. = 51 +/- 9 kg), BMI (19.9 +/- 2.6), and BMISD (-0.15 +/- 1).

Conclusions: NR in hospital for an average of 5 weeks, using high caloric density formula and food by an expert dietitian, resulted in a significant weight gain and improvement of BMI and significant correction of hormonal abnormalities. Improvement was maintained for 6 months after discharge.

	On admission	On Discharge
Age (yr)	14.9 +/- 1.7	15.1 +/- 1.7
2ry Amenorrhea	57%	28%*
Weight (Kg)	41.6 +/- 7.3	46.4 +/- 7.6*
Height (cm)	159 +/- 7	161 +/- 6.5*
BMI	16.3 +/- 2.2	19.9 +/- 2.6*
BMISDS	-1.7 +/- 1	-0.5 +/- 1*
Caloric intake Kcal/day	753 +/- 347	2457 +/- 543*
Vitamin D (low %)	(21 +/- 17) (41%)	(32.5 +/- 11) (0%)*
Free T4 pmol/L (low %)	11 +/- 4.5 (35%)	12.8 +/- 3.9* (20%)
TSH (ng/dL)	2.3 +/- 1.8	1.5 +/- 1
Prolactin (mcg/L)	397 +/- 200	185 +/- 137*
LH (mIU/mL)	2.1 +/- 2.4	3.2 +/- 2.2*
FSH (mIU/mL)	5.1 +/- 3.4	5.1 +/- 0.7
ALT (U/L)	15.0 +/- 9	17.6 +/- 8.1
Creatinine (µmol/L)	61 +/- 10.6	58.4 +/- 11.5
Hb g/dl	12.2 +/- 1.1	12.4 +/- 1.5

* p < 0.05 after vs before NR

P2-280

Outcomes in growth hormone-treated Noonan syndrome children: impact of PTPN11 mutation status

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Objectives: Mutations in *PTPN11* are known to be associated with Noonan syndrome (NS), accounting for approximately 50% of cases. Data from a non-interventional and phase 3 study of Norditropin (somatropin; Novo Nordisk A/S, Denmark) were used to assess the impact of *PTPN11* mutation status on growth outcomes in children with NS receiving growth hormone therapy (GHT).

Methods: The ANSWER (NCT01009905) programme is a non-interventional, multicentre, observational study conducted in the United States; GH LIQUID-4020 (NCT01927861) is a 4-year, randomised, double-blind, multicentre trial in Japanese patients. In this analysis, data from patients in these studies with clinically diagnosed NS were pooled to assess the impact of *PTPN11* mutation status on growth outcomes over 4 years of GHT. Data are presented for the subgroup of patients who were GHT-naïve and prepubertal at baseline.

Results: A total of 69 patients with known *PTPN11* mutation status were included in the analysis: 49 tested positive for a mutation (*PTPN11*-positive) and 20 were *PTPN11*-negative; 47 were male and 22 were female. Gene mutations identified in *PTPN11*-negative patients included *BRAF* (n=1), *KRAS* (n=1), *RAF1* (n=3),

Table 1. Change from baseline in height SDS

		PTPN11-positive				PTPN11-negative		
		Year	N	Mean	SD	N	Mean	SD
Height SDS (general population)	Change from baseline	1	41	0.742	0.364	19	0.755	0.407
		2	38	1.086	0.531	19	1.201	0.562
		3	32	1.272	0.685	19	1.399	0.624
		4	30	1.258	0.839	19	1.488	0.743
Height SDS (Noonan population)	Change from baseline	1	40	0.719	0.352	19	0.711	0.363
		2	38	1.058	0.565	19	1.161	0.492
		3	32	1.292	0.695	19	1.412	0.550
		4	30	1.370	0.759	19	1.522	0.651

RIT1 (n=1), *SHOC2* (n=1) and *SOS1* (n=2). Cardiovascular comorbidities were present in 55% of patients at baseline, including atrial septal defect (n=16; 23.2% of patients), pulmonary valve stenosis (n=9; 13.0%), pulmonary artery stenosis (n=7; 10.1%) and hypertrophic cardiomyopathy (n=7; 10.1%). Baseline characteristics were generally similar between *PTPN11*-positive and negative patients. Mean (standard deviation [SD]) age at GHT start was 6.4 (3.3) years in *PTPN11*-positive and 6.4 (2.5) years in *PTPN11*-negative patients. Mean (SD) GHT dose at baseline was 0.047 (0.015) mg/kg/day in *PTPN11*-positive patients and 0.054 (0.016) mg/kg/day in *PTPN11*-negative patients. Change from baseline in height SD score (SDS) is shown in **Table 1**; no significant differences between *PTPN11*-positive and *PTPN11*-negative patients were observed.

Conclusions: GHT over 4 years resulted in improved growth outcomes in GHT-naïve, prepubertal NS patients, irrespective of *PTPN11* mutation status.

P2-281

Endocrinological assessment in patients with fanconi anemia

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Introduction: Fanconi anemia (FA) is a rare genetic disease that presents with aplastic anemia. Around 60% have short stature (SST), with a mean height of -2.2 SD. However, studies assessing the etiology of SST not having reached relevant conclusions.

Aim: Our aim was to evaluate the clinical features and endocrine status in relationship to SST in patients with FA.

Methods and Patients: A cross-sectional study was carried-out between 2019-2020 in 31 pediatric patients (19 females) with FA. Auxological assessment, biochemical analysis, study of the hypothalamic-pituitary axis and an MRI of the hypothalamic-pituitary area were performed.

Results: At birth, the mean weight was -1.62 SD (IQR: -2.1; -1.2), being lower than -2 SD in 34.6% (9/26) of the patients. The mean length was -1.67 SD (IQR: -2.36; -0.88), being lower than -2 SD in 41.6% (10/26).

The mean age at first evaluation was 9.7 ± 4.2 years [Tanner I (n=21), Tanner II (n=1), Tanner III (n=1), Tanner IV (n=2), Tanner V (n=6)]. Mean height was -2.07 SD (IQR: -2.96, -1.09) and was below -2 SD in 54.8% (17/31), with 86% (19/22) being shorter than their target height (TH). The mean BMI was -0.74 SD (± 0.83). Six female patients reached final height and were -2.3 SD (± 0.82) from their TH. Hematopoietic cell transplant (HCT) was performed in 16 patients. The attributable fraction of exposure to HCT in patients with SST was 42% [CI95% (71-85)], p>0.05. No correlation was found between height and anthropometry at birth. Only 5 patients had endocrinological alterations: 2 had adrenal insufficiency secondary to corticosteroid treatment, 2 had hypergonadotropic hypogonadism after transplantation, and 1 had GH deficiency. Serum levels of IGF-1 and IGFBP-3 were within the normal range in all patients, with the exception of GH-deficient patient. The GH/IGF axis was assessed in 23 patients, observing a decrease in stanniocalcin 1 (STC1) [311.3 IQR(1166.7-554.9)] and STC2 [23.2 IQR(18.5-26.9)] and an increase in free IGF-1 levels [6.4 ng/mL IQR(2.95-10.3)] in pubertal patients compared to healthy controls. Pituitary morphology was assessed in 9 patients. The volume of the pituitary gland was normal [0.45SD (IQR: -0.21; 0.75)], except in the patient with GH deficiency, who had a volume of -2.98SD with ectopic neurohypophysis.

Conclusions: Short stature is an integral feature of FA but does not seem to be related to a GH deficiency. However, an alteration in the peripheral regulation of the GH/IGF axis cannot be excluded.

Brain-derived neurotrophic factor and matrix metalloproteinases as markers of metabolic status in girls with Turner syndrome

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Background: Turner syndrome (TS) predisposes to obesity and related metabolic disorders and presents a high risk of congenital heart defects. Growth hormone (GH) treatment used in TS girls also affects the parameters of carbohydrate-lipid metabolism. Thus, the search for new markers that could be early predictors of metabolic disorders seems to be justified.

Objective and Method: The assessment and comparison of MMP-1, MMP-2, MMP-9 (matrix metalloproteinase-1, -2, -9), BDNF (brain-derived neurotrophic factor), GDNF (glial cell line derived neurotrophic factor) and VEGF (vascular endothelial growth factor) and basic clinical makers (total cholesterol, HDL cholesterol, triglycerides, glucose, aminotransferases-ALT, IGF1, TSH and fT4) in 12 untreated (before GH therapy) TS girls vs. 17 healthy short stature girls (control group). Consecutively evaluation of shifts in markers concentrations in 9 TS girls after at least 3-month GH treatment period.

Results: We found no differences in mean age, weight, BMI Z-Score and hSDS between study and control group. Groups differed in mean baseline values of ALT (18.2 ± 4.2 vs. 14.2 ± 4.1 , $p=0.02$), as well as BDNF [29951.5 ($26176.9 - 41271.9$) vs. 23131.7 ($18392.4 - 28313.3$), $p=0.01$] and MMP-2 [91.8 ($71.7 - 111.0$) vs. 143.6 ($123.7 - 244.5$), $p<0.001$]. The regression analysis in all subjects revealed a positive correlation between MMP-2 and HDL concentration ($\beta = 0.502$, $t(17) = 2.393$, $p=0.029$), while BDNF significantly predicted BMI Z-score ($\beta = 0.582$, $t(17) = 2.948$, $p=0.009$). A significantly higher concentration of MMP-2 was found in patients undergoing GH treatment than before the onset of therapy (132.1 ± 42.3 vs. 105.0 ± 45.5 , $p=0.045$). There were no statistically significant differences between the untreated vs. GH-treated groups in the concentrations of remaining markers.

Conclusion: The higher concentrations of BDNF and lower of MMP-2 in TS girls without metabolic syndrome may reflect the formation of metabolic status. Shifts in MMP-2 concentration during GH therapy may be considered as connected with metabolic alterations.

Assessment of genetic defects, baseline characteristics and adverse events reported in the Increlex® registry

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Background: Certain genetic defects in the growth hormone (GH)/insulin-like growth factor1 (IGF-1) axis are associated with severe primary IGF-1 deficiency (SPIGFD) and short stature. Detection of genetic defects may confirm short stature aetiology alongside clinical/biochemical features. Increlex® is a recombinant human IGF-1 (rhIGF-1) approved for children/adolescents with SPIGFD.

Methods: The Increlex® registry is an ongoing, multicentre, open-label, observational study monitoring safety and effectiveness of rhIGF-1 in children/adolescents with growth deficiencies (NCT00903110). Eligible individuals: aged 2-18 years, receiving rhIGF-1. This complementary analysis describes reported genetic testing in patients enrolled in 10 European countries from Dec2008-May2019. Details of genetic testing methodology and/or functional analyses are not reported in the registry.

Results: At the time of analysis, 281 patients (missing=3) were enrolled at 118 sites. At least one genetic test was reported in 57.9% (161/278) patients; ≥ 1 abnormality was detected in 34.8% (56/161), of whom 96.4% (54/56) had ≥ 1 gene abnormality classically associated with SPIGFD (*GHR*[$n=42/54$, all with Laron syndrome diagnoses]; *GH*[$n=7/54$]; *IGF1*[$n=4/54$]; *STAT5B*[$n=2/54$]; *IGFALS*[$n=1/54$]). Genetic testing of 2/54 patients showed ≥ 2 abnormalities including mutation/deletion in *GH* and *IGF-1* genes and mutation/deletion in *GHR*, *GH* and *SHOX* genes. 2/56 patients had a mutation/deletion in *PTPN11* only. Patients with ≥ 1 reported genetic abnormality had shorter mean height standard deviation score at rhIGF-1 commencement ($n=48$; mean:4.68; 95%CI:5.18, 4.17) versus patients without abnormalities ($n=98$; mean:3.78; 95%CI:4.01, -3.55; t-test: $p=0.002$) and patients not reported to have had genetic testing ($n=102$; mean:-3.37; 95%CI:3.58, 3.16; t-test: $p<0.001$). No other differences in baseline characteristics were found; proportions of patients with SPIGFD at Baseline were 91.1% (51/56) in those with reported genetic abnormalities, 81.9% (86/105) in those without and 89.7% (105/117) in those not reported to have had genetic testing. Some patients (49.1% [27/55]) with reported genetic abnormalities were naïve to rhIGF-1 treatment and prepubertal at rhIGF-1 commencement. Incidences of targeted treatment-emergent adverse events (TEAEs) in patients with reported genetic abnormalities, without reported abnormalities and not reported to have had genetic testing were 66.1% (37/56), 49.5% (51/103) and 43.5% (50/115) (Chi-square test: genetic abnormality versus none, $p=0.045$; genetic abnormality versus no testing, $p=0.006$). The most common TEAE was hypoglycaemia.

Conclusions: Genetic testing was reported for >50% patients. Patients with versus without reported genetic abnormalities had shorter stature at first rhIGF-1 dose and more TEAEs. Further work is required to understand the role of genetic testing in clinical practice.

P2-284

Associations between height and health-related quality of life (HRQoL) and functional independence in children with achondroplasia

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Background and Objectives: Achondroplasia (ACH) is characterized by severe short stature with a height deficit of approximately 6 SDS below that of average stature. Our objective was to evaluate the impact of height deficit on health-related quality of life (HRQoL) and functional independence in children with ACH.

Methods: Height Z-score, HRQoL, and functional independence data were obtained from children with ACH who enrolled in the vosoritide Phase 3 trial (study 111-301; EudraCT number, 2015-003836-11). Subjects completed at least six months of a baseline observational growth study (study 111-901; ClinicalTrials.gov number, NCT01603095) prior to enrolling in the Phase 3 trial and the subsequent open label extension study (study 111-302; ClinicalTrials.gov number, NCT03424018). Height Z-scores were assessed every 3 months. The Pediatric Quality of Life Inventory (PedsQL), the Quality of Life in Short Stature Youth (QoLISSY), and the Functional Independence Measures in Children (WeeFIM) questionnaires were completed every 6 months. All visit matched pairs of height Z-score and HR-QOL data pooled from studies 901, 301 and 302 were analyzed using a mixed effect model to assess the relationship of a 1 SDS decrease in height deficit on domain scores of the PedsQL, QoLISSY, and WeeFIM, without reference to treatment assignment or timepoint.

Results: 121 children (64 boys, 57 girls; mean age 8.71 ± 2.47 years, age range 5.1 – 14.9 years), were included in this exploratory analysis. For all instruments, mean scores were generally lower in subjects with greater height deficit (≤ -6 SDS) compared to taller subjects with height Z-score greater than -4 SDS. Clear linear relationships between height Z-scores and several domain scores were observed, most notably in the PedsQL Physical domain (caregiver and self-reported, with slope estimates (mean, [95% CI]) of 4.36 [1.87, 6.85] and 2.10 [-0.25, 4.45], respectively), the height-specific QoLISSY Physical domain (caregiver and self-reported, slope

estimates of 4.83 [2.34, 7.31] and 3.83 [1.10, 6.56], respectively), and the WeeFIM Self-care and Mobility domains (slope estimates of 0.71 [0.27, 1.15] and 1.36 [0.32, 2.40], respectively).

Conclusions: Height deficit in ACH impacts HRQoL and function. These data suggest that therapies that have the potential to reduce height deficit in ACH may also improve HRQoL and functional independence.

P2-285

COVID 19 impact on Pediatric Endocrinology care – a short story from Romania

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Background: Worldwide, the COVID 19 pandemic has influenced pediatric endocrine care, with quick implementation of telemedicine services, but at the same time suboptimal chronic disease management and delayed presentation/diagnosis. In Romania strict measures imposed between March and May 2020 led to ensuring only outpatient care in this period with telemedicine services reimbursed, but with no specific infrastructure developed for it.

Aim: The current secondary data analysis is an audit of the pediatric endocrine care provided in a tertiary center (Targu-Mures) from Romania in 2020 compared to 2019.

Materials and Methods: An electronic database secondary analysis was performed including outpatient and inpatient consultations for the two years. Main diagnosis, gender and age were recorded. Ethics approval was obtained from the Hospital Ethics Committee.

Results: There was a reduction of 26.67% in the number of outpatient consultations in 2020 compared to 2019 with most common diagnosis short stature (41.60%), small for gestational age (13.31%), precocious puberty (9.66%) and Turner syndrome (5.74%), all of them receiving specific treatment required to be prescribed by a specialist. For inpatient care, the number of admissions decreased by 53.76% from 796 in 2019 to 428 in 2020, but representing the same percentage of total admissions in the clinic (18%) and with an increase of 10% in the number of day-care admissions (81.78% in 2019 and 92.05% in 2020). Most common diagnosis were growth impairment (29.17%), thyroid disorders (14.95%), obesity/overweight (11.11%) and puberty disorders (8.82%). In 2020 there were 117 new diagnosed patients and 83 (17.81%) lost to follow-up. Gender distribution favored girls (1.3:1 ratio) and mean age at diagnosis was 11 years

Conclusions: The addressability decreased both in the outpatient and inpatient care, but following the same pattern as for adult care, with hospital admissions reduced twice as much as outpatient consultations. Short stature and thyroid disorders are the main reasons for referral and day-care admissions represent the majority of inpatient consultations, with outpatient referrals mainly for treatment prescription.

Keywords: COVID 19, Pediatric Endocrinology, inpatient, outpatient

Single nucleotide variations associated with short stature in Baka Pygmies as identified by Whole Exome Sequence (WES)

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Introduction: Human growth is a multifactorial process involving genetic, hormonal, nutritional and environmental factors. Genome-wide association studies (GWAS) have shown that >400 genes are associated with adult height. African Baka Pygmies represent an isolated and well-confined small population with short stature of unknown etiology. In previous studies we reported an 8-fold reduced GH receptor gene expression and reduced serum levels of IGF-I and GHBP compared with sympatric adult Bantu individuals, while GH concentrations were normal. However, no association was found with sequence variants of the GHR gene. So far, in none of the pygmy populations the genetic cause of short stature has been discovered.

Materials and Methods: In an effort to discover the genetic cause of the pygmy phenotype, we enrolled 84 Baka Pygmies and 20 sympatric normally-statured Bantu neighbors living in South-east Cameroon. Mean height SDS was -3.96 in male pygmies compared to -1.24 SDS in sympatric Bantu males, and -2.09 in female pygmies and -1.02 in Bantu females ($p < 0.05$). All subjects signed informed consent to participate in this study which was approved by the Research Ethic Committee of the University of Pavia. On DNAs from phenotypically selected 8 representative Baka Pygmies and 5 Bantu individuals, whole exome sequencing (WES) was performed to detect variants in genes and their regulatory regions associated with the pygmies' reduced stature. Bioinformatic analysis and functional classification of the variants were carried out and results were validated in 76 Baka and 15 Bantu individuals.

Results: WES data analysis revealed 29 single nucleotide polymorphisms (SNPs) significantly associated with reduced height in the Baka population. Remarkably, Baka Pygmies exhibited a significant increase in novel identified SNPs compared to Bantu subjects (i.e. 515.25 ± 63.7 vs 330.4 ± 39.5 , $p = 0.014$ ANOVA One-Way). Around 1% of the identified variants in Baka Pygmies were predicted as high-impact (i.e. producing truncation, or loss of protein function). The selected variants were then validated in the larger cohort. A promising variant was rs7629425, a C/T SNP located in the 5'-UTR of the HYAL2 gene, 9 nucleotides upstream of the exon 2 coding sequence. The frequency of the alternative allele was significantly increased compared to African and non-African populations ($p = 0.032$, Chi-Square). An *in vitro* luciferase assay in HeLa cells showed significant differences in transcription modulation of the reporter gene for the rs7629425, C/T alleles ($P = 0.024$).

Conclusion: Our results suggest that the HYAL2 gene variant may play a role in the etiology of short stature in Baka pygmies.

Novel LZTR1 mutations in subjects with features of Noonan Syndrome and GH insensitivity negatively regulate GH-induced IGF-I production and hyperactivate GH-induced ERK1/2 activation in response to GH *in vitro*

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Background: Noonan Syndrome (NS) can overlap clinically and biochemically with growth hormone insensitivity [GHI; short stature (SS), low IGF-I and normal/elevated GH levels]. Mutations in multiple genes regulating RAS/MAPK pathway have been identified in NS including LZTR1 variants. Function of LZTR1 is poorly understood and its role in growth retardation is unknown.

Objectives: To functionally characterise 6 novel LZTR1 variants (5 previously published¹ and 1 identified in our GHI patient cohort) and determine their impact on the GH-IGF-I axis.

Methods: A novel heterozygous missense LZTR1 variant (c.466A>G; p.K156E) was identified in a GHI subject (V1) by our SS whole genome panel. 5 previously published NS-associated heterozygous inactivating missense LZTR1 variants [c.742G>A; p.G248R, c.850C>T; p.R284C, c.740G>A; p.S247N, c.356A>G; p.Y119C and c.859C>T; p.H287Y (V2-6, respectively)] were also studied. V1-6 LZTR1 vectors were generated by site-directed mutagenesis and verified by Sanger sequencing. Western blot (WB) analysis of transfected HEK293 cell lysates was performed using anti-c-Myc & anti-ERK/anti-pERK antibodies (anti-beta-actin/GAPDH antibodies as controls). Supernatant from transfected & GH-stimulated (24 hours) HepG2 cells were assessed by ELISA. Cell lysates from transfected (with V1, 2 & 5) & GH-stimulated (20 minutes) HepG2 cells were subjected to WB analysis (anti-ERK/anti-pERK antibodies & anti-STAT5/anti-pSTAT5 antibodies).

Results: All 6 subjects had characteristic facial features of NS and cardiac defects. 2 subjects (V1 & 2) had features of SS & GHI (height/IGF-I SDS of -2.3/-2.3 and -2.1/-2.2 respectively). All variants showed significantly reduced LZTR1 protein expression and increase in p-ERK/total ERK ratios compared to WT, latter suggesting up-regulation of RAS-MAPK pathway. Compared to WT (0.54 ± 0.12), GH-induced mean IGF-I levels were significantly lower in V1 & 2 (0.28 ± 0.03 & 0.29 ± 0.07 , respectively; both $p < 0.05$), but not in V3-6. IGF-I rise following GH stimulation in all 6 subjects correlated negatively with the subject's height SDS ($p < 0.001$). Following GH stimulation, as compared to WT,

a significant increase in p-ERK/total ERK ratios but no difference in p-STAT5/total STAT5 ratios were observed in V1 & 2. This suggests GH-induced ERK1/2 hyperactivation and upregulation of RAS-MAPK pathway in variants causing SS.

Conclusion: Novel *LZTR1* variants in NS cause reduced *LZTR1* protein expression and enhanced RAS-MAPK signalling, similar to that observed in *PTPN11* and *SOS1* mutations. GHI-causing *LZTR1* mutants negatively regulate GH-induced IGF-I production and hyperactivate ERK1/2 activation in response to GH *in vitro*. This suggests that dysregulation of GH-induced RAS-MAPK pathway could contribute to growth retardation.

Reference

- ¹ Yamamoto GL, Aguen M, et al. Rare variants in *SOS2* and *LZTR1* are associated with Noonan syndrome. *J. Med. Genet.* 2015;52: 413–421.

P2-288

Comorbidities in Turner Syndrome patients controlled in our center since the 80's

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Introduction: Turner syndrome (TS) is a genetic condition with different phenotypic expressions depending on karyotype. Due to genetic prenatal testing, its prevalence is getting lower.

The objective was to analyze the presence of different comorbidities associated with TS according to the karyotype and evaluate if there is follow-up in adulthood.

Methods: Descriptive retrospective study including all the patients genetically diagnosed with Turner syndrome between 1984 to 2019 at our hospital. Patients were classified according to karyotype (monosomy X/mosaicism/isochoromosome). Variables collected (growth hormone treatment, hormone replacement therapy and comorbidities such as celiac disease, thyroiditis, diabetes mellitus, arterial hypertension - HTN - osteoporosis, neuropsychological complications, neoplastic disease, renal or cardiologic disease). Follow-up to adulthood, gynecology screening and pregnancy were also registered.

Results: We analyzed the data of 70 patients (22 of them prenatally diagnosed and aborted, 48 postnatal diagnosed). We present data from 38 patients (median age of 32.6 years old, SD 17.7): 16 (42.1%) monosomy X, 14 (36.8%) mosaicism and 3 (7.8%) isochoromosome.

Fifty percent of patients had received growth hormone treatment (89% of them were born in the last 25 years), and 73% had used hormone replacement therapy.

Comorbidities were found in 33 patients (86.6%): celiac disease (7.9%), thyroiditis (50%), diabetes mellitus (10.5%, 1 case I and the rest II), HTN (34.2%), osteoporosis (15.8%) and neuropsychological complications (31.6%).

Neoplastic disease was registered in 3 patients (non gonadal tumors and none of them related to Y chromosome). Two of them were benign tumors and 1 patient died because of lung carcinoma.

Echocardiographic screening was done in 81.6% of patients (4 cases of bicuspid aortic valve, 2 coarctation of the aorta and 3 aorta dilatation). Renal echography was realized in 81.5% of patients (normal 27 cases, 3 cases of renal fusion and 1 case of abnormal renal rotation).

All the patients with isochromosome had autoimmune disorder, while only in 50% of monosomy X and 60% of mosaicism was found.

Transition from pediatric to adult healthcare had been done in 52.6% of patients older than 18 years of age. Sixty-three % had gynecology screening and 7.9% of women achieved pregnancy.

Conclusions:

- Comorbidities are the main issue in follow-up of TS as most patients present
- Since most patients do not have follow-up in adulthood, it is important to take special care on transition from pediatric to adult healthcare.

P2-289

Familial Mosaic Turner Syndrome with short stature and spontaneous puberty due to a ring X chromosome with distal Xp22.3 and distal Xq26 deletion

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Abnormal phenotypes in patients with ring chromosome X can be ascribed to failed or partial X inactivation due to loss of XIST on Xq13. We describe a mother and 1 daughter with the same mosaic karyotype, and another daughter with 45,X.

KZ, 12 years old and recently moved from Poland, was investigated for short stature (Ht SDS -2.1), her mother was 142.9 cm, father 176.1cm. Both were healthy and not dysmorphic. Birth weight at 37 weeks was 2.63kg (20th centile Polish growth chart), length 54cm (99.5th centile). KZ was well and could converse in English, unlike both parents. KZ's sister PZ was noted to be tall for the family (see table). On examination, KZ was proportionate with no dysmorphisms and was in Tanner stage B3. Bone

	2015	2016	2017	2018	2019	2020
KZ (height in cm TS HtSDS)	133.8 (+0.92)	141.5 (+1.64)	144.8 (+1.63)	146 (+1.26)	147 (+1.26)	
PZ (height in cm TS HtSDS)	120.4 (+1.79)			133.4 (+2.11)	141.8 (+2.83)	149.1 (+3.1)

	KZ (12.75 yrs, B4)	PZ (11.25 yrs, B3)	PZ (12.16 yrs, B3)	PZ (13.5 yrs, B4)
LH (U/L)	54.6	1.0	10.6	3.4
FSH (U/L)	34.0	12.9	46.9	6.5
17B Oestradiol (pmol/L)		183 (55.1 - 58.7)	98 (98-571)	245 (134 - 719.5)
AMH (pmol/L)	<1		<3	

age was 11 years at a chronological age of 12.25 years. No short fourth metacarpals were noted but there was some bowing of the radius. Karyotyping for KZ showed mosaic Turner Syndrome, 45,X[20]/46,X,r(X)(p22.3q26)[10]. Her mother also had mosaic Turner karyotype, 45, X[48]/46,X,r(X)(p22.3q26)[2], found after PZ's results. Mother's result was known in Poland but was not shared in the first consultation. She was told that she would have problems with puberty and fertility, however puberty was spontaneous and menarche was at aged 13. Mother required treatment to conceive. KZ had spontaneous menarche aged 12.8 years, and was started on growth hormone aged 13. PZ was referred aged 11 with karyotype results of 45,X. She was not dysmorphic, with spontaneous puberty and menarche aged 12. Mother and daughters have normal renal and cardiac structures. Pelvic ultrasound scans in both sisters identified normal appearance of ovaries. Auxology and blood results are presented for the sisters.

It is likely that the regions controlling ovarian development and maintenance are proximal to Xp22 and Xq26, with ovarian function intact in this family at varying degrees.

P2-290

Linear growth response to growth hormone therapy in underweight versus normal-weight children with idiopathic short stature (ISS)

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Introduction: Growth hormone (GH) increases lean body mass and reduces fat mass. However, the long-term changes in weight status during growth hormone treatment, according to age and weight status at the onset of treatment, have not previously been reported in large data sets.

Aim: To identify the growth response to GH therapy in underweight versus normal weight short children.

Patients and Methods: We looked at the growth data of 78 short, pre-pubertal children (HtSDS < -2 SDS below the mean for age and sex) with normal GH secretion. They were divided according to their BMI into 19 children with underweight (BMI SDS < -2) and 59 children with normal BMI SDS (> -2). All children received a daily subcutaneous dose of GH (0.03 – 0.05 mg/kg/day) to keep their IGF1 level between 0 and 2SD, for two years, showed that underweight children responded as well to GH treatment as non-underweight children.

Table. Absolute changes in HtSDS after versus before vs therapy and in relation to mi parental height SDS (MPH SDS)

	Low BMI	NL BMI		Low BMI	NL BMI
HtSDS1	-2.345 0.530	-2.203 0.599	HtSDS1-MPH SDS	-0.91 1.066	-1.212 0.879
HtSDS2	-2.00 0.540	-1.830 0.584	HtSDS2-MPH SDS	-0.35 1.307	-0.575 1.138
P	0.320	0.001	P	0.230	0.020

1 = before treatment, 2 = after treatment

Results: Before GH treatment, the underweight group had a significantly lower IGF1 level versus the normal weight group. The age and HtSDS did not differ among the two groups. Treatment with GH for two years was associated with a significant increase in the BMI SDS in the underweight group (BMI-SDS increased by 0.45 SD) but not in the normal-weight group. The HtSDS increased significantly in both groups after GH therapy but the increase was greater in children with normal weight vs those with underweight.

Conclusion: GH therapy for 2 years significantly increased IGF1 level and improved BMI, BMI SDS, and HtSDS in underweight children with ISS. However, the increase in the HtSDS of underweight children was significantly lower compared to ISS children with normal weight.

P2-291

Linear Growth and Weight gain in Infants with Significant Neonatal Hypoglycemia during the first two years of age: Comparison of infants of Diabetic Mothers (IDM) versus infants of non-diabetic mothers (INDM) with transient hyperinsulinemia (non-ketotic hypoglycemia)

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Objective: Infants born to mothers with glucose intolerance are at an increased risk of having growth abnormalities at birth and postnatally. This study evaluated the growth pattern of IDMs from birth to the age of 2 years.

Research Design and Methods: Anthropometric measures (z scores) from birth, 2,4,6,12,18 and 2 years were measured in 60 IDM and 40 infants of non-diabetic mothers who presented with significant neonatal hypoglycemia (plasma value less than 20-25 mg/dL that required proper therapy (IV glucose bolus followed by IV glucose infusion) for two days or more.

Results: IDM had Wt. z score = -0.73 +/- 1.6, L Z score = -0.57 +/- 1.7 and Wt. for L Z score = -0.82 +/- 1.5. They had higher GA and were heavier and taller than the INDM group who had GA (36.4 +/- 2.4 weeks), Wt. Z score = -2.5 +/- 1.8, and wt. for L = -2.8 +/- 2. ($p < 0.01$).

IDM had a progressive gain in the wt-z score that occurred during the first 12 months (from -0.7 to 0) followed by stable Wt. Z score during the second year of age. INDM had a progressive gain in the wt-z score from birth to 18 months of life. This was followed by a stable wt-z score. The wt. Z score gain during the first year of life was significantly higher in the INDM versus IDM. At 18 months of age the wt. z score did not differ between the two groups.

IDM had a progressive increase in the LSGS for 6 months (from -1 to -0.5) that was followed by stable LSGS (normal growth velocity) for the next 18 months. In INDM, there was a progressive gain in the LSGS in the first 12 months (from -2.1 to -0.56) that followed by a stable LSGS. By the age of 12 months, the LSGS did not differ between IDM and INDM.

In Conclusion: IDM were born heavier and taller than INDM. IDM remain heavier and taller than INDM for the first 12 months

of life. INDM had faster LSGS gain the first 12 months of life compared to the IDM. By the age of 18 months, there was no statistical difference between the two groups in all the anthropometric data. During the first 18 months of life, the change (delta) in weight z score and LSGS were reduced in IDM compared to INDM.

P2-292

Timing of infancy-childhood growth spurt in healthy Turkish children

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Aim: The onset of the infancy-childhood growth spurt (IC spurt) is identical with the onset of the childhood component of the infancy-childhood-puberty growth model. The aim of this study was to determine the timing of IC spurt and to investigate the factors affecting it in healthy children.

Materials and Methods: The files of 231 healthy children who were followed up regularly (at 0, 2, 4, 6, 12, 15, 18, 24, 30 and 36 months) at the Istanbul University – Cerrahpasa, Healthy Child Outpatient Clinic between January 2014 and December 2016 were retrospectively evaluated and the parents were asked questions about their socioeconomic and education status, family composition, condition of their houses, hygienic conditions, children's nutritional and infection histories, and sleep patterns through a questionnaire. Infancy component was determined by using an exponential function and the childhood component was determined by using a polynomial function. For each child, the age at onset of childhood phase of growth was determined as normal onset (6-12 months) or delayed onset (after 12 months).

Results: The percentage of children with normal onset was 61.9 and 38.1 had delayed onset. Mean time of onset was 13.08 ± 5.68 months with no difference between girls and boys. Among the factors investigated in terms of affecting the timing of IC spurt, only the education level of families was significant. A delayed IC spurt was statistically more probable in the children whose parents had a postgraduate degree than those who had not ($p = 0.04$). Besides, the longer was the total education years of both parents, the earlier was childhood growth spurt ($p = 0.003$ $R = -0.194$). Height at 6, 9, and 12 months and height velocity between 6 - 9 months were greater in children in the delayed onset group compared to children with normal onset group ($p = 0.008$, $p = 0.001$, $p = 0.001$ and $p = 0.032$, respectively). There were significant differences between the onset periods of the children from our study and the children from Sweden, Shanghai and Pakistan ($p < 0.001$, $p = 0.014$ and $p < 0.001$, respectively).

Conclusion: Differences at the timing of childhood growth spurt were found between our study and the studies from different countries. The most significant finding of our study was that the education level of the parents had a statistically significant effect on the timing of IC spurt.

Effects of GH replacement therapy on body composition and muscle health in children and adolescents with GH deficiency: one-year prospective case-control study

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Background: The effects of GH deficiency (GHD) and GH replacement therapy (GHRT) on body composition and functional measures of physical fitness are largely unknown particularly in children.

Study Aim: To evaluate body composition, muscular strength and flexibility, and exercise tolerance in GHD children at baseline and after one-year GHRT.

Patients and Methods: We enrolled 19 children and adolescents with untreated GHD (mean age 10.54±1.66 years), and 19 healthy children (mean age 11.08±2.61 years) with normal GH reserve matched for age, stature and sex. At study entry, all subjects underwent: anthropometric measurements, multifrequency bioimpedance, a battery of tests evaluating exercise capacity (6-minute walking test (6MWT)), muscle strength (handgrip, jumping, sit-to-stand tests (STS)) and flexibility (sit-and-reach test). All the parameters were re-assessed after 1 year of GH treatment in GHD subjects.

Results: At baseline, GHD children had abnormal body composition, as indicated by higher values of waist-to-height ratio (WtHR) (0.50±0.08 vs 0.45±0.03, p=0.02), fat mass (FM) (26.99±6.03 vs 22.78±5.52 %, p=0.03), and lower fat-free mass (FFM) (22.45±5.11 vs 28.68±7.39 kg, p=0.03), compared to healthy controls.

GHD children exhibited lower hand-grip strength (11.29±3.49 vs 14.03±4.7 kg; p=0.04), vertical jump (12.78±4.17 vs 15.42±2.99 cm, p=0.03), long jump (104.91±28 vs 114.03±34.3 cm, p=0.03), and sit-and-reach test results (8.50±9.21 vs 14.50±7.75 cm, p=0.03), 6MWT distance (505.31±67.25 vs 547.12±52.09 m, p=0.04) compared to controls, indicating reduced muscular strength and flexibility and exercise tolerance. No differences were found in baseline (STS) or STS-5 repeats (STS-5R) tests between patients and controls.

One-year GHRT in GHD patients improved body composition (FFM increased at 28.68±7.39 kg, p=0.004, while FM% and WtHR reduced at 22.61±6.84%, p=0.03, and 0.45±0.06, p=0.02, respectively), handgrip strength (14.56±4.91, p=0.001), vertical jump (16.02±4.81, p=0.03), long jump (120.81±34.73, p=0.03), 6MWT distance (603.31±79.45, p=0.005) and sit-and-reach results (15.60±8.95, p=0.02).

Conclusions: Preliminary results of our study provide the first evidence that untreated GHD is associated to altered body composition, and a reduction in functional measures of physical fitness, such as muscle strength and flexibility, and exercise tolerance, which are much relevant for the patient's quality of life. Moreover, GHRT led to a normalization of such functional parameters over 1 year.

The spectrum of the Prader-Willi-like phenotype and genotype

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Background/aims: Prader-Willi syndrome (PWS) is a rare genetic syndrome, caused by the loss of expression of the paternal chromosome 15q11-q13 region. Over the past years, many cases of patients with characteristics similar to PWS, but without the typical genetic aberration of the 15q11-q13 region, have been described. These patients are often labelled as Prader-Willi-like (PWL). PWL is an as-yet poorly defined syndrome, potentially affecting a significant number of children and adults. In the current clinical practice, patients labelled as PWL are mostly left without treatment options. Considering the similarities with PWS, children with PWL might benefit from the same multidisciplinary care and treatment as children with PWS. In order to gain more knowledge on PWL, we performed a literature study with the aim of providing a complete overview of published cases of patients with the PWL phenotype.

Methods: We conducted a Pubmed Search to identify papers published between January 1963 to May 2020 using the keywords overweight/obesity and intellectual disability. This led to inclusion of 86 papers for review. Data extraction focused on clinical features related to PWS, distinguishing clinical features and the genetic diagnosis.

Results: Overall, 368 individual cases with 35 distinct genetic diagnoses were included. The most common genetic diagnoses were Temple syndrome (formerly known as maternal uniparental disomy 14), Schaaf-Yang syndrome (truncating mutation in the MAGEL2 gene), 1p36 deletion, 2p deletion, 6q deletion, 6q duplication, 15q deletion, 15q duplication, 19p deletion, fragile X syndrome and Xq duplication. The most prevalent symptoms in the entire group were developmental delay/intellectual disability (76%), speech problems (64%), overweight/obesity (57%), hypotonia (56%) and psycho-behavioral problems (53%).

Conclusion: We describe mutations and aberrations for consideration when suspicion of PWS remains after negative testing and summarize the characteristics most prevalent in possible PWL conditions. In addition we propose a diagnostic approach to patients with a PWL phenotype for (pediatric) endocrinologists. PWL comprises a complex and diverse group of patients, which calls for multidisciplinary care with an individualized approach.

An Italian survey on GH stimulation tests and their adverse side effects

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Introduction: The diagnosis of GHD requires the coexistence of anamnestic, auxological and laboratory data. The latter are burdened by the poor accuracy and adverse effects of the stimulation tests. A recent European audit (*Horm Res Paediatr* 2019;92(3):150-156) on GH diagnostic reported as preferred tests in Italy Insulin tolerance test (ITT), glucagon, clonidine, arginine and Arg-GHRH. We conducted a survey to explore which of them are most used in Italy and which are the most frequent adverse events.

Materials and Methods: We have proposed an on-line 14 multiple choice questionnaire to 46 pediatric centers of 38 Italian towns to detect the stimuli used for the diagnosis of GHD and the adverse effects observed.

Results: 29/46 centers answered the questionnaire. 40% of the centers performed more than 100 tests/year and the remaining between 20 and 100 tests/year. The most commonly stimuli used

as primary screening were arginine (70% for all ages), glucagon (10% <3-year-old) and clonidine (23% ≥3-year-old). The most commonly stimuli used to confirm GH deficiency were glucagon (40%), arginine (23%) and Arg-GHRH (13%) in <3-year-old children, and ITT (20%), Glucagon (20%), Clonidine (20%) and Arginine (17%) in older children. The most commonly used stimulus for retesting was Arg-GHRH (88%). The choice of the types of stimulus to be used was independent of the number of tests carried out per year in each center. 18 centers (60%) reported side effects. The most frequent side effects referred to ITT [prolonged hypoglycemia (6) with (3) or without loss of consciousness (3) or seizures (1) reported by 6 centers], arginine [hematuria (3) or extravasation necrosis (2) with keloid outcome (1); reported by 6 centers], clonidine [prolonged hypotension (12); or prolonged sleepiness (1) reported from 13 centers] and glucagon [prolonged hypoglycemia; reported from 6 centers].

Conclusions: On the basis of the present survey, the most frequently used stimuli for the diagnosis of GHD were arginine, as first test, glucagon as confirming test in < 3 year old children, ITT, Glucagone and Clonidine, with equal frequency, as confirming test in older children and Arg-GHRH as retesting at the end of the therapy. Although all tests for GH secretion assessment have adverse side effects, most centers prefer to avoid ITT due to the hypothetical risk of severe hypoglycemia with loss of consciousness or seizures. Unfortunately there are no reliable data on the real frequency of such adverse events during ITT.

Comparing the efficacy of nutritional supplementation of different caloric concentrations on linear growth and weight gain in late childhood, a longitudinal study

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We evaluated the growth parameters of 30 children with low weight gain who did not have any systemic illnesses and assessed their response to nutritional supplementation using two different formula supplements (1cal/1 ml) versus 1.5 cal/1ml) for one year.

Patients and Methods: Thirty underweight children (BMI SDS < -1.5), aged 9 ± 4 years, were divided into two groups according to the type of NS given by different dietitians. Group 1 included 10 children who received high caloric supplements (400 ml/day divided on two or three times/day) (1cal/1 ml) and Group 2 (N=20) received NS (1.5 cal/1ml). We recorded their anthropometric measurements and lab data for all the children for a year.

Results: At presentation, there was no statistically significant difference in BMISD between groups 1 and 2. Height SDS was < -2SD in both groups. Linear growth velocity increased significantly during the year of NS from 5.36 ± 2.9 cm/yr to 8 cm ± 2/yr in group 1 and from 6.15 ± 1.8 cm/yr to 7.76 ± 2.5 cm/yr in group 2. (Table 1). The weight gain/day increased to 9.85 g/day and 11.6 g/day after 1 year of the NS in groups 1 and 2 respectively. After NR, there was

Table 1.

	At presentation					
	Age (yr)	N.	HtSDS	BMI SDS	Wt gain/d	GVSD
Group 1	8.9	10	-2.25	-1.08		-1.1
	4.8		0.8	0.9		1.3
Group 2	10.1	20	-2.1	-1.3		0.4*
	3.8		0.7	0.8		1.8

After 6 months				After 1yr			
HtSDS	BMI SDS	Wt gain/d	GVSD	HtSDS	BMI SDS	Wt gain/d	GVSD
-1.99	-1.2	8.65	0.36	-1.7**	-1.2	9.85	1.2**
0.8	1	3.98	1.29	0.8	1.09	4.7	1.5
-2.05	-1	14.1*	0.08	-1.9**	-1.2	11.6	1.3**
0.6	0.9	10.8	1.4	0.7	1.1	6.6	2.0

Table 2.

			At presentation	After 1 year
	HSD	MPH	HSD - MPHSD	HSD - MPHSD
Group 1	-2.25	-0.43	-1.825	-1.31**
	0.82	0.72	1.09	0.84
Group 2	-2.13	(-1.09) *	(-1.03) *	-0.801**
	0.67	0.74	0.74	0.78

a significant improvement in the difference between the HtSDS and MPHSD in both groups which was higher in group 1. (Table 2)

Discussion and Conclusion: Oral NS improved the nutritional and anthropometric status of old children. There was a significantly better weight gain/day in the group on NS (1.5 cal/ 1ml) compared to the group on (1cal/ml) during the first 6 months with a significant improvement in the HtSDS in both groups after 1 year of NS.

P2-297

The efficacy and safety of recombinant biosimilar growth hormone treatment in children with GHD and SGA: a Czech retrospective national longitudinal study

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Objectives: Recombinant growth hormone (rhGH) treatment helps to achieve a final height close to the parental growth potential

in children with GH deficiency (GHD) and small for gestational age (SGA). Less is known about efficacy and safety of long term therapy with biosimilar rhGH. The aim of our study is to assess height gain and safety of therapy with biosimilar rhGH (Omnitrope®, Sandoz) in Czech children with GHD and SGA over the first three years of treatment and to compare our data with longitudinal international study GeNeSIS Italian Cohort (Humatrope®, Eli Lilly).

Methods: In total 165 Czech children included in PATRO (Omnitrope®, Sandoz study) (103 M, 62 F) were enrolled, 100 with idiopathic GHD and 65 SGA. GH treatment started at the age 7.2 years (2.7–15.7) in GHD and 5.9 years (2.9–14.3) in SGA cohort (median, range). All subjects were treated with Omnitrope® in 8 Czech specialised tertiary centres, GHD group for 42.6±19.2 months and SGA 45.9±21.4 months (mean±SD). Auxological data to assess height gain were compared with published data of GeNeSIS study. Adverse events (AEs) were analysed as well.

Results: At the start of therapy, our GHD cohort was shorter compared with the GeNeSIS (-2.9 SD versus -2.4 SD). During first year of therapy, mean growth velocity increased from 4.2 cm/year to 9.4 cm/yr in GHD and from 4.7 to 9.1 cm/year in SGA group (both p<0.001), which is similar gain as in the GeNeSIS study. Height SDS increased during first year of GH therapy in GHD cohort from -2.9±0.7 to -2.1±0.5 (mean±SD) (p<0.001), similarly in SGA cohort from -3.0±0.6 to -2.3±0.6 (p<0.001). The increment corresponds to the reference GeNeSIS study. A comparison of the difference between the current and target height after 3 years of treatment showed an improvement in our GHD group from -2.2±0.7 to -0.8±0.6 and from -2.2±0.5 to -0.9±0.6 in SGA (not

evaluated in the GeNeSis study). No serious AEs considered to be related to GH were reported in our cohort. Only the minor AEs observed in 29.6% of our patients are probably not related to GH treatment (acute respiratory infections, diarrhea, urinary tract infections, injuries).

Conclusions: Our data confirm significant improvement of growth parameters and safety of therapy with biosimilar rhGH Omnitrope® in Czech children with GHD and SGA which is consistent with results from international database GeNeSis study.

P2-298
A qPCR based approach for rapid detection of Turner Syndrome and its variants

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Background: Turner syndrome (TS) is a common aneuploidy diagnosed by peripheral-blood-cell (PBC) karyotyping. Karyotyping is costly, time-staking and subject to manual errors. Quantitative real-time PCR (qPCR) is a cheap molecular diagnostic test which can detect several samples of TS within hours.

Objective: To assess the performance of qPCR in detecting TS and variants.

Methods: Genomic DNA was isolated from 50 TS patients (45, XO: 23, XO/XX mosaics: 10, Isochromosome-Xq: 12, XO/XY mosaics : 5), 25 normal females (46, XX) and 5 males (46, XY). qPCR was done using 96-well plates, fast real-time PCR. Four primers were used – two on Xp [SHOX and ARSE] and two on Xq [VAMP7 and XIST]. Autosomal gene HBB was used as house-keeping-gene. The $\Delta\Delta CT$ method was used for calculation of the ‘X gene-dose’ with respect to housekeeping gene and X-genes from karyotype-normal (46, XX) females. ROC curves were plotted to determine cut-offs for the genes.

Results: Using a criterion for either SHOX < 0.752 or ARSE < 0.885, all TS cases could be detected (Table 1). TS cases thus diagnosed should undergo qPCR for VAMP7 dose and a value > 0.723 would indicate presence of isochromosome-Xq. For non-

isochromosome cases, SHOX < 0.511 indicates classic TS (45,X) and SHOX > 0.511 means 45,X/46,XX mosaic. A qualitative PCR for the SRY on all diagnosed TS cases could detect XO/XY mosaics. Next, we analysed samples of nine girls with phenotypic diagnosis of TS but karyotype from 30-PBC being 46,XX in six and 46,XY in three. Using our novel approach, we found that the qPCR-diagnosis for 5 girls having 46,XX on 30-PBC karyotyping was 45,XO/46,X,iXq (n = 2) or 45,XO/46,XX (n = 3) and in all the three girls with 46,XY, the qPCR-diagnosis was 45,XO/46,XY. We did a 100 cell karyotyping for these nine samples and found that the qPCR based diagnosis matches with 100 cell karyotype result in 8 out of the 9 cases, Cohen’s κ statistic being 0.72 indicating substantial agreement.

Conclusion: Our qPCR based method involving multiple X-primers can be used for rapid and cost-effective diagnosis of all TS variants, including cases with dubious results on 30-PBC karyotyping.

P2-299
Case report: Tall stature, obesity and hip dysplasia in Weaver syndrome due to a loss-of-function variant in EHZ2

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Case Report: We describe a male with tall stature (final height 210.5cm), macrocephaly (63.5cm, +5.5SD), obesity (BMI 44.6 kg/m²) and mild learning difficulties. Birth weight was 4.6kg (+2.3SD). He had slightly delayed developmental milestones. He was referred at the age of 5 for tall stature (+6.2SD), with a head circumference on the 98th centile, growing at a rate of 10cm/yr. He had thick doughy skin, a mild squint, somewhat coarse features, large hands, feet and ears, but no clear arachnodactyly. He developed hip pain from the age of 6 with restriction of movement and abnormalities on imaging. He had a right hip subluxation and avascular necrosis aged 8 and a left femoral neck fracture aged 9, requiring multiple orthopaedic interventions and a total hip replacement aged 18. He developed obesity from young age. His height continued on the same centile and he reached near final height aged 16-17. Parents are consanguineous Pakistani. Father is 195cm, mother 161cm.

Table 1. qPCR in TS diagnosis

Criterion	Percentage of TS cases detected			
	TS (All karyotypes) (n= 50)	Classic TS(45,X) n = 23	TS variants n= 27	Missed cases
SHOX< 0.752	89.4	100	79.2	5
ARSE< 0.885	83.4	87.4	92.6	8
Either SHOX<0.752 OR ARSE<0.885	100	100	100	0

TFTs, gonadotropins, testosterone, oestradiol, IGF1, IGFBP3, HbA1c, and urine homocysteine were normal. GH was normally suppressed in OGTT. Brain and pituitary gland were normal on MRI, and bone mineral density was normal. The skeletal survey showed mild arachnodactyly and prominent supraorbital ridges, but was insufficient to make a diagnosis. Ophthalmological and cardiac assessments were normal. Microarray, karyotype and *FraX* were normal. Sanger sequencing showed a common NSD1 variant c.7636G>A (p.Ala2546Thr) in the patient and his father, not suggestive of Sotos Syndrome. NSD1 MLPA analysis was normal. Eventually, a tall stature gene panel (*DIS3L2*, *DNMT3A*, *EZH2*, *GPC3*, *NFIX*, *NSD1*, *OFD1*, *PTEN*, *ZBTB20*) showed a heterozygous pathogenic loss-of-function missense variant in *EZH2* (*enhancer of zeste homolog 2*), c.1876G>A (p.Val626Met), once previously described, confirming Weaver syndrome. Testing of the father is in progress.

Discussion: *EZH2* is part of the Polycomb Repressive Complex 2 (PRC2) and can modify histones. Loss-of-function *EZH2* variants result in reduced H3K27 histone methyltransferase activity, and so suppress the activity of genes essential for normal growth, such as cell cycle genes. Weaver syndrome is characterized by tall stature, macrocephaly, mild intellectual disability, characteristic facial features (hypertelorism, retrognathia with stuck-on chin appearance, large ears), camptodactyly, kyphoscoliosis, advanced bone age, soft and doughy skin, umbilical hernia, abnormal muscle tone and hoarse, low-pitched cry. Joint stiffness can be seen, and congenital hip abnormalities have been described once before. Early genetic diagnosis is essential to avoid multiple investigations.

P2-300

Association of Daily Growth Hormone Injection Adherence and Height among Children with Growth Hormone Deficiency

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Background: Use of recombinant human growth hormone (somatropin) is recommended for children with growth hormone deficiency (GHD) to normalize adult height and avoid extreme short stature. Prior research conducted among small study samples, across different study populations and health care systems, has suggested an association between adherence to somatropin and clinical outcomes, including height velocity. There is a need for further research, using real-world data (RWD) among additional populations, to establish and quantify a definitive link between adherence to somatropin and height.

Objective: To investigate the association between adherence to somatropin and change in height among children with GHD.

Methods: This retrospective cohort study utilized IQVIA PharMetrics® Plus and Ambulatory Electronic Medical Records databases. Patients were aged 3-15 years, had ≥1 diagnosis code for GHD, and newly initiated somatropin treatment between January 1, 2007 and November 30, 2019. Patients were followed for a minimum of 6 months and up to 12 months post-treatment initiation. Adherence was measured using the medication possession ratio (MPR); patients were classified as adherent (MPR ≥0.8) or non-adherent (MPR <0.8). Mean patient growth trajectories for each adherence group were modelled in the 12 months pre- and post-treatment initiation using a mixed model for repeated measures (MMRM), controlling for age, gender, and weight. Separate estimates of patient growth pre- and post-treatment initiation were included in the model.

Results: Among 201 patients newly initiated somatropin, 74.6% were male and mean age was 11.4 (SD 3.0) years. Approximately 76.6% of patients were adherent to daily somatropin therapy over the variable follow-up (mean duration of 343.3 days). Adherent and non-adherent patients were generally similar in terms of demographic and baseline clinical characteristics. In the MMRM, adjusted growth trajectories were similar between the adherent and non-adherent patients pre-treatment initiation (p=0.15). However, growth trajectories post-initiation were significantly different (p=0.001). On average, patients who were adherent gained an additional 1.8 cm over 1 year compared to non-adherent patients (height velocity in cm/year [95% CI]: 9.4 [8.9-9.9] vs 7.5 [6.6-8.5]), adjusted for covariates.

Conclusion: This study corroborates prior research suggesting that greater adherence to somatropin therapy is associated with improved height velocity, using RWD from a national US population. Given that suboptimal adherence to daily somatropin therapy is an issue for children with GHD, novel strategies to improve adherence may improve growth outcomes in this population.

P2-301

The evaluation of growth velocity, height, weight, elementary laboratory tests and hormonal function in the patient with Floating-Harbor syndrome treated with growth hormone for 20 months – case report, preliminary report

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Introduction: Patients with Floating-Harbor syndrome have broad spectrum of clinical presentation, but most of them have short stature, low birth weight, delayed bone age, delayed speech development, typical craniofacial features, anomaly of fingers and toes, cryptorchidism in males, renal anomalies, strabismus. Some of them are treated with growth hormone.

Case Report: 4 year old male patient with mutation in SRCAP gene Gln2622Ter/- with short stature, with SGA (birth weight 2700g in 40Hbd), started growth hormone (rGH) therapy for SGA patients. Phenotype manifestation was typical in this patient, except renal abnormalities and cryptorchidism. Patient's bone age was significantly delayed (BA: 6 months). Tanner stage I and testis

in scrotum were examined. Measurements before rGH therapy: Height 88,3cm, HSDS -4,29SD; body weight 10,5kg, BMI 13,5 kg/m²; BMI-SDS -1,46SD. Growth velocity (GV) before treatment was 3,4cm/year. After 12 months of rGH significant acceleration of GV was noticed: 8,7cm per year; measurements were respectively: height 97cm; HSDS -3,35; body weight 12,5kg, BMI 13,3 -1,59 SD; BA was between 9 and 12 months. The patient is continuing treatment till now, for 20 months. He is 6 year old boy now; growth velocity is actually 8,3cm per year; measurements are as follows: height 102,5cm; HSDS -2,86 SD; body weight 14kg; BMI 13,3 BMI-SDS -1,46 SD.

In additional the evaluation of serum: TSH, IGF-1, BP-3, 25OHD, fasting glucose, HbA1c, Na, K, Ca, P, ALT, creatinine, total cholesterol, HDL-, LDL-cholesterol and triglycerides were performed before, after 12 and 20 months of rGH treatment. Serum TSH, 25OHD, HbA1c, Na, K were in the target range before and during the treatment. IGF-1 and BP-3 normalized during the treatment. Fasting glucose level elevated till normal value. Lipids profile and surum Ca and P improved after the rGH treatment, but not normalized. The evaluation of kidney and liver function did not reveal abnormality before and during rGH therapy.

The rGH treatment was well tolerated all the time, none side effects were reported.

Conclusions: The rGH treatment in the male diagnosed with Floating-Harbor syndrome with short stature and SGA is safe and effective during 20 months of observation.

P2-302

Two Sibling Cases with Growth Hormone Receptor Mutation: Variable Clinical Expressivity in Laron Syndrome

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Background: Laron syndrome (LS) is a disorder of primary growth hormone (GH) resistance caused by genetic defects in GH and insulin-like growth factor 1 (IGF-1) axis. Here, we present the variable clinical spectrum in two sibling cases of Iraqi Arab origin with GH receptor (GHR) mutation.

Cases: Two siblings referred to our clinic with the chief complaint of short stature. They had been born with a normal weight at term. Their parents were first-degree cousins. The target height for the sister and the brother was 160 cm (-0.53 SDS) and 173 cm (-0.52 SDS), respectively.

Case 1 (11 years 9 months, female): The patient had a height of 127.5 cm (-3.86 SDS), body weight (BW) 31.5 kg (-1.89 SDS), body mass index (BMI) 19.3 kg/m² (0.16 SDS), Tanner Stage II puberty, and Stage I pubic hair growth. Her bone age (BA) was 12

years. She had basal levels of GH 1.28 ng/mL, IGF-1 82 ng/mL (<-2 SDS), and insulin-like growth factor binding protein-3 (IGFBP-3) 2.586 µg/mL (<-2 SDS), and responses of 27.8 ng/mL peak GH to GH stimulation test, and 31% increase to IGF-1 generation test.

Case 2 (14 years 10 months, male): The patient had a height of 139 cm (-4,27 SDS), BW 35.9 kg (-3.2 SDS), BMI 18.58 kg/m² (-0.97 SDS), testicular volume 5/6 mL, and Stage I pubic hair growth. His BA was 13 years. He had basal levels of GH 26.6 ng/mL, IGF-1 97.7 ng/mL (<-2 SDS), and IGFBP-3 2.06 µg/mL (<-2 SDS), and 118% response to IGF-1 generation test.

The cases did not have the typical LS phenotype. Their genetic analysis revealed a homozygous c.344A> C (p.Asn115Thr) mutation in the 5th exon of GHR. The siblings did not receive treatment because they did not attend follow-up appointments. They had reached their final heights when they presented three years later (sister: 138.3 cm [-3.92 SDS], brother: 156.3 cm [-3.17 SDS]).

Conclusion: In the literature, three cases are reported with the same mutation as in our cases, all being of Arab origin and having severe LS phenotype and lower final height SDS values and IGF-1 levels than our cases (-4.5 SDS in a female case, and -6.8 and -6.9 SDS in two males). The milder phenotype in our patients despite the same genotype suggests a variable GHR activity potentially due to other modifiers such as downstream variants in the GHR gene in the GH pathway.

P2-303

A literature review of the potency and selectivity of FGFR-selective tyrosine kinase inhibitors, such as infigratinib, in the potential treatment of achondroplasia

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Background: Germline mutations in fibroblast growth factor receptor (*FGFR*) genes 1–3 can cause skeletal dysplasias such as achondroplasia (ACH), which is caused primarily by a G380R substitution in *FGFR3*. Infigratinib (BGJ398), a potent and selective *FGFR1–3* tyrosine kinase inhibitor (TKI), demonstrated preclinical efficacy at low doses in an ACH mouse model. The objective of this analysis is to evaluate dose dependency and toxicity profiles of *FGFR*-selective TKIs like infigratinib in preclinical skeletal dysplasia models.

Methods: A review of the literature was performed to investigate non-clinical data from studies of *FGFR*-selective TKIs relevant to *FGFR*-driven skeletal dysplasias. Major databases (e.g., PubMed, Medline) were searched for relevant articles from the past decade and conference archives (e.g., ENDO, ESPE, ISDS, ASHG, ASBMR) for relevant abstracts from the past 5 years. Full text was included where possible. Key search terms were: achondroplasia, *FGFR* inhibition, infigratinib, tyrosine kinase inhibitor.

Results: Of 683 publications identified, 10 relevant articles and 2 abstracts were selected for review. Due to direct relevance, 5 additional publications were included (total 17 included). Key results from studies of infigratinib, the most commonly identified TKI, included: *FGFR3* IC₅₀ 1.0 nM, *FGFR3*-K650E IC₅₀ 4.9 nM.

In vitro data showed inhibition of FGFR1–3 activity at concentrations of 5–100 nM, including reversal of established growth arrest in chondrocytes at 7 nM. *In vivo* studies revealed dose-dependent improvements in foramen magnum and long bone length in *Fgfr3*^{Y367C/+} mice at 0.2–2 mg/kg/day. No studies reported a survival disadvantage, and one showed a significant survival advantage for infigratinib-treated ACH mice. In relation to other FGFR TKIs, one study showed that AZD4547 decreased survival in mice treated at doses of 1x10⁶ to 2x10⁶ nM, and another showed limb malformation in chicken embryos treated with PD173074 at doses of 1x10⁶ to 50x10⁶ nM. While these studies suggested toxicity with FGFR-selective TKIs, the studies were not conducted with pharmacologically relevant doses for ACH, nor were they replicated in the literature. *In vivo* studies reporting treatment in mouse models of ACH with low doses of infigratinib or ASP5878 did not result in any of these abnormal findings.

Conclusions: Recent studies indicate preclinical efficacy of infigratinib, including a survival advantage in *Fgfr3*^{Y367C/+} mice. Given the totality of evidence, low-dose infigratinib appears to be a potentially safe option for further development in children with ACH.

P2-304

Impact of estrogen therapy on pubertal growth in Turner syndrome

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Short stature and hypogonadism are frequent symptoms in Turner syndrome (TS). In most cases, puberty must be induced but pubertal induction modalities are not consensual. Moreover, pubertal induction impact on final height and pubertal growth spurt has not been studied in depth. Our aim was to study factors influencing final height during pubertal induction in TS.

Retrospective cohort of 45 TS girls followed in a single center: Bicetre hospital. We recorded auxological parameters, karyotype, growth hormone therapy, bone age and oestrogenic treatment modalities for pubertal induction. Univariate and multivariate regression analyses of final height, pubertal growth spurt and the probability to attain 153 cm were performed with R software.

Final height was significantly associated with: height at pubertal induction ($\beta=0,72$; $p<0,0001$), cumulated estrogen dose over induction ($\beta=0,26$; $p=0,0001$) , and negatively with estrogen dose during the first year of induction ($\beta= -0,80$; $p=0,0008$).

Pubertal growth spurt was positively associated with pubertal induction duration ($\beta=2,6$; $p=0,0005$).

Height at initiation of pubertal induction was the only factor associated with the probability to reach at least a final height of 153 cm ($\beta=1,004$, $p=0,008$).

In conclusion, to allow TS patients to reach the highest possible final height, it seems important to start pubertal induction at a high enough height (140 cm if a final height greater than 150 cm is desired), with very low dose of estrogen, increased slowly, over a period of at least 3 years.

P2-305

Anastrozole improves height prediction and near final height as monotherapy or in combination with growth hormone

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Introduction: The wide aromatization of androgens during puberty is responsible for the rapid bone maturation at this age. In this context, the use of aromatase inhibitors (AIs) has been justified by the potential to slow down the advancement of bone age and thus improve growth. For more than two decades, studies have pointed out the validity of AIs to improve the predicted final height (PFH). However, data on near-final height (NFH) of children treated with AIs are scarce.

Objective: This study aimed to evaluate the PFH and NFH of boys treated with anastrozole (ANZ) either as monotherapy or in combination with Growth Hormone (GH).

Methodology: Seventy-five boys presenting with PFH below the family target height (TH) between 11 and 18 years old received either ANZ as monotherapy or in combination with GH for at least 12 months. Measurements were made on the same height meter by the same examiner. The follow-up included clinical examination performed by the same examiner, laboratory tests (general blood count, glucose, lipid chart, LH, FSH, testosterone, estradiol), and bone X-ray. The calculation of the Final Height Prediction (PEF) was performed using the Bayley Pinneau method.

Results: Among the adolescents, 29 used ANZ regularly for 1 year, 30 used it for 2 years and 16 used it for 3 years of treatment. Fifty-seven boys used ANZ+GH, and 18 received ANZ as isolated therapy. The correlation between TH, PFH at 1, 2, and 3 years of treatment and NFH demonstrated $p<0,001$, regardless of the use or not of GH. Regarding the initial PFH, in those who did not use GH, there was an average increase of 5.73 cm, 7.60 cm, and 7.15 cm in predicted height after 1, 2, and 3 years of ANZ, respectively, and 2.67 cm when compared to NFH. In the ANZ+GH group, this increase was 6.82 cm, 10.27 cm, 7.44 cm, and 6.26 cm, respectively. The increment in final height compared to the basal PFH was 0.82 cm in the ANZ group and 5.55 cm in the ANZ+GH group. The whole group of adolescents who reached NFH exceeded TH by 1.22 cm.

Conclusion: Anastrozole therapy was safe and effective in improving the PFH and NFH in boys with poor height prediction, either as monotherapy or in combination with growth hormone.

Keywords: adolescents, aromatase inhibitors, anastrozole, short stature.

Growth hormone deficiency (GHD) with high circulating insulin-like growth factor-1 (IGF-1) in an adolescent with celiac disease: Is it IGF-1 insensitivity?

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Impaired growth in children with Celiac Disease (CD) results mainly from nutritional deficits. Withdrawal of gluten from the diet is frequently associated with a marked improvement of linear growth. Some CD patients still have impaired growth despite good gluten elimination. GH secretion should be evaluated in CD patients showing no catch-up growth. We describe a case with CD and severe linear growth retardation due to possible IGF-1 resistance.

Case Presentation: A 16 years old girl, a known case of celiac disease, diagnosed at age of 10 years. She has been compliant with a Gluten-free diet. She was born at term with a weight of 2.5kg, followed by insignificant neonatal history. She was growing well until the age of 7 years. There was no family history of short stature or growth abnormalities. She did not reach menarche yet and her mother and sister had menarche at age of 14-15 years. By examination: she had no apparent dysmorphic features, no goiter or webbed neck, and normal hands. She was at Tanner stage 4 breast developments. Her growth parameters were: Height SDS: -3.76, BMI SDS: -0.85, Mid-Parental Height SDS: -1.2, and weight gain was normal. Investigation revealed normal hemogram, renal, liver, and thyroid profile. She had negative celiac antibodies (TGA). Her IGF-1 level was 436 ug/L= +1.2 SDS). The bone age was 14 years. Two growth hormone provocation tests done and showed a low peak as (1.15 and 4.6 mcg/L, respectively). Her gonadal hormonal profile was (LH:16.9 IU/L, FSH=6.3IU/L, Estradiol, 238pmol/L, Progesterone:1310 nmol/L) and prolactin level: 418 mIU/L. Pituitary MRI showed normal pituitary size with no focal lesion. A trial of growth hormone therapy (0.05mg/kg/day) was given. However, after 2 months she complained of significant headache, not associated with vomiting or visual changes. Repeat IGF-1 level was (713 ug/L= +3 SDS), which necessitated stopping GH therapy.

Discussion and Conclusion: The finding in this adolescent girl with CD, severe linear growth retardation, and high IGF-1 (highly suggested IGF-1 insensitivity of the growth plate and pituitary level) causing her defect in linear growth. To our best of knowledge, this was not described before.

Postnatal Linear Growth and Weight Gain in Infants of Diabetic Mothers (IDM) Who Were Born at or Near Term and Had Severe Neonatal Hypoglycemia Without Other Comorbidities

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Growth abnormalities at birth and abnormal postnatal pattern of weight gain have been reported in infants born to mothers with gestational diabetes (IDM).

This study evaluated the growth pattern from birth to the age of 2 years of 60 IDMs who were born at or near term with significant hypoglycemia.

Anthropometric measures (z scores) from birth, 2,4,6,12,18 and 2 years were measured in 60 IDM who presented with significant neonatal hypoglycemia (plasma value less than 20-25 mg/dL (1.1-1.4 mmol/L)) that required proper therapy (IV glucose bolus followed by IV glucose infusion) for two days or more. Their anthropometric data were compared to standard growth for normal age and sex-matched infants (WHO growth standards)

Results: Their gestational age (GA) at delivery of IDM was 37.36 +/- 1.9 weeks. They had Wt. z score (WAZ) = -0.73 +/- 1.6, length Z score (LAZ) = -0.57 +/- 1.7 and Wt. for L Z score (WLZ) = -0.82 +/- 1.5.

At birth 13/60 had LAZ < -2, 17/60 had WAZ < -2 and 14/60 had WLZ < -2. After an initial decrease in WAZ for the first two months, they had a progressive gain in WAZ that occurred during the first 12 months (from -0.7 to 0). This was followed by a stable WAZ during the second year of age. After an initial deceleration of LAZ for 2 months, they had a progressive increase in the LSDS for 6 months (from -1 to -0.5) that was followed by stable LSDS (normal growth velocity) for the next 18 months. By the age of 12 months, 6/60 had LAZ < -2, 5/60 had WAZ < -2, and 5/60 had WLZ < -2. None had WLZ > 2. By the age of 2 years, none had LAZ < -2, 2/60 had WAZ < -2 and none had WLZ < -2. 3/60 had WLZ > 2 (overweight).

Conclusion: IDMs born at or near term with severe hypoglycemia had a special growth pattern during the first two years of life. Although a considerable % had growth abnormality at birth, by the age of 2 years all these abnormalities disappear with a tendency to overweight.

Age (mon)	Birth	2	4	6	12	18	24
WAZ	-0.73	-0.97	-0.72	-0.46	0.08	0.09	0.04
WLZ	-0.82	-0.02	-0.05	-0.15	0.39	0.36	0.36
LAZ	-0.57	-1.03	-0.82	-0.47	-0.38	-0.43	-0.42

Evidence that non-syndromic familial tall stature has an oligogenic origin including ciliary genes

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Human growth is a complex trait. A considerable number of gene defects have been shown to cause short stature, but there are only few examples of genetic causes of non-syndromic tall stature. Besides rare variants with large effects and common risk alleles with small effect size, oligogenic effects may contribute to this phenotype. Exome sequencing was carried out in a tall male (height 3.5 SDS) and his parents. Filtered damaging variants with high CADD scores were validated by Sanger sequencing in the trio and three other affected and one unaffected family members. Network analysis was carried out to assess links between the candidate genes, and the transcriptome of murine growth plate was analyzed by microarray as well as RNA Seq. Heterozygous gene variants in *CEP104*, *CROCC*, *NEK1*, *TOM1L2* and *TSTD2* predicted as damaging were found to be shared between the four tall family members. Three of the five genes (*CEP104*, *CROCC* and *NEK1*) belong to the ciliary gene family. All genes are expressed in mouse growth plate. Pathway and network analysis indicated close functional connections. Together, these data expand the spectrum of genes with a role in linear growth and tall stature phenotypes.

Early-onset growth hormone treatment in Prader-Willi syndrome attenuates the risk of transition to severe obesity

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Background: Following a phase of feeding difficulties and underweight in early life, children with Prader-Willi syndrome (PWS) develop hyperphagia and a tendency towards severe obesity. Growth hormone therapy (GH) has been approved in PWS to compensate their growth failure but may exert also additional effects on muscle component and body composition as well.

Objectives: We aimed to test if an early initiation of GH therapy within the first two years of life may positively influence the trajectory of body mass index (BMI) in PWS, if compared to PWS children with later therapy onset.

Methodology: We analyzed individual trajectories of BMI in 98 patients with PWS from the REPAR – Czech national registry of patients treated with GH (54 boys and 44 girls; mean age at start of treatment 5.5 ± 4.3 years; mean $\pm$ SD). Patients were divided into two groups according to age at the start of GH treatment: early-onset GH therapy – treatment started till 2 years of age ($n = 55$; age 0.8 ± 0.4 years; mean $\pm$ SD), late-onset GH therapy – treatment started thereafter ($n = 43$; age 7.0 ± 4.6 years; mean $\pm$ SD).

Results: Children within the late-onset GH therapy group were obese already at treatment initiation (SDS BMI 2.9 ± 2.1 ; mean $\pm$ SD). Within the first year of GH treatment, their BMI significantly declined by 0.9 SDS ($p = 0.009$). After five years, mean BMI decreased below the obesity limit to $1.7 (\pm 1.8)$ SDS. On the opposite, children with early-onset GH therapy were underweight

before GH treatment (mean SDS BMI -1.0 ± 1.2). Between 3rd and 7th year of treatment, their BMI significantly increased to borderline obesity range (2.1 ± 2.6 SDS; $p < 0.001$). After 5 years of therapy, BMI-SDS did not differ between both groups ($p = 0.45$). However, most children with an early-onset GH therapy apparently avoided the phase of severe obesity.

Conclusion: Early initiation of GH administration in children with PWS has the potential to prevent transition to severe obesity within their entire childhood, at least in 60 % of children. Following five years of GH therapy, no differences persist in BMI between those who were treated early or late. Nevertheless, the long-term effective prevention of obesity in PWS unavoidably also requires adjustment of eating habits.

P2-310

Incidental pituitary adenoma detection in two patients affected by Williams Syndrome: only a coincidence?

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Case Reports: *Patient 1* was diagnosed with Williams Syndrome (WS) when she was 11 years-old. She presented typical facial features, mental retardation (IQ 34) and chronic constipation. Pregnancy and neonatal period were unremarkable. Her growth has always been satisfying. No cardiac defects were detected at echocardiogram. Cerebral MRI showed enlarged pituitary (height of 9 mm) in the context of which a mass with suprasellar extension was detected. Thyroid and adrenal function were normal, prolactin wasn't raised, IGF-1 was in normal range for age and sex, no hypercalcemia was detected, FSH and LH were mildly increased in concordance with her pubertal development (Tanner stages P4, B4). *Patient 2* was born small for gestational age; during infancy she presented failure to thrive, dysmorphic features and mild neurodevelopmental retardation. Diagnosis of WS was made when the girl was 20 months old. Echocardiogram was normal. Later, growth hormone deficiency was diagnosed. At the age of 10 years Tanner stage were P1, B2; LH and FSH mildly increased. At that age cerebral MRI showed a lesion 5 mm large sited at the anterior side of the pituitary stalk at an intra-suprasellar level. Thyroid and adrenal function were normal, no hypercalcemia was measured, prolactin was in range. Both patients didn't complain visual problems nor headache. Up to today, radiological follow-up has been indicated for both girls.

Discussion: Pituitary adenomas (PAs) are rare in pediatric age; only 3.5-8.5% of all PAs are diagnosed prior to the age of 20 years. The reported prevalence in children is 1 per million. Their frequency increases during adolescence but PAs remains approximately only 3% of all diagnosed intracranial tumors in childhood. Only 2-6% of treated pituitary tumors occur in children. Micro-

adenoma are more common than macroadenoma; non secreting adenomas are less common than secreting adenomas with different percentages according to the reported series. Growth delay could be an early symptom and should be promptly detected. PAs represent an incidental finding in 0.2% of children undergoing brain imaging. PAs are described in some familial syndromes caused by germline genetic defects; also some somatic genetic defects have been described associated with PAs. To the best of our knowledge, PAs have not been described yet in association with Williams syndrome.

Conclusions: Growth delay, visual disturbances, headache or endocrine disorders could suggest PAs diagnosis. Further investigations are needed to understand the possibility of a correlation between PAs and WS.

P2-311

Efficacy of recombinant growth hormone therapy in TRPS 1 syndrome coexisting with growth hormone deficiency

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Introduction: The tricho-rhino-phalangeal syndrome type 1 (TRPS 1), also known as Langer-Giedion syndrome, is an uncommon genetic disorder. This disease is characterized by short stature, cone-shaped ends of the long bones (epiphyses), and distinctive facial features linked to skeletal abnormalities since early childhood. The experience with recombinant growth hormone (rGH) therapy in TRPS 1 is relatively poor.

The aim of the study is to present the results of rGH therapy in a 14-year-old boy with TRPS1, coexisting with growth hormone deficiency and osteoporosis.

Patient Report: The patient was born at 37th Hbd, with a birth weight 2890g. Target height based on parental height was 174 cm. He presented delayed motor development in the first months of life. Since the age of 2y, the height was classified below the 3rd centile.

At the age of 4y, because of distinctive facial dysmorphism such as round face, hypertelorism, wide eyebrows, bulbous nose, long philtrum, thin upper lip, low-set posteriorly rotated ears, hypertrichosis, and short stature TRPS 1 was suspected. Molecular testing revealed a submicroscopic deletion localized on the long arm of chromosome 8 (region 8q23.1-q23.3), which involved the TRPS1 gene, confirming the diagnosis.

Due to short stature and deceleration of growth velocity at the age of 3y, GH secretion testing was performed. After clonidine and arginine stimulation, the peak GH level was 5.7 ng/ml and 2.1 ng/ml, respectively. GH deficiency was diagnosed. IGF-1 level was also below the normal range for age and sex (32 ng/ml). MRI of the pituitary was normal. rGH treatment was started at the age of 5.5 y when his height was 101 cm (htSDS = -3). At the age of 6y, he had a fracture of the clavicle and elbow bone. Low mineral density was

observed in densitometry (Z-score of lumbar region -2.3). Vitamin D3 and oral calcium supplementations were initiated.

Currently, at the age of 14y, his height reached 155.5 cm (htSDS = -1.4), and the predicted adult height (PAH) is 180 cm. The current pubertal stage is as follows: A3, P3, and testicular volume 15 ml. No side effects of rGH treatment were observed to date.

Conclusions: Almost nine-year observation of rGH therapy confirms its efficacy in TRPS 1. Moreover, initiation of rGH therapy early in life resulted in increased growth velocity, gives a satisfactory prognosis for PAH in further treatment.

P2-312

Results from the Implementation of a Growth Disorders Related Twinning Programme (Partners4Growth) at tertiary pediatric endocrinology clinics

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It is well known that early diagnosis of growth disorders in children and their timely treatment are important for better outcomes.

Objective: To evaluate the results from the implementation of the Partners4Growth Twinning Programme at Bulgarian tertiary pediatric endocrinology clinics.

Materials and Methods: Since 2019 Partners4Growth started operation at 6 centers – 3 experienced in growth disorders reference centers and 3 twin centers, with the main aim of aligning their practices in the shortest possible time. Education of twin centers' personnel was organized and the methods for growth evaluation and follow-up were standardized. Paper growth charts and/or regulated web-based growth applications were used. With the support of the Programme all centers obtained certified equipment and reagents for previously unavailable hormonal and growth hormone (GH) stimulation tests. A questionnaire was implemented at baseline and at the 18th month of the Programme collecting 1 answer per center. The questionnaire consisted of 41 questions concerning diagnosis of GH disorders and their management.

Results: A total of 104 new patients with growth disorders were diagnosed - 65 (63%) with GH deficiency, 16 (15%) with Turner syndrome, 12 (12%) with Prader-Willi syndrome and 11 (10%) children born small for gestational age without postnatal catch-up. Of those, 91 children, 59 (65%) boys, started treatment with GH at the mean age of 10.3±5.5 (2.1 – 17.9) years, representing more than 1/3 (35.8%) of all currently GH treated Bulgarian children. Compared to previous diagnostic campaigns in Bulgaria, Partners4Growth more than doubled newly diagnosed growth disorders.

To confirm GH deficiency (GHD), 2 stimulation tests were performed. The first choice of provocative stimuli was primarily glucagon (n=4; 66.7%), and arginin in 2 centers (33.3%). Insulin tolerance test was the second choice in 3 centers (50%), followed by glucagon (n=2, 33.3%) and arginin (n=1; 16.7%). Imaging and fundoscopy were performed in all patients with GHD at diagnosis. All participants' first imaging choice was pituitary MRI, in 33.3% of centers replaced by CT scan occasionally. Karyotype was available at all centers, but DNA methylation tests and identifying genomic deletions or duplications were still accessible only in the experienced reference centers (n=3).

Conclusion: Partners4Growth facilitated the alignment of the tertiary pediatric endocrinology centers competences thus leading to better geographic access to diagnosis and treatment of growth disorders. For its short existence, the Programme has significantly increased the number of newly diagnosed and treated patients. Further decrease of age at diagnosis remains a challenge.

P2-313

Co-occurrence of Turner (46,X-ring/45,X0 mosaicism) and Mayer-Rokitansky-Kuster-Hauser Syndromes: a case report

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Introduction: The co-occurrence of Turner Syndrome (TS) and Mayer-Rokitansky-Kuster-Hauser Syndrome (MRKHS) has been rarely described in literature. The resulting clinical picture includes congenital aplasia of the uterus and of the upper two-thirds of the vagina and ovarian dysgenesis.

Case Report: We hereby report the case of a 14-year-old girl referred to our endocrine outpatient clinic for pubertal delay.

Her previous medical history encompassed strabismus, mild-to-severe intellectual disability and recent-onset epilepsy requiring anticonvulsant therapy.

Upon examination, she presented with shield chest, slightly dysmorphic features and onychopathy. From an auxological perspective, she showed overt short stature (height -4,25 SDS, WHO), while her puberal stage was B2PH4AH1.

Baseline blood test showed findings consistent with primary ovarian failure (FSH 97.4 mUI/ml, LH 16.5 mUI/ml, undetectable oestradiol).

The combination of clinical and biochemical findings prompted the prescription of an arrayCGH, that detected two cellular lines, in the setting of a mosaic genotype: 46,XrX (X ring chromosome) and 45,X0, as confirmed by a subsequent karyotype. Accordingly, the patient was diagnosed with TS.

A pelvis ultrasound showed streak ovaries, but -unexpectedly- no visible uterus was detected. A pelvis MRI confirmed these findings, while a gynecological evaluation outlined a severely hypoplastic vagina. No anatomical abnormalities involving either the kidneys or the spine were detected.

Given the diagnosis of pubertal arrest in the setting of ovarian failure, pubertal induction with progressively increasing doses of beta-oestradiol was undertaken. Despite a progression of secondary sexual features, the sequential sonographic assessment of internal genitalia did not show any signs consistent with oestrogenization and no uterus was detected upon last evaluation, 12 months later.

Discussion: Though the relationship between TS and MRKHS may be regarded as coincidental, the fact that the co-occurrence of the latter with several syndromic conditions (such as Sotos' syndrome) has been already described may support the hypothesis of a causative association. In addition, while historically deemed as the result of sporadic anomalies involving the embryogenesis, several genes such as *KLHL4*, *LHX1* and *WNT4* have recently been implicated in its pathogenesis.

Conclusion: In conclusion, the aim of the present report is to increase the awareness about a possible association between TS and MRKHS, in order to lower the threshold for prescribing MRI when a pelvis US does not detect the uterus in TS patients.

P2-314

Shox Gene Pathologies In Children With Short Stature And Madelung Deformity

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Introduction: SHOX deficiency is the most common cause of monogenic short stature and results in short stature with a highly variable phenotype. In this study, we aimed to detect SHOX gene pathologies in patients who applied to the pediatric endocrine outpatient clinic with short stature and who were found to have Madelung deformity on hand-wrist radiography, and to evaluate the clinical, laboratory features and responses to growth hormone (GH) treatment.

Method: SHOX gene FISH analysis was performed in 21 of 23 cases who applied with short stature and who were found to have Madelung deformity on hand-wrist radiography, and microarray test was performed in 2 cases. For Madelung deformity; the criteria were triangularization of the distal radial epiphysis, lucency of the ulnar border of the distal radius, enlarged diaphysis of radius plus bowing of radius, shortening of the 4th and 5th metacarpals, pyramidalization of the carpal row, and convexity of distal radial metaphysis. SHOX gene sequence analysis and MLPA test were planned to be performed for cases where deletion was not found in the FISH analysis.

Results: Deletion in SHOX gene was found in 13 (56%) of 23 patients. Clinical characteristics, anthropometric measurements, age at onset of growth hormone treatment, initial height and

treatment responses of the patients were evaluated. Nine of the 13 cases (69.2%) were female and 4 were male. Average age on application was 6.4 years (0.5-14.3), average height SDS was -2.97 ((-4.88) - (-0.56)), 9 cases were prepubertal, 4 cases were pubertal. The mean age at diagnosis was 9.4 years (2.9-20). GH treatment was given to nine patients. GH treatment onset mean age was 6.6 years (2.4-10.6), mean height SDS was -2.8. In patients who had received growth hormone treatment median first-year change-in-height SDS of +0.53. Treatment of three patients was completed, and the mean duration of treatment was 24.6 months (12-58), and the mean final height was 143 cm (133.3-160).

Conclusion: In our study, we found SHOX gene pathology in 56% of cases with short stature and Madelung deformity. MLPA test and gene sequence analysis studies continue in cases with normal FISH analysis. There is a need for increased experience with early growth hormone therapy in SHOX deficiency.

P2-315

Characteristics of Patients with Noonan Syndrome Carrying a PTPN11 Mutation: The Recombinant Growth Hormone Treatment and Long-Term Follow-Up

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Introduction: Noonan Syndrome (NS) is a heterogeneous group of diseases with a genetic etiology affecting the RAS/MAPK signaling pathway known as RASopathy. Genes known to cause NS are PTPN11, KRAS, SOS1, RAF1, BRAF, SHOC2 and RIT1. There are sufficient studies indicating that recombinant growth hormone (rhGH) therapy can be given without increasing risk of developing cancer in NS cases with PTPN11 mutations from different centers. In this study, it was aimed to evaluate the genotypic and phenotypic characteristics, the experience of the rhGH therapy and long-term follow-up of the patients with NS in single center.

Method: The cases who were admitted to our pediatric endocrinology clinic between 01.01.2010 and 31.12.2020 due to short stature were considered to be diagnosed with NS with van der Burgt criteria and who underwent genetic analysis were included. Genetic, clinical and follow-up data of patients were obtained from the patient files.

Results: Of the 29 cases whose PTPN11 gene mutation analysis was performed, 11 were heterozygous mutation and one polymorphism was found (12/29, 41%). The rhGH therapy was given to 11 patients with heterozygous mutations. On admission, the mean chronological age of patients was 9.35±3.35 (3.5-14.5) years, average height standard deviation score (SDS) was -3.11±1.10 [-5.33-(-1.98)], the average target height and SDS were 162.7±7.2 (154.5-174) cm, -1.40±1.12 [-3.44-(-0.36)], duration of rhGH therapy was 3.01±1.96 (0.25-7.1) years and the average follow-up time was 7.56±2.91 (3.1-11.5) years. In 9 patients who reached final

height with rhGH therapy, the mean delta-height SDS was 0.16 ± 0.54 $[-0.73- (1.08)]$. No side effects were observed in the cases.

Conclusions: Similar to the literature, in our cases it was found that body composition improved, body mass index did not change, and serious side effects were not observed with rhGH therapy.

P2-316

Determining factors of a good response to treatment with growth hormone for the first 2 years

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Objectives:

- To establish the main factors on which a good response to GH treatment depends.
- To study the optimum adherence values.
- To study the impact of the loss of adherence in the treatment with GH.

Materials and Methods: This is a non-interventional, retrospective observational study, by reviewing medical records of patients undergoing GH treatment for at least 2 years due to GHD or SGA. Patients received treatment with Saizen®, allowing to assess adherence to treatment through the EasyPod Connect platform.

Statistical significance has been considered when $p \leq 0.05$.

Results: 110 patients (51.4% boys, 48.6% girls), 69% GHD, 31% SGA.

Patients with the lowest height velocity (HV) SDS are those with the highest adherence ($r = -0.230$, $p = 0.017$) and achieve a higher HV gain in the first year ($r = -0.499$, $p = 0.000$).

At first year, IoR1 is associated with a higher height SDS ($r = 0.573$, $p = 0.000$), HV SDS ($r = 0.615$, $p = 0.000$), height SDS in the 2nd year ($r = 0.581$, $p = 0.000$) and higher HV SDS 2nd year ($r = 0.398$, $p = 0.000$).

More adherence during the first year correlates to higher HV during the first year, compared to the previous one at the beginning (HV1-HV0) ($r = 0.182$, $p = 0.04$), and a better adherence and IoR2 persist the 2nd year ($r = 0.836$, $p = 0.000$, $r = 0.246$, $p = 0.01$, respectively).

Patients with an adherence $> 90\%$ during the first year, have more frequently a HV > 1 SDS ($p = 0.025$) and higher height SDS ($p = 0.003$) and height-gain SDS ($p = 0.000$).

In the 2nd year, a higher IoR1 correlates to height SDS ($r = 0.581$, $p = 0.000$) and the HV SDS ($r = 0.398$, $p = 0.000$). A higher height SDS in the first year correlates to higher height SDS the 2nd year ($r = 0.887$, $p = 0.000$) a higher IoR2, height SDS ($r = 0.201$, $p = 0.035$) and HV SDS ($r = 0.401$, $p = 0.000$).

Adherence during the 2nd year is better in those with higher HV1-HV0 ($r = 0.201$, $p = 0.035$), better adherence the first year ($r = 0.836$, $p = 0.000$), and in those with a higher IoR2 ($r = 0.298$, $p = 0.002$).

There is a positive correlation between the educational level of the father and mother and adherence the first ($r = 0.031$, $p = 0.006$,

$r = 0.21$, $p = 0.04$, respectively) and the 2nd year ($r = 0.35$, $p = 0.00$, $r = 0.24$, $p = 0.03$, respectively).

In patients with GHD, every 10% loss of adherence means a loss of HV of 1.1 cm/year, being 0.6 cm/year for SGA patients. Adherence could explain 33.4% of the response to treatment with GHD, while if we include the total number of patients in the study, it could explain 38.8%.

Conclusions: Adherence is a determining parameter in the response to treatment with GH; a value $> 90\%$ is estimated as optimal for a better response the first year of treatment, and $> 85\%$ the second. The percentage of adherence is higher in those patients with greater growth restriction at the beginning and remains high in those with higher HV.

P2-317

Noonan syndrome patients with short stature at a single pediatric endocrinology centre

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Introduction: Noonan syndrome (NS) is caused by mutations in RAS/MAPK signaling pathway genes. About 70% of the NS patients have short stature, and human recombinant growth hormone (rhGH) is an established yet not fully standardized treatment.

Objective: To assess the first 2 years rhGH treatment effectiveness in NS patients at a single centre.

Materials and Methods: A total of 20 (16 male) NS patients diagnosed clinically based on the van der Burgt criteria, and followed regularly (2011-2020) were included. Of these, 11 (55%) patients underwent DNA testing, 9 (45%) had cardiac defects, and 8 (40%) had short stature. GH deficiency (GHD) was confirmed in 5 patients who started rhGH treatment. Two additional patients were treated as small for gestational age children without postnatal catch-up. Bone age (BA, by Greulich & Pyle) was estimated at the start and once yearly thereafter. Patients underwent anthropometry, clinical and laboratory investigations 6-monthly, and echocardiography yearly. All patients had at least 2 years of follow-up after the start of rhGH treatment.

Results: DNA test results of the 7 rhGH treated patients showed that 2 (28.5%) had PTPN11 mutation, 1 (14.5%) had KRAS mutation, in 2 (28.5%) patients no mutation was found, and in 2 (28.5%) the genetic work-up is not yet finalised.

The mean age at NS diagnosis was 7.8 ± 3.4 years ($1.3 - 10.5$), and at rhGH start 9.1 ± 1.5 years ($7.5 - 10.7$). The overall treatment period was 38.3 ± 15.3 months. At the start of the rhGH therapy, SDS_{height} was -3.42 ± 0.58 ($-4.1 - -2.6$), SDS_{weight} -3.07 ± 0.58 ($-3.73 - -2.27$), and SDS_{IGF1} -1.12 ± 0.98 ($-2.44 - 0.25$). The mean BA at diagnosis was delayed by 2.6 ± 0.9 years. The rhGH starting dose

was 0.035 ± 0.005 mg/kg/d, the 1st year dose was 0.036 ± 0.002 mg/kg/d, increasing to 0.037 ± 0.003 mg/kg/d during the 2nd year.

The growth velocity for the 1st year of treatment was 8.9 ± 1.4 cm, and for the 2nd year 6.9 ± 1.1 cm. The first year Δ SDS_{height} was 0.72 ($p=0.002$), Δ SDS_{weight} was 0.83 ($p=0.025$). The 2nd year Δ SDS_{height}, Δ SDS_{weight} and Δ SDS_{BMI} increased insignificantly. The Δ SDS_{IGF1} were 1.70 ($p=0.067$) and 0.25 (n.s.), respectively. By the end of the 2nd year, the mean BA remained significantly delayed. No treatment side effects were observed.

Conclusion: Our study shows that NS patients follow the general patterns for the first 2 years of rhGH treatment. In order to improve outcomes, the treatment should be further standardized.

P2-318

Thyroid status in children with Turner syndrome

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Objectives: To evaluate the prevalence and characteristics of thyroid diseases in children with Turner syndrome (TS).

Methods: This is a retrospective study, analyzing clinical data from medical records of 167 patients with TS from 3 to 18 years, who were regularly followed-up in the University hospital (Minsk). Depending on the karyotype, 4 groups of patients were identified: the first group with karyotype 45,X ($n=83$), the second group with mosaic variant 45,X/46,XX (45,X/47,XXX/46,XX, 45,X/47,XXX) ($n=23$), the third group with isochromosome iXq ($n=23$) the third group with other karyotypes ($n=38$). All patients were evaluated for thyroid function (TSH and free T4) and autoimmunity (anti-TPO antibodies (ATPO)), thyroid ultrasound examination was performed. The results were processed using SPSS.22.

Results: TS was diagnosed in patients with characteristic phenotypic signs according to the results of karyotyping at the age of 9.8 [3.8-12.8] years. 55.1% of girls ($n=92$) had normal thyroid function with TSH level of 2.72 ± 0.74 μ IU/ml, 36.5% ($n=61$) had subclinical hypothyroidism (TSH - 7.12 ± 1.68 μ IU/ml and normal level of fT4). Overt hypothyroidism was diagnosed in 6.0% ($n=10$) patients, hypothyroxinemia - in 1.8% ($n=3$) girls, secondary hypothyroidism in one child (0.6%). Mean age at thyroid dysfunction diagnosis was 10.7 [7.7-13.3] years. The largest number of patients with normal thyroid function was noted in the group with monosomy X (66.3%). The prevalence of ATPO positivity was found to be 32.9% ($n=55$). Most of ATPO positive patients were girls with isochromosome iXq (39.5% of patients, $n=15$). Patients with elevated anti-TPO antibodies showed statistically significant differences in the incidence of thyroid hypofunction (65.5%) in comparison with girls with normal anti-TPO antibodies (35.2%) ($\chi^2 = 12.3$; $p < 0.001$). There were no changes in the structure and size of the thyroid gland in 38.7% ($n=29$) of girls with thyroid dysfunction according to ultrasound. Signs of autoimmune thyroid disease (AITD) were found in 36% ($n=27$), thyroid hypoplasia - in 20% ($n=15$).

Conclusions: Our data showed high frequency of thyroid function in girls with TS (44.9% of patients). Subclinical hypothyroidism is the most common manifestation of thyroid dysfunction in children with TS. Thyroid autoimmunity in TS patients is more often detected in the presence of isochromosome iXq.

P2-319

Rare case report: A Chinese boy with MDPL syndrome cause by *POLD1* gene mutation

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Background: Mandibular hypoplasia, deafness, progeroid features, and lipodystrophy (MDPL) syndrome is a genetic disorder which was first recognized in 2010. MDPL syndrome is comprised of mandibular hypoplasia, deafness, progeroid features, lipodystrophy, hypogonadism and metabolic disorders. It is caused by an autosomal dominant mutation in the polymerase delta 1 (*POLD1*) gene, with <30 genetically confirmed cases to date.

Case: A 13.42-year-old boy came to our clinic for his short stature. He was born at full term to non-consanguineous parents with a normal birth appearance (birth weight 3.2kg and birth height 50cm). He had a poor appetite and grew very slowly (no actual data was recorded). His intelligence and motor development were normal. He was nearsighted, while no hearing lost or hyposmia were noticeable. His height was 132.6cm (-3.9SD) and his weight was 20kg (-2.2SD for Ht). His BMI was 11.37kg/m². He couldn't close his mouth probably due to mandibular hypoplasia. Subcutaneous fat loss was noted predominantly on his extremities. His testes were 1ml and soft in texture. The stretched penile length was 2.5cm. Laboratory investigations revealed results within the reference ranges for the electrolyte, renal, liver, glucose, insulin, adrenal and thyroid function, without dyslipidemia. GH provocative tests revealed that his maximum serum GH was 3.36 μ g/L (L-Dopa and Pyridostigmine bromide). IGF-1 was 126.45ng/mL. The baseline follicle-stimulating hormone (FSH) was 16.56 IU/L and luteinizing hormone (LH) was 4.31 IU/L. The luteinizing hormone-releasing hormone (LHRH) test showed 24.73 IU/L in FSH and 18.55 IU/L in LH in 60mins. The testosterone was 0.17ng/mL. His bone age was 9 yrs.

Genetic Analysis: Whole exome sequencing (WES) was performed for his severe short stature, lipodystrophy and hypogonadism. WES revealed a de novo three-base deletion (c.1812-1814delCTC, p.Ser605del) in the *POLD1* gene, which is located in Exon15, 19q13.33. Moreover, it's the most common kind of *POLD1* gene mutation, which is 75% (18/24) up to date.

Conclusion: We report a rare case of MDPL syndrome cause by *POLD1* gene mutation, whose chief complain was short stature. It strongly supports that severe short stature (< -3 SDS for the population or > 3 SD lower than mid-parental target height) should require genetic testing, especially along with other abnormalities.

An Unusual Case of Gastrointestinal Bleeding; Expecting the Unexpected

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Introduction: To investigate the association between Turners Syndrome (TS) and Gastrointestinal Stromal tumours (GIST) in a single case study. There is a known link between RASopathies such as TS and solid tumours (gonadoblastoma, neuroblastoma and brain tumours,) however no known link between TS and GIST. The aim is to increase awareness into a rare condition and discuss growth hormone (GH) therapy.

Case: An 11-year-old girl with background of TS presented due to acute large volume haematemesis and abdominal pain. Emergency department assessment revealed shock; tachycardia, pallor, peripherally shut down with prolonged capillary refill time. Apart from a recent cough she had no other symptoms. Past medical history included TS, cerebral palsy, autoimmune hypothyroid and surgically corrected scoliosis. Medication included oestrogen replacement, GH therapy and levothyroxine. Blood results showed a metabolic acidosis, raised lactate and acute kidney injury. Initial haemoglobin 142, this reduced to 99 following fluid resuscitation, requiring 40ml/kg total fluid bolus.

Urgent CT abdomen with contrast showed a large extra luminal active bleed from the stomach causing massive haemorrhage. Emergency laparotomy found a ruptured 7cm exophytic tumour in the lesser curvature of the stomach that was completely excised with clear margins. Later histopathology confirmed this to be a GIST tumour.

Discussion: This case presents insight into a rare paediatric tumour in a patient with known TS. GIST in children are mesenchymal in origin and rare, typically presenting in the second decade with a female predominance. They can occur anywhere in the gastrointestinal tract with the stomach and small intestine being the most common sites of disease. Presentation is with anaemia from chronic blood loss, however acute haematemesis and melaena is an unusual presentation and mandates the consideration for rare causes. There is differing histopathology between paediatric and adult GISTs with the paediatric form typically being benign. In this instance tumour molecular analysis revealed the most common paediatric histopathology of a Wild type GIST. Growth hormone (GH) therapy is recommended for Turners syndrome if proven GH deficient. Large-scale studies have shown an association between GH therapy and secondary malignancies on GH supra-physiological doses. In this case supra-physiological GH treatment was withheld and monitored for reoccurrence with a risk from pyloric perforation and potential for peritoneal seeding of tumour cells.

There is an increased risk of certain solid tumours in TS with no documented risk associated with rarer GISTs; it is an interesting case to document for future incidence.

Alterations in Metabolic profile and Body Composition in children with Silver Russell syndrome

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There is little information on metabolic profiles and Body Composition in children with Silver-Russell syndrome (SRS).

Methods: 31 SRS patients [16 subjects with 11p15 loss of methylation (11pLOM) and 15 subjects with maternal uniparental disomy of chromosome 7 (mUPD7); mean age 7.4 ± 4.3 years] and non-SRS subjects [34 small for gestational age (SGA), 13.4 ± 2.7 years, and 44 appropriate for gestational age (AGA), 6.9 ± 1.4 years] were enrolled. All patients underwent a cross-sectional evaluation for anthropometrics, biochemical glucose [fasting blood insulin and glucose (FBG), Homeostatic Model Assessment for Insulin Resistance standard deviation (HOMA-IR-SD)] and lipid (triglycerides and cholesterol) profiles; total body (TBLH) and lumbar spine (L1-L4) BMD Z-score, TB fat mass percentage (FM %) and limbs/TB fat ratio were measured by Dual-energy X-ray absorptiometry (DXA)

Main Results: Height SD in SRS (-2.1 ± 1.2 SD) was significantly lower than AGA (0.02 ± 1.3 ; $p < 0.001$), but similar to SGA (-1.96 ± 1.1 SD). Body Mass Index (BMI) was significantly lower in SRS (-1.6 ± 1.2 SD) than in SGA (-0.7 ± 1.2 ; $p < 0.04$) and AGA (-0.1 ± 1.1 ; $p < 0.003$) groups and it was lower in SGA than in AGA ($p < 0.04$). SRS children had higher fasting insulin (10.5 ± 7 μ U/mL) and HOMA-IR SD (0.72 ± 1.8) than AGA (4.2 ± 3.9 μ U/mL; -0.7 ± 1.3 ; $p < 0.001$). In particular, children with 11p15LOM had a significantly higher FBG (92.5 ± 7.5 mg/dl) than AGA (85 ± 7 mg/dl; $p < 0.018$). Similar results were found in SGA group, that showed higher insulin (14.5 ± 9 μ U/mL; $p < 0.0001$), FBG (91 ± 13 mg/dl; $p < 0.003$) levels and HOMA-IR SD (1.3 ± 1.7 ; $p < 0.0001$) than AGA. Glucose profile was not dissimilar in SRS and SGA. SRS (77.9 ± 40.6 mg/dl; $p < 0.002$) and SGA (76.2 ± 34 mg/dl; $p < 0.001$) groups showed higher triglycerides levels than AGA (53.5 ± 21.3 mg/dl). A significantly higher FM was found in SRS ($27.5 \pm 6.8\%$) than AGA ($22.9 \pm 9.5\%$; $p < 0.03$); a higher lower limbs/total body fat ratio was found in AGA (0.44 ± 0.04) than in SRS (0.4 ± 0.05 ; $p < 0.0002$) and in SGA (0.39 ± 0.07 ; $p < 0.0003$). TBLH and L1-L4 BMD Z-score were significantly lower in SRS (-1.3 ± 0.6 , $p < 0.0001$ and -0.85 ± 1 , $p < 0.01$, respectively) and SGA groups (-1.7 ± 2.8 , $p < 0.0001$ and -1.01 ± 0.9 , $p < 0.009$) compared to AGA group (0.1 ± 1.1 and -0.26 ± 1.2 , respectively).

Conclusions: BMI, glucose, lipid profiles and body composition assessments are mandatory in children with SRS. A higher FM% in SRS points toward sarcopenia.

P2-322

Growth abnormalities in patients with Type 1 diabetes

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Key-Words: Type 1 diabetes - growth abnormalities

Introduction: Autoimmune type 1 diabetes is the most common endocrine disease in children. Like any other chronic disease, it can affect their growth. The aim of our work was to describe the different growth abnormalities observed in type 1 diabetic patients followed-up in the department of Endocrinology-Diabetology-Nutrition of Mohammed-VI University Hospital Center of Oujda, in the eastern of Morocco.

Patients and Methods: This is a retrospective descriptive and analytical study including 183 type 1 diabetic patients, under the age of 21, hospitalized in the department of Endocrinology-Diabetology-Nutrition of Mohammed-VI University Hospital Center of Oujda. Weight and height were read into Sempe-Pedron growth curve.

Results: The mean age was 14.9 ± 4 years, sixteen percent of patients were below 10 years old and the sex ratio (Boy/Girl) was 1. The duration of diabetes was less than 13 months for half of patients, with a mean duration of 3.2 years. Twenty percent of patients had an onset of type 1 diabetes. All of the patients were poorly controlled patients with an average of HbA1C of 10.9 ± 2.5 %. Seventy-eight percent of patients had a normal weight ($-1SD \leq \text{Weight} \leq +1SD$) and 84% had a normal height ($-1SD \leq \text{height} \leq +1SD$). Fourteen percent of our patients had a weight $\geq 2SD$, and only 8% had a weight below 2SD. On the statural level, 10% of patients had a height $\geq 2SD$, and short stature was observed in only 5% of cases ($\leq 2SD$). In our series, no statistical correlation was found between diabetes duration, diabetes imbalance and growth abnormalities.

Discussion-Conclusion: The effect of glycemic control on growth is debated in literature. At the time of diabetes diagnosis, some studies reported a statural advantage in diabetic children compared to non-diabetic children. The incidence of short stature in type 1 diabetes is rare; its presence is often correlated with the existence of other chronic diseases, like celiac disease. Therefore, it seems necessary to investigate growth delay in the presence of type 1 diabetes.

P2-323

A novel CEP57 mutation of mosaic variegated aneuploidy syndrome in a Chinese girl: a case report and review of literature

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Background: Mosaic variegated aneuploidy syndrome (MVA) is a rare genetic disease characterized by mosaic aneuploidies, intrauterine growth restriction, developmental delay, microcephaly, facial dysmorphism, mental retardation, and susceptibility to tumor. It is autosomal recessive and caused by mutations in BUB1B, CEP57, and TRIP13. This study hereby presents a 9-year-old girl with intrauterine growth restriction, short stature, microcephaly, facial dysmorphism, brachydactyly and dental dysplasia, who was identified a novel nonsense mutation in CEP57.

Methods: We retrospectively analyzed the clinical data of a 9-year-old girl, genetic and karyotype analysis were performed.

Results: Karyotype analysis revealed 21 aneuploidies in 100 lymphocytes from peripheral blood. Whole-exome sequencing and Sanger sequencing revealed c.312T>G, a novel homozygous nonsense mutation, leading to the termination of protein translation (p.Tyr104*).

Conclusion: We present the first case of MVA in a patient with CEP57 mutation in China, identifying a novel homozygous missense mutation in CEP57 gene (p.Tyr104*). The phenotypes were mildly different from those described in the literatures.

P2-324

A Patient with Turner Syndrome (45X/46XX) and Congenital Adrenal Hyperplasia: A Case Report and Literature Review

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Background: The combination of Turner syndrome (TS) and congenital adrenal hyperplasia (CAH) caused by 21-hydroxylase deficiency is rare. These two diseases affect children's growth and development through different endocrine hormone metabolic dysfunction.

Case Presentation: A patient suffering from ambiguous genitalia was referred to our hospital when she was 2 months old. Her length was 58 cm (+0.9 standard deviation, SD) and weight was 5.34 kg (+0.2 SD). A genital examination showed a 1.5 cm phallus, normal external urethral orifice, and incomplete fusion of the labia. Laboratory investigations showed normal blood electrolyte levels, hyperandrogen, decreased cortisol levels, and increased adrenocorticotrophic hormone and 17-OHP levels. Deficiency of 21-hydroxylase was confirmed with the diagnosis of CAH owing to mutation of the CYP21A2 (cytochrome P450-family 21-subfamily A-polypeptide 2) gene. She was also diagnosed with TS because

her karyotype showed a 45X/46XX pattern. Additionally, Sanger sequencing of SRY (sex-determining region Y) gene showed a negative result. After diagnosing the patient received hydrocortisone replacement therapy and was followed-up every three months. Our recent follow-up showed that the level of adrenocorticotrophic hormone level returned to normal normal and her clitoris length had not increased and even appeared to have declined. Her length was 81 cm (+2.17 SD) and weight was 10.75 kg (+1.22 SD) when she was 1 year old.

Conclusion: CAH patients always have advanced bone age and TS patients in childhood and adolescence have low growth rate of height, both of these two diseases will lead to short stature. Furthermore, CAH patients with hyperandrogenia and TS patients with ovarian dysfunction both will lead to female infertility. Therefore, long-term regular follow-up and multidisciplinary combination therapy are particularly important in the treatment process. Additionally, in clinical diagnosis, if a known genetic disease cannot explain all of the clinical manifestations, the possibility that another genetic disease exists simultaneously should be considered.

Key Words: Turner syndrome, congenital adrenal hyperplasia, CYP21A2

P2-325

Impact of oral nutritional supplements on growth outcomes in underweight children (5: 12 years) with no systemic disease

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Background: Liquid nutritional supplements (ONS) are used successfully in the management of underweight infants and young children with undernutrition. However, their use in healthy old children and adolescents with underweight and/or poor weight gain has not been reported.

Aim: This study describes the effect of ONS on nutritional outcomes in healthy underweight children and adolescents with no systemic illness.

Methods: 20 underweight children (BMI SDS < -1), aged 10.1 ±3.8 years, received ONS (1.5 cal/1ml, 500 kcal/day) in addition to their habitual diet for one year. We recorded their anthropometric measurements including weight, height, BMI, weight gain /day (WGD), height growth velocity (GV), height SDS (HtSDS) for a year.

Results: WGD and linear GV markedly improved during the year of ONS. After 6 months of ONR, there was a significant increase in the BMI SDS and GVSDS. After a year of ONS, GVSDS continued to increase and there was a significant increase in the HtSDS. After ONS, there was a significant decrease in the difference between the HtSDS and their mid parental HtSDS (MPHt SDS).

Conclusions: ONS is effective in improving nutritional/growth outcomes in underweight older children and adolescents with slow weight gain and poor appetite who had no systemic illness.

P2-326

Differential diagnosis of pre- and postnatal short stature revisited: 3-M syndrome

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Introduction: The 3 M- syndrome is a rare autosomal recessive disease, which was named after the three first authors Miller, McKusick and Malvaux. It is characterized by pre- and postnatal disproportionate short stature with micromelia, relative macrocephaly, and radiological bone dysmorphism. It is based on a mutation in one of the three genes CUL7, OBSL1 or CCDC8.

At presentation						
	Age (yr)	N.	WGD1	HtSDS1	BMI SDS1	GVSD1
Mean	10.1	20	5.7	-2.1	-1.3	-.4*
SD	3.8			0.7	0.3	1.8

After 6 months				After 1yr			
HtSDS2	BMI SDS2	WGD2	GVSD2	HtSDS3	BMI SDS3	WGD3	GVSD3
-2.1	-1	14.1*	0.08	-1.8**	-1.2	11.6	1.3**
0.6	0.9	10.8	1.4	0.7	1.1	6.6	2.0

Methodology: We report on a meanwhile 4 4/12- year- old girl who presented to in our pediatric endocrinology outpatient department at the age of 11 months because of short stature and body dysproportion. A chorionic villus biopsy washad been performed in the XX th week of gestation due to a thickened neck fold (3.7 cm), which was normalshowing a normal result. The birth was carried out byShe was born via secondary caesarean section with due to birth arrest after 41 + 5 weeks, with a weight of 2430 g (0.4 kg <3rd P), a body length of 44 cm (4 cm <3rd P), and a head circumference of 33. 5 cm (10th-25th P). A chorionic villus biopsy was performed due to a thickened neck fold (3.7 cm), which was normal. The U2After birth, showed short tubular bones, especially in of the upper extremities were noted.

Results: The U2 showed short tubular bones, especially in the upper extremities. Radiographically there 12th ribs were missing and 12th ribs and signs of spondyloepiphyseal dysplasia were evident. At the age of 4 4/12 years of age, growth was clearly disproportionate (ratio between torso length of 48.2 cm in relation to theand total body length of 83.6 cm was clearly above +2 SDS; the quotient ratio betweenof subischial leg length to torso length was of 0.76 and thus significantly reduced. Genetic diagnostics showed a Mutation in the CUL7 gene.

Conclusions: With this case report, we recall the 3M-syndrome as a rare but important differential diagnostic option for in the delineation of primordial short stature. The differential diagnosis entity must be differentiated from Silver-Russel syndrome, Bloom syndrome, Dubowitz syndrome, Rubinstein-Taybi syndrome, floating Harbor syndrome, Mulibrey nanism and fetal alcohol syndrome. Children with 3M syndrome develop abnormal clinical radiographic signs of disproportionation that enable diagnosis. The diagnosis is confirmed by detection of mutations in one of the three genes mentioned.

P2-327

A case of a Floating-Harbor syndrome in a child with severe short stature

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Introduction: Floating-Harbor syndrome is a rare autosomal dominant genetic disorder caused by mutations in *SRCAP* gene. This condition is characterized by dysmorphic facial features, short stature and expressive language delay. Here we present a clinical case of a child with Floating-Harbor syndrome.

Clinical Case: A girl to consanguineous healthy parents was born at 37 gestation weeks with height 47 cm (SDS=-0.46) and weight 2240 g (SDS=-1.6). Poor growth has been noticed since birth. The examination at 3,5 years of age showed severe proportional short stature (height SDS =-3.6) with significantly delayed bone age (15 months), normal IGF 1 (108.7 ng/ml), normal pituitary hormones and a peak growth hormone response of 18,7 ng/ml (> 8 ng/ml) on standard glucagon stimulation test. The girl has distinctive dysmorphic features such as bluish sclera, long

eyelashes, wide columella, short filter and broad mouth with thin upper lip, teeth hypoplasia and brachydactyly, and was diagnosed with expressive language delay. A known *denovo* heterozygous c.7330C>T:p.R2444X mutation in *SRCAP* gene was identified using whole exome sequencing. Based on genetic results Floating-Harbor syndrome was diagnosed, fully explaining patient's phenotype.

Follow up examination at the age of 4 years showed progression in growth retardation (height SDS = -4.11) and the girl was started on recombinant growth hormone (rGH) therapy with a dose of 0.033 mg/kg/day.

Conclusion: Floating-Harbor syndrome is a rare cause of severe short stature in children. Further studies are necessary to evaluate the effectiveness and safety of rhGH therapy in these patients.

P2-328

Excessive body hair, short stature and advanced bone age in a girl: Hypertrichosis versus adrenarche?

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A 6-year-old girl presented with hypertrichosis all over the body. She was born at term with a birth weight of 2 kg. She had a paralytic squint with excess body hair since birth. She had delayed developmental milestones. She had HTSDS = -1.3, BMI SDS = 0.66. Her Mid-parental HtSDS = 0. She had no other signs of puberty. (breast Tanner 1). Investigations revealed DHEAS = 3.3 Umol/L, Estradiol = 43 pmol/L, FSH = 1.5 IU/L, LH = 0.5 IU/L, Testo: 0.63 nmol/L, IGF1 = 200 ug/L, FT4 = 14 pmol/L, TSH = 1.66 mIU/L. She had slow learning abilities attending a regular school. She had normal cardiac function by Echocardiography.

At the age of 12, she continued to have learning difficulties, hypertrichosis, hairy elbow, ptosis, and squint (underwent corrective surgery). She had gastritis and digestion complexities. Her HtSDS = -1.3 (normal growth rate) BMI = 1.5). She started menstruation at the age of 11.5 years. She had normal renal and hepatic functions and a normal hemogram. Her 17OHP = 4.7 nmol/L, Androstenedione = 7.6 nmol/L, DHEAS = 4.5 pmol/L, Estradiol: 147.0 pmol/L, FSH: 7.8 IU/L, FT4: 16.2 pmol/L, , IGF1: 479.0 ug/L, LH = 9.3 IU/L and Testosterone = 1.76 nmol/L (25/04/21). Her bone age = 14.5 years (advanced). Her predicted adult height was = 150 cm. Her CT of the head revealed normal optic chiasm, normal pituitary, and para-sellar structures. Visualized brain and the ventricles are unremarkable.

Whole Exome sequencing plus mito (WES+) revealed that she is heterozygous for a De Novo Pathogenic Variant in *KMT2A* gene associated with Autosomal Dominant Wiedemann-Steiner Syndrome which is consistent with her reported clinical features. As both parents tested negative for the variant, it is suggested that it arose de novo in the child.

Pathogenic variants in the *KMT2A* gene have been identified with hypertrichosis cubiti, intellectual disability, short stature,

and characteristic facial features. Additional features may include cardiac, renal, and skeletal anomalies, hypotonia, gastrointestinal dysfunction, and delayed or advanced bone age.

In Conclusion: This girl with Wiedemann–Steiner syndrome (WSS) had significant hypertrichosis, short stature (compared to her mid-parental height), with normal IGF1 level and advanced bone age. She had normal pubertal tempo and hormones. She had mild developmental delay. WSS shall be considered in children with hypertrichosis and short stature with mild developmental delay

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P2-329

Cornelia de Lange syndrome: a case report

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Introduction: CORNELIA DE LANGE Syndrome (CdLS) is a rare syndrome, first described in 1933 by the Dutch pediatrician CORNELIA DE LANGE. This syndrome represents a multi-systemic disorder with physical, cognitive and behavioral characteristics. It is evident in the typical or classical form (cranio-facial appearance, short stature and limbs deformities). However, not all individuals with CdLS present with the classic phenotype, as the clinical presentation can vary widely, from mild to severe forms. We report a case of CORNELIA DE LANGE syndrome discovered at the age of 11,5 years at the department of Endocrinology-Diabetology-Nutrition of Mohammed-VI University Hospital, Oujda, in the eastern of Morocco.

Observation: An 11 and a half years old female patient, from a non-consanguineous marriage, with no notable pathological history apart from a school failure consulted for a short stature at -2.8 standard deviations (SD). The clinical examination found a malformative syndrome and hirsutism with a clinical score of 10 (of which 02 criteria were cardinal) evoking a CdLS. The biologic and radiologic explorations excluded all chronic or endocrine pathologies that could explain this statural delay and hirsutism. The search for a sensitive disorder revealed hypoacusis and amblyopia. In view of these findings, the diagnosis of CdLS was made according to the recommendations of the latest consensus on the diagnosis and management of CdLS (without recourse to molecular biology). Growth hormone treatment was not indicated because of the good response to the GH stimulation test by GLUCAGEN/PROPRANOLOL and the absence of marketing authorization for CdLS in MOROCCO.

Discussion and Conclusions: The recommendations provide a framework for improving the diagnosis and management of CdLS. CdLS is a complex disorder, in which many body systems are affected. It is important that a principal clinician be identified for each patient to ensure coordination of the many aspects of care in both childhood and adulthood. The proposed clinical and molecular diagnostic pathways are intended to be universally practiced.

P2-330

Short stature and efficacy of growth hormone treatment in a child with Nail-Patella Syndrome.

A case report

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Background: Nail-Patella syndrome (NPS) or hereditary onycho-osteodysplasia (OMIM: 161200) is an autosomal dominant disorder characterized by nail and elbow dysplasia, patellar aplasia or hypoplasia, nephropathy and intra-ocular hypertension. The diagnosis confirms by pathogenic variant in the *LMX1B* gene. There are reports of short stature in patients with this syndrome, however, data of the use of somatropin have not been presented. We describe the case of a 10-year-old boy with NPS and growth retardation who received growth hormone treatment with a positive effect.

Case Report: The patient was born from normal pregnancy; his weight and height were 3.1 kg and 52 cm, respectively. The family history was unremarkable. Mom's height was 163 cm; father's height was 175 cm. A violations of extension in the elbow joints were noted from birth. The hypoplasia of patella was revealed at 1 year old, and the NPS was diagnosed. The patient presented with nephrotic syndrome at the age of 3 years, he receives ACE inhibitors to the present. A proportionate short stature was detected at 3.5 years old: height 91 cm (SDS = -1.8). The boy was examined at the hospital at 8 years old: height 113 cm (SDS = -2.3), height velocity (HV) 3 cm/year, IGF-1 - 110 ng/ml, euthyroidism, proteinuria up to 0.3 g/l. His bone age retarded on 4 years from chronological. The organ of vision was without pathology. Hypoplasia of the adenohipophysis was on MRI of the brain. The parents refused to conduct GH-stimulation tests. The diagnosis of NPS was confirmed at 9 years old by detecting of heterozygous pathogenic variant in the *LMX1B* gene (c.706G>C). This mutation was not identified in his parents. Growth hormone therapy was started at 9.5 years old at a dose of 0.033 mg/kg/day with height 118 cm (SDS=-2.7) and HV 3 cm/year on start moment. A good growth effect was after 1 year of therapy (at 10.5 years old): height - 127 cm (SDS=-1.9), HV 9 cm/year. The normoglycemia and euthyroidism were during therapy, IGF-1 - 173 ng/ml, no side effects are noted. The therapy was continued.

Conclusion: The good effect of one year of growth hormone therapy has been described in a boy with the NPS. To determine the effect of somatropin on the final growth and the incidence of side effects in NPS, it is necessary to exchange experience in the treatment of such children.

P2-331

Final and Near-final Adult Height and BMI after Long-term Growth Hormone Treatment in Patients with Turner Syndrome (TS)

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Objectives: To assess the long-term effect of growth hormone (GH) therapy in children with Turner Syndrome (TS)

Patients and Methods: We evaluated retrospectively the anthropometric data of 10 girls with TS short children (height SDS <-2) who were diagnosed and treated with GH (0.05 mg/kg/day) between January 2007 till 2018 in our tertiary care center. Before and during GH treatment, auxological and biochemical parameters including Height (Ht), weight (Wt), Ht z score (HtSDS), BMI, and BMI SDS were recorded every 6 months and bone age (BA) was recorded every 12 months. The total increment ratios of HT-SDS were calculated over the period of all years of GH therapy till the final or last visit height.

Results: GH therapy was started at a mean age of 9.1 ± 3.7 years, and the treatment duration was 7.4 ± 3.1 years. After an average of 7 years of treatment, they had a significant increase in HtSDS (+1 SD) when using the normal children WHO curve. Half of the HtSDS gain occurred during the first year of treatment. Their final adult height = 148.8 ± 2.88 cm with HtSDS = -2.34 on the normal children WHO curve and with HtSDS = 1.23 ± 0.5 on TS growth curve. No significant change was detected in the BMI SDS after long treatment with GH. Only one child had BMI SDS = 2.4 and another had BMI SDS = 1.8. The delta HtSDS gain was correlated negatively with the HtSDS and BMI SDS before treatment and positively with HtSDS at the end of treatment ($r = -0.34$, -0.7 and 0.43 respectively, $p < 0.04$). The final HtSDS was correlated negatively with the age at the start of treatment ($r = 0.57$, $p < 0.01$)

Conclusions: Children with TS exhibited moderate increases in HtSDS when treated with GH for 7 years. GH administration at an early age is important for final height gain. The change in the BMI SDS was not statistically significant after vs before GH therapy.

P2-332

Evaluating Safety, Efficacy, and Pharmacokinetics of Weekly TransCon CNP in Children with Achondroplasia: Design of the ACcomplish Trial

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Achondroplasia (ACH) is the most common form of dwarfism, occurring in 1:20,000 births. ACH is caused by gain-of-function mutations in the fibroblast growth factor receptor 3 (FGFR3) gene that interfere with endochondral ossification. Clinically significant morbidities are frequent in ACH; however, there are currently no approved therapies that target the underlying pathobiology. C-type natriuretic peptide (CNP) is an attractive target as it has the potential to inhibit the overactive FGFR3 signalling pathways.

TransCon CNP is an investigational once-weekly prodrug of CNP in development for children with ACH. In the Phase 1 trial, doses up to 150 µg CNP/kg of TransCon CNP were well-tolerated in healthy adult male volunteers, with no clinically significant trends observed in laboratory assessments, vital sign measurements, ECG parameters, or physical examination findings.

Conducted at approximately 20 sites, the primary objective of the phase 2 ACcomplish trial is to evaluate the safety and efficacy of once-weekly TransCon CNP compared to placebo at 12 months in prepubertal children, aged 2-10 years old, with ACH. Following screening and genetic confirmation of clinical ACH, approximately 60 subjects will be randomized to receive either TransCon CNP or placebo and will remain within the dose cohort for 52 weeks of treatment. TransCon CNP will be dosed 6 to 100 µg

Turner syndrome	Age 1	HTSDS 1	BMI SDS	Age 2	HtSDS 2
mean	8.7	-3.47	0.85	9.9	-2.95
SDS	3.69	1.38	1.16	3.69	1.13
	Age F	HTSDS F	BMI SDS F	Delta BMI SDS	Delta HTSDS
mean	15.9*	-2.43*	1.05	0.13	0.99
SDS	3.02	1.09	0.98	0.45	0.44

F = final adult height, * $p < 0.05$

CNP/kg/week across 4 cohorts, with an optional 5th cohort at a higher dose. After completing 52 weeks of their assigned cohort dose, participants who fulfill the rollover criteria can continue into the 104 week open-label extension.

The primary efficacy endpoint will evaluate annualized height velocity at 52 weeks treatment of TransCon CNP or placebo. Key secondary endpoints will examine change from baseline in upper to lower body segment ratio at Week 52. The trial will also examine other endpoints associated with weekly TransCon CNP, including safety, pharmacokinetics (PK), and quality of life (QoL).

CNP is targeted specifically to the underlying pathology of ACH through inhibition of FGFR3 signaling. TransCon CNP is designed to provide sustained exposure of CNP over one week. This ongoing Phase 2 ACcomplish Trial is designed to assess the safety, efficacy, QoL, and PK of TransCon CNP by weekly administration compared to placebo.

Multisystem Endocrine Disorders

P2-333

An Early Diagnosis of Prohormone Convertase Deficiency

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Introduction: Prohormone convertases are a family of proteins that mediate the processing and activation of peptide hormones and neuropeptide precursors. Homozygous mutations of the PCSK1 gene result in prohormone convertase 1 deficiency that is characterized by diarrhea, hypoglycemia, multiple pituitary hormone deficiency beginning from neonatal period and obesity beginning after infancy.

Case: A 35-day-old boy was referred to our hospital with hypoglycemia and metabolic acidosis. He was born 3400 grams at term; received phototherapy with indirect hyperbilirubinemia at the age of 3 days; readmitted with deterioration in general condition, dehydration, hypoglycemia, metabolic acidosis and hyperbilirubinemia at the age of 13 days; recovered after blood exchange, fluid and inotrop therapy but metabolic acidosis and hypoglycemia repeated after refeeding. Parents had 4th degree consanguinity and his mothers cousin who died at the age of 18 months had homozygous PCSK1 mutation. His body weight was 3280 g (-1.82 SD), height was 51 cm (-1.3 SD), and physical examination was normal except for hypotonicity at admission. His pituitary functions were evaluated with the pre-diagnosis of prohormone convertase deficiency and hydrocortisone treatment was initiated

after detecting low cortisol levels. In the follow up diarrhea began after the first month and his diet was arranged with Basic-CH formula and pancreatin treatment. A likely pathogenic homozygous change, NM_000439.5 c: 635G> A (p.Cys212Tyr) was detected in the PCSK1 gene whole gene sequence analysis.

Conclusion: In the presence of hypoglycemia and metabolic acidosis in the newborn and infant period; in case diarrhea is added; prohormone convertase deficiency should be considered in the differential diagnosis.

P2-334

Serologic Testing for Celiac Disease and Gluten Intolerance in a Singaporean paediatric endocrine and growth clinic

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Up to 10 % of short stature has been estimated to be due to celiac disease. Celiac disease has been considered a rare condition outside of the Western world but recent publications (Singh P et al, Clin Gastroenterol Hepatol 2018 Jun 16 (6): 823-836, Yuan J et al, Clin Gastroenterol Hepatol 2017 Oct;15(10):1572-1579) have shown that celiac disease is also present in Asians. While Tissue Transglutaminase IgA (tTg-IgA) has been considered to be a sufficiently sensitive test to exclude celiac disease on its own, a recent paper (Hujoel IA et al, J Clin Gastroenterol 2021;55:327-334) argues that its sensitivity has been over-estimated due to a failure to account for verification bias.

I have observed that many patients who consulted me for problems of short stature and endocrine disorders have had positive serology for celiac disease. Over an 8 year period from 2012 -2020, 456 patients (including 150 Singaporeans), were found to be positive for one or more celiac serology tests as defined by kit manufacturer's standards (Euroimmun for tTg-IgA, DGP IgA and DGP IgG, Orgentec for tTg-IgG) and performed at a single government hospital lab (TTSH Clinical Immunology Laboratory).

The 456 patients, of whom Males 243, Females 213, and 395 were <19 yrs old, comprised 230 ethnic Chinese, 80 Caucasians, 40 Indians, 22 Indonesian/Malay and 84 others. The vast majority (380) came for some form of growth disorder, eg short stature, growth faltering, or lack of a normal pubertal growth spurt, while 34 had Type 1 diabetes mellitus, 28 were screened because of a positive 1st degree relative and 14 presented for a thyroid condition. Many but not all had GIT symptoms. Of 115 patients positive for Ttg-IgA, 98 (85%) were <19 yrs at presentation and came mainly for growth issues. Of the 98 TTg-IgA positive patients < 19yrs of age, 44% are of Chinese origin, 23.5% are of Caucasian origin, and 71.5% are of broadly Asian origin. Among 217 patients positive for Ttg IgG, 50% were ethnic Chinese vs Caucasians (13%). There were 251 patients positive for DGP IgA, (135 ethnic Chinese, 45 Caucasians), and 46 positive for DGP IgG (11 Caucasians). A total of 4 patients were positive for all 4 antibodies, 18 were positive for 3 antibodies and 40 were positive for 2 out of 4 tests. The association of positive Celiac Disease serology and growth impairment is not uncommon in Singaporeans and Asians.

P2-335**Obesity, vaginal bleeding and ovarian mass in a 5-year-old female girl with autoimmune hypothyroidism**

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Case presentation: We report a five-year-old girl who presented for evaluation of obesity, abdominal distension, vaginal bleeding for two days, and abdominal distention. There was no history of local trauma or vaginal discharge associated with the vaginal bleeding and no suspicion of abuse. There was no purpura or bleeding from other sites. Her HtSDS = -1.3 SD and BMI SDS = +1.5 SD. A large abdominal mass was palpable. There was no hepatomegaly, splenomegaly or lymphadenopathy. She had no breast development nor pubic hair. Her investigations revealed TSH = 2288 uIU/ml and FT4 = 0.09 ng/dl, LH = 0.11 mIU/ml, FSH = 1.2 mIU/ml, and Anti TPO = 600 U/ml and anti-thyroglobulin antibody = 296 U/ml. CT of the abdomen showed bilateral adnexal multilocular masses. The right = 8x7.5x10.5 cm and the left = 4.5 x 8.5 x 7 cm. There were no enhancing solid components identified. There was a diffuse mural vaginal thickening and endo-vaginal collection and bulky uterus. L thyroxine was prescribed 75 ug/OD. After a month on thyroxine therapy, FT4 = 2.6 ng/dl, TSH = 2.43 mIU/ml. Her Ultra-sonographic evaluation showed marked regression of the two adnexal lesions, right = 5.3 x 4.3 x 3.1 cm and left = 4.4 x 3.5 x 2.9 cm. The uterine body measured 4.7 x 1.7 cm. After 2 months of therapy, complete regression of the masses occurred.

Discussion: Van Wyk-Grumbach Syndrome (VWGS) is a constellation of symptoms including precocious puberty without adrenarche, delayed bone age, ovarian cysts, and hypothyroidism.

In this case it appeared that high TSH could produce FSH and LH like activity leading to multiple ovarian cysts. Significant regression of the ovarian masses occurred as early as one month after replacing thyroid hormone and normalization of TSH in this girl with VWGS. The etiology of her hypothyroid status was autoimmune. Given the presence of significant ovarian masses, a surgical emergency such as ovarian torsion or rupture must be ruled out. Even when the diagnosis of VWGS is confirmed, practitioners must be watchful to consider surgical intervention in the presence of uncontrolled vaginal bleeding, hemodynamic instability, or failure of regression of ovarian cysts with exogenous thyroid hormone replacement.

Conclusion: VWGS should be considered in the differential diagnosis of young girls with ovarian masses with vaginal bleeding and hypothyroidism. The prognosis is good with thyroid replacement therapy.

P2-336**Endocrine and metabolic complications according to genotype in Prader-Willi syndrome**

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Objective: Prader-Willi syndrome (PWS) is a complex genetic disease associated with hypothalamic-pituitary dysfunction, severe obesity and metabolic dysfunctions. The aim of this study was to describe endocrine and metabolic profiles in PWS children and young adults. We also investigated the differences in clinical outcomes according to genotype.

Methods: Data of 64 children and adults with genetically verified PWS aged more than 2 years old (36 male and 28 female, age 10.3±6.1 years) from single center were studied. The clinical characteristics and laboratory findings were reviewed retrospectively.

Results: Among 64 subjects, 49 had 15q11-13 deletion and 15 had uniparental disomy (UPD). Thirty-three (51.6%) were obese, 8 (12.5%) had fatty liver. Nine (6.7%) patients had diabetes mellitus and 32 (50.0%) showed dyslipidemia. Fifty-six patients (87.5%) were treated with growth hormone. Standard deviation score of bone mineral density (BMD-SDS) was below -2 in 5 (16.7%) patients. Scoliosis was present in 47 (73.4%). Central precocious puberty and hypogonadism were present in 12 (18.8%) and 8 (32.0%) patients, respectively. Patients with UPD had lower HbA1c and lower fasting blood glucose level than those with deletion (5.3 vs 6.0 %, p=0.005 and 97.8 vs 133.3 mg/dL, p=0.005, respectively)

Conclusions: Our report gives an overview of endocrine and metabolic dysfunctions recorded in Korean children and young adults with PWS. Careful monitoring and treatment of these conditions are required to improve health and quality of life of PWS patients.

P2-337**Van Wyk-Grumbach Syndrome in an Egyptian Female Pediatric Patient: a rare presentation of a common disease**

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Background: Van Wyk-Grumbach syndrome is a rare presentation of long standing pre-pubertal hypothyroidism characterized by bilateral multicystic ovaries, vaginal bleeding and delayed skeletal growth in case of female.

Case Presentation: we present a clinical course, diagnosis and management of a case of Van Wyk-Grumbach syndrome in

a 10-years old Egyptian counselled for recurrent vaginal bleeding and pubertal advancement for age. She was noted to have Tanner 4 breasts with no pubic hairs. Laboratory investigation revealed very high levels of thyroid stimulating hormone along with very low free thyroxine, suggesting long-standing untreated hypothyroidism. A pelvic ultrasound was done, which showed multiple simple cysts in both ovaries. Bone age was delayed. The diagnosis of Van Wyk-Grumbach syndrome was made based on the clinical and laboratory criteria. L-thyroxine therapy was initiated and successfully reversed the symptoms in 2 months duration.

Conclusion: This case shows the importance of early identification of the presence of precocious puberty, delayed bone age and ovarian cyst as a manifestation of hypothyroidism to prevent serious complications like Van Wyk-Grumbach syndrome. Precocious puberty associated with delayed bone age should attract attention to the diagnosis of this unique condition. The rapid initiation of thyroid hormone replacement therapy can totally reverse this condition; stopping the rapid progression of precocious puberty, ovarian cystic enlargement allowing for adequate final adult height achievement.

P2-338

Diagnostic and Follow-up Problems of Medical Care for Prader-Willi Syndrome Children in Resource-Limited Settings

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Prader-Willi syndrome (PWS), a multisystem disorder, results of the absence of expression of paternal genes from chromosome 15q11.2-q13; it occurs with the prevalence of 1/10000-1/30000 in different populations. In real clinical practice PWS still remains a challenge for doctors, especially in resource-limited settings.

We describe clinical course in 10 pediatric PWS patients (3M; 7F) aged 7,4±3,3 years (1,7÷12,3), all have microdeletion of paternally inherited 15q11.2-q13 region. Mean follow-up time is 4,1±2,6 years (0,5÷7,6).

In all mothers their gestational course was remarkable for intrauterine hypoxia. Five term babies (1M; 4F) had IUGR. C-section was done in 6/10 mothers. All babies developed severe muscle hypotonia soon after birth and needed feeding tubes; boys had chryptorchidism. All patients were examined by neurologists and clinical geneticists, however, no one baby was send to PWS molecular diagnosis as neonate. The mean age of PWS genetic diagnosis in our group was 2,4±1,9 years (0,4÷6,3). All children had facial dysmorphism, hypotonia and speech delay. The mean age of the first visit to pediatric endocrinologist was 3,2±1,6 years (0,5÷5,4), all patients were overweight or obese. In 2 children growth hormone stimulation tests were performed and confirmed growth hormone deficiency; bone age (BA) was delayed in all studied PWS cases. Five patients are under levothyroxine replacement and two are put on metformin due to impaired glucose tolerance; orchidopexy was done in 3 boys. Mean age of GH initiation was

5,2±2,9 years (1,0÷11,8). The starting daily GH dose was 1,1±0,4 mg/m². After first year on GH growth velocity (GV) was 10,7±1,1 cm/year. Average time of GH treatment was 1,9±1,2 years. In 5/10 children GH was stopped due to high IFG-1 level, BA progression (isolated pubarche in girls) or high metabolic risks. The treatment was restarted in 1,2±0,4 years (GH daily dose 0,8±0,4 mg/m²), as growth velocity was poor, weight was progressing and eating behavior control became much more difficult, also hypotonia and speech problems got worse without GH. Polysomnography was done in 1 girls due to apnoeae episodes under GH interruption. The mean height-SDS, BMI-SDS and IGF-1-SDS have been improved under GH treatment.

Our experience demonstrates poor awareness and lack of knowledge about PWS in different pediatric specialists. Limitations in genetic and other diagnostic facilities worth patients quality-of-life and require medical and social appeal for special care system creation for PWS patients.

P2-339

Three generations of MEN-1: the importance of family screening

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Background: Multiple Endocrine Neoplasia type 1 (MEN-1) is a rare and underdiagnosed syndrome caused by inactivating mutations of the tumor suppressor gene MEN-1 that predisposes to multiple tumors classically situated in the anterior Pituitary, Parathyroid, and Pancreas.

The mutation is transmitted in an autosomal dominant way, and for this reason, the screening of all first-degree relatives is mandatory after identifying an index case.

Case Report: We describe a three-generation family with MEN-1 diagnosis.

Index Case: 71-year-old men with neuroendocrine pancreatic tumor and parathyroid hyperplasia. The classic combination of pancreas and parathyroid (2P's) led to the clinical suspicion of MEN1 syndrome. Genetic testing was then performed, and a germinal mutation in exon 8 of MEN-1 gene was detected: c1087G>T(p. Glu363STOP). He was submitted to subtotal parathyroidectomy and pancreatectomy, followed by adequate substitution therapy.

The same mutation was found in his asymptomatic 35-year-old son. His analytical and imaging screening also detected parathyroid hyperplasia and a neuroendocrine pancreatic tumor, for which he was submitted to the same treatment.

Screening in his grandchildren identified the mutation in two asymptomatic 16 and 12-years old males. The oldest one already has primary hyperparathyroidism with parathyroid hyperplasia and also a solid nodular pancreatic lesion. He is now waiting for surgical removal. Until now, the youngest boy does not present any analytic or imaging abnormalities.

Discussion: Identifying grandfather's MEN-1 mutation allowed its detection in 3 younger asymptomatic relatives. This allowed periodic screenings and timely therapeutic interventions to reduce morbidity and mortality associated with this syndrome.

According to international guidelines, clinical, analytical and imaging screening should start at 5 years old, with a frequency of every 3-5 years.

P2-340

Follow-up and management of endocrine and metabolic disorders after hematopoietic stem cell transplantation in a patient followed for Fanconi anemia

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Introduction: Fanconi anemia (FA) is a very rare, complex and chronic genetic disorder. The diagnosis is most often made at pediatric age. Hematopoietic stem cell transplantation (HSCT) is the only curative treatment for bone marrow failure. FA on its own as well as its treatment can affect the endocrine system. We report the case of a child followed for 12 years after HSCT for FA.

Observation: A patient has been followed since the age of 7 for FA complicated by aplastic anemia. She had an allogeneic bone marrow transplant when she was 8 years old. During her follow-up, the diagnosis of GH deficiency (GHD) was made at the age of 10 years and the patient had treatment with growth hormone for 2 years. She had had chronic kidney failure since the age of 13. She had menarche at the age of 13 with regular periods.

Currently she is 20 years old. On physical examination, his final height was 1.36 m with a BMI of 24.4 kg / m². In biology, the synacthen test was normal. TSH was 16.4 µIU / L and FT4 was 6 ng / L (VN: 9-19) controlled at 0.05 µIU / L and 9.3 ng / L respectively. Anti-peroxidase antibodies are negative. She had pre-diabetes with hypertriglyceridemia and hypercholesterolemia. The pituitary MRI is without abnormality. She was put on L-thyroxine and dietetic rules.

Discussion: The GHD in our patient would most likely be secondary to total body irradiation (TBI) during the HSCT preparation protocol. The final height was very delayed which could be further explained by the FA. Some mutations are more at risk of small stature.

Interpretation of the thyroid workup was difficult in our patient because hypothyroidism could be either secondary to autoimmune thyroiditis post HSCT or secondary to thyrotropic insufficiency due to TBI.

Interpreting the metabolic balance is tricky. Dyslipidemia could be of multifactorial origin: Chronic renal failure, FA or secondary to HSCT. Indeed, even after the interruption of immunosuppression, allogeneic HSC transplant patients seem to have an increased risk of diabetes and metabolic syndrome.

Conclusion: At present, allogeneic HSCT remains the only treatment to most patients with FA. All patients who have received an allogeneic HSCT are likely to develop late complications. A multidisciplinary team caring for these patients should include a pediatric or adult endocrinologist and work closely with other FA specialists to ensure appropriate and optimal patient care.

P2-341

Neonatal McCune Albright Syndrome Presenting with Diabetes Mellitus

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Cafe au-lait skin macules, Cushing syndrome (CS), hyperthyroidism, liver and cardiac dysfunction have been described as presenting features of neonatal McCune Albright Syndrome (MAS). Despite being defined, neonatal diabetes mellitus due to hypercortisolism is a rare presenting feature. Outcome of patients presenting in neonatal period is usually unfavorable, though spontaneous resolution of hypercortisolism have been reported.

Newborn girl was born at 38 weeks of gestation via C/S weighing 2340g following an uneventful pregnancy as second child of healthy, nonconsanguineous couple. On her first day, she was hospitalized due to respiratory distress, liver enzymes were elevated. Neonatal sepsis was suspected, intravenous antibiotic was started. On 7th day, she was discharged. She was referred to our hospital due to weight loss and deterioration of well-being on 11th day.

Hypotonia, round facies, hypertrichosis on forehead and extremities, large hyperpigmented macules on trunk were observed. Elevated liver enzymes and persistent hyperglycemia were noted (blood glucose: 240 mg/dl, insulin: 18 mIU/ml, urinary ketone: negative). Subcutaneous intermediate acting insulin (0.5 U/kg/day) was started. On 20th day, hypertension was evident, antihypertensives were started. Further endocrinologic evaluation revealed increased serum cortisol (225 mg/dl), suppressed ACTH (10 pg/ml). 24-hour urinary free cortisol was 25 times the upper limit, high dose dexamethasone did not suppress cortisol. Further endocrine evaluation was normal otherwise. Mutation of GNAS was not detected by sequence analysis in peripheral blood.

Metyrapone was preferred as liver functions were impaired. On 25th day, as soon as metyrapone (300 mg/m²/day) was initiated, insulin and antihypertensives were ceased and she was discharged.

Despite gradual increase in metyrapone (1850 mg/m²/day), cortisol and liver enzymes remained elevated, adrenal androgens increased and virilization was observed. As persistent hypercortisolism led to growth retardation, developmental delay, severe osteoporosis and left ventricle hypertrophy, right total and left three quarters adrenalectomy was performed at nine months. Cortisol (8 mg/dl) and adrenal androgens decreased substantially, ACTH (<5 pg/ml) remained suppressed. Due to symptoms of steroid

withdrawal and hypoglycemia, oral hydrocortisone was started. Adrenal tissue *GNAS* sequence analysis detected pathogenic heterozygous missense mutation (c.2530C>A (p.Arg844Ser)), bilateral nodular hyperplasia was noted.

This case underlines the unique phenotype of MAS specific to neonatal period. Persistent hyperglycemia was caused by initial excessive cortisol, which may be a negative prognostic factor for response to medical treatment and spontaneous resolution, an indication of early adrenalectomy. Three quarters adrenalectomy is an effective treatment option for CS due to MAS.

P2-342

Combined pituitary hormone deficiency associated with Graves' disease

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Introduction: Graves' disease is a common etiology of hyperthyroidism. The association of Graves' disease and idiopathic combined pituitary hormone deficiency (ICPHD) is rare. We report the case of a patient followed for ICPHD who developed Graves' disease during follow-up.

Observation: A 13-year-old patient consults for stature delay. She had a family history of idiopathic hypogonadotropic hypogonadism in a 25-year-old brother.

On examination, her height was -3 SD with a bone age 2 years less than chronological age. The Insulin hypoglycemia test, performed after sex steroid priming, confirmed complete Growth Hormone (GH) deficiency as well as corticotrophic insufficiency with inappropriate ACTH at 8.3 pg / mL. The thyroid workup, on the other hand, was normal. The pituitary MRI was without abnormality. The karyotype was normal.

The diagnosis of ICPHD was retained and the patient was put on Hydrocortisone and recombinant human GH with good response to rhGH treatment. She had her first period at the age of 15.

During follow-up, the patient presented with an acute adrenal crisis with symptoms of thyrotoxicosis at the age of 16. Anti TSH receptor antibodies were positive hence the diagnosis of Graves' disease was made. The patient was put on methimazole with good clinical outcome.

Discussion and Conclusion: The patient had corticotrophic and somatotrophic insufficiency. The thyroid tests were monitored regularly in order to detect thyrotrophic insufficiency in time. However, the patient developed Graves' disease during follow-up revealed by acute adrenal crisis, thus a rare association of ICPHD and Graves' disease.

P2-343

Autoimmune polyendocrine syndrome type 2 and precocious puberty: a rare association

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Introduction: Precocious puberty is a common problem affecting up to 29 per 100,000 girls per year. It is defined as the development of secondary sexual features, at a younger age than the accepted lower limits for age of onset of puberty, namely 8 years in girls and 9.5 years in boys. We report the case of a precocious puberty in an 8-year-old and 11 months girl with diabetes mellitus type 1 and autoimmune hypothyroidism followed-up in the department of Endocrinology-Diabetology-Nutrition of Mohammed-VI University Hospital Center, Oujda, in the eastern of Morocco.

Case Report: An 8-year-old and 11 months girl was admitted for the first time to our department for unbalanced diabetes type 1 that was discovered at the age of 5 years, for which she was put on basal bolus insulin regimen. The physical examination at admission revealed a breast development stage III according to Tanner staging and a development of pubic hair stage II. The age of onset of secondary sexual characteristics was around 8 years; unfortunately the parents were not alarmed and didn't consult earlier. The young girl had an advanced height at +1SD (standard deviation) with a bone age of 8 years and 6 months. The patient underwent gonadotropin-releasing hormone (GnRH) stimulation test that revealed a peak luteinizing hormone (LH) concentration at 6,47 mUI/mL. Pituitary magnetic resonance imaging (MRI) was normal. Therefore, the diagnosis of idiopathic central precocious puberty was confirmed. Nonetheless, since the patient had a normal growth velocity and a comforting bone age, GnRH agonists were not used. Furthermore, the screening for autoimmune diseases in the patient revealed positive *thyroid peroxidase antibodies (TPO antibodies)* at 38,47 UI/mL (normal range < 34 UI/mL). The young patient developed hypothyroidism 2 months later and was put on substitutive hormone therapy. During a regular follow-up of one year, the patient had a sustained normal growth velocity.

Discussion-Conclusion: A review of literature of puberty in girls with diabetes type 1 concluded that the age of onset of puberty in young girls with diabetes mellitus type 1 seem to be within normal limits, however some patient experience pubertal delay due to poor glycemic control [1]. Our patient presented with a precocious puberty, this association with autoimmune polyendocrine syndrome type 2 has never been described before. Further investigations are necessary in order to comprehend the particularities of this unusual association.

Reference

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P2-344

Thermoregulatory delays in Greek PCOS adolescents

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In this case-control study 19 Greek adolescents with Polycystic Ovary Syndrome (PCOS) and 21 non-PCOS controls were assessed for their hormonal, somatometric and autonomic nervous system profile in supine position. The study adhered to the Helsinki Guidelines of Good Clinical Practice. Significant differences were found only in very low frequencies (VLF) ($p=0.008$) and Power spectral density RR (PSD) ($p<0.001$) between adolescents with PCOS and controls. PSD was found decreased, a finding when combined with the VLF points to thermoregulatory delays. VLF is related to renin-angiotensin-activity, suggesting early onset of hormonal fluctuations and/or cardiometabolic manifestations related to the syndrome. The fact that no other autonomic nervous system or cardiac marker was disturbed, suggests that in this early stage no cardiovascular disease onset was detected. The finding suggests future research should focus on the role of cholinergic and vagal innervation to the development and persistence of the disease.

P2-345

Endocrine manifestations in familial neurofibromatosis type 1: a case report

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Introduction: Type 1 neurofibromatosis (NF1), also called Recklinghausen's disease, is one of the most common genetic diseases. It is autosomal dominant inherited. Its diagnosis is based on the presence of a familial history of NF1 in a first-degree relative and on the presence of a set of clinical arguments. Endocrine manifestations may exist. The most common are pheochromocytoma and precocious puberty, but other endocrine disorders can be observed more rarely, namely delayed puberty, which we will discuss in this observation.

Observations: These are 3 patients with NF1. They are 1st degree relatives (first cousins) followed in the internal medicine and endocrinology department of Mahdia.

Case 1: 20-year-old male patient with NF1, who consulted for delayed onset of secondary sexual characteristics. In the family history we noted a NF1 in his father and a simple puberty delay in his mother.

On examination, the patient presents a deep voice, an A1 P3 G5 stage according to Tanner's classification, the beard is absent. The examination of the external genitalia was normal. The penis has a normal size at 8 cm at rest. The scrotal skin is well wrinkled and normally pigmented. The hormonal dosage shows testosteroneemia at 3.67 ng / mL, FSH at 1.99 IU / L, LH at 3.25 mIU / L, prolactinemia at 13.78 ng / mL, and TSH level at 2.091 mIU / L.

The hormonal dosage shows a central hypogonadism, which may be in favor of organic damage to the hypothalamic-pituitary axis or simple puberty delay. A pituitary MRI was requested to guide the diagnosis.

Case 2: 21-year-old male patient with NF1, followed since the age of 14. In the family history we noted a NF1 in his father and his paternal aunt. The patient has no clinical or biological evidence for a hormonal disorder. He entered puberty at the age of 14 and the course of puberty was normal.

Case 3: 21-year-old female patient with NF1, followed since the age of 15. In the family history we noted a NF1 in her father, her paternal aunt and uncle. Clinical examination and biology revealed no evidence for an endocrine disorder, and for puberty, her menarche was at the age of 14.

Conclusion: Patients with NF1 have special problems because of their disease. That's why the identification of endocrine disorders can surely improve the life quality of these patients.

Pituitary, Neuroendocrinology and Puberty

P2-346

The clinical and biochemical spectrum of pituitary lesions in children compared to adults: experience from a single tertiary center

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We present a monocentric cross-sectional study of 55 children referred between 2000 and 2020 for pituitary lesions, who underwent a complete pituitary function assessment. These data were compared to results obtained in a group of 295 adults carrying pituitary lesions undergoing a complete pituitary screening. Follow-up data was available for 50 children and 248 adults.

The mean age at diagnosis in children was 12.2 ± 3.7 years (range 2.1-17.9), while in adults was 48.7 ± 15.5 years (range 18.0-89.7).

In the pediatric group, there was a male preponderance compared to adults (69% vs 37%, $p < 0.0001$). The most frequent lesions among children were pituitary hypoplasia (31/55), Pituitary Stalk Interruption Syndrome (11/55) and expansive lesions (microadenomas or craniopharyngiomas: 8/55), while in adults the most frequent lesions were secreting microadenomas (56/295) or macroadenomas (52/295) and primary empty sellas (82/295). Secreting adenomas were significantly less represented in children compared to adults (7% vs 37%, $p < 0.0001$).

In children, radiological findings were performed following endocrine work-up, mainly driven by poor growth or pubertal delay while in adults they were mostly incidental and preceded endocrine evaluation (90.9% vs 62%, $p < 0.0001$).

Children presented with at least one pituitary deficit compared to adults (89.1% vs 48.8%, $p < 0.0001$) and this was homogeneous throughout years of examination.

Even considering similar pituitary lesions such as primary empty sellas and small anterior pituitaries taken together, children with these lesions showed more frequently at least one pituitary deficiency compared to adults (94.1% vs 51.1%, $p < 0.0001$).

GH deficiency was statistically more frequent in children (83.3% vs 14.8%, $p < 0.0001$) and central hypothyroidism tended to be lower than in adults (10.9% vs 21.5%, $p = 0.072$), while hypogonadism, hypoadrenalism, diabetes insipidus and prolactin deficiency did not differ in prevalence between children and adults.

During a median follow-up of 54.6 months [interquartile range 23.5 – 103.8], a similar risk of worsening of pituitary function was observed in children and adults (8.0% vs 15.7%, $p = 0.156$).

To our knowledge, this is the first monocentric report aimed to analyze the differences between children and adults presenting with a pituitary lesion. Pituitary lesions in children are rarer than in adults, but present more likely with pituitary deficiencies and growth defects account for the vast majority of their presentations. At variance with adult patients, children with empty sellas and small anterior pituitaries typically present functional pituitary defects.

P2-347

Optic tract glioma and endocrine disorders- comparison between patients with and without NF1- a single center experience

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Background and Aims: Optic pathway gliomas (OPGs) represent 2-5% of brain tumors in children. OPGs are classified by the anatomic location and whether they are associated with neurofibromatosis type 1 (NF1).

Children with OPGs face sequelae related to tumor location and treatment modalities, including visual dysfunction, neurological deficits, and endocrine dysfunction.

The aim of our study was to assess the prevalence of endocrine dysfunctions in patients with OPGs and to compare the outcomes between those with and without NF1.

Methods: This retrospective single center study included patients diagnosed with OPGs between 1990 and 2020, younger than 18 years at diagnosis, followed at our endocrine clinic. Data about demographic parameters, presence/absence of NF1, OPGs treatment related data, growth and puberty parameters and occurrence of endocrine dysfunction were retrieved from their medical records.

Variables were compared between groups (OPGs with and without NF1).

Results: Of the 59 patients (29 males) fulfilling the study criteria, 36 (61%) had NF1, with higher rates of isolated optic nerve involvement ($p < 0.01$).

Patients without NF1 compared to those with NF1 were significantly younger at diagnosis of OPGs (1.5 vs. 4.2 years, $p = 0.04$), older at the last visit (14.7 ± 6.3 vs. 11.5 ± 5.0 , $p = 0.03$), and a higher percentage of them were treated with surgery (65% vs. 8%, $p < 0.01$), chemotherapy (83% vs. 31%, $p < 0.01$) or cranial radiation (14% vs. 3%, $p = 0.13$).

At the last visit, patients without NF1 compared to those with NF1 had lower height SDS (-0.97 ± 1.39 vs. -0.72 ± 1.13 , $P = 0.45$), and higher BMI SDS (1.08 ± 1.26 vs. 0.37 ± 1.02 , $p = 0.02$). No significant difference was found between the groups in the age at pubertal onset.

Patients without NF1 had higher rates of endocrine complications (65% vs. 28%, $p < 0.001$), including: central hypothyroidism (48% vs. 2.8%, $p < 0.01$), hypogonadotropic hypogonadism (22% vs. 2.8%, $p = 0.02$), diabetes insipidus (26% vs. 2.8%, $p = 0.01$) and hyperlipidemia (35% vs. 8.3%, $p = 0.01$), without significant differences in the rate of growth hormone deficiency or precocious puberty.

Median age at the time of diagnosis of the first endocrinopathy was younger in patients without NF1 compared to those with NF1, 3.75 years (1.18 - 10.87) vs. 8.25 years (6.72 - 8.62), respectively, $p = 0.341$.

In a multivariate regression analysis, surgery was the independent predictor of endocrine dysfunctions (OR 13.3 [2.23-79.53]; $P < 0.01$).

Conclusions: Patients with OPGs without NF1 had a higher rate of endocrine dysfunction presenting at a younger age compared to patients with NF1, which may be associated with tumor location and more aggressive treatments.

P2-348

Endocrine manifestations of paediatric intracranial germ cell tumour: from diagnosis to long-term follow-up

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Introduction: Endocrinopathies are common features of intracranial germ cell tumours (IC-GCTs), either as presenting symptoms caused by tumour itself or as side effects of treatments.

Aims: We examined the development of endocrine dysfunctions in a cohort of paediatric patients with IC-GCTs at diagnosis and during follow up.

Methods: We collected clinical, radiological, histopathological and hormonal data in 55 patients. Diabetes insipidus (DI), growth hormone deficiency (GHD), hypothyroidism, adrenal insufficiency (AI), precocious puberty (PP), hypogonadotrophic hypogonadism (HH), obesity and hyperprolactinemia were diagnosed clinically and confirmed biochemically. The prevalence of endocrine sequelae was compared to survival rates.

Results: 55 patients (67.3% males) diagnosed with IC-GCT at a median age of 12 (range 1–17.9) years and with a median follow-up of 78.9 months (range 0.5–249.9) from diagnosis were included. 63.6% had germinomas, 14.5% teratomas, 12.7% mixed GCT and 3.6% yolk sac tumour. 10.9% of cases were metastatic at diagnosis. IC-GCTs were suprasellar (41.8%), pineal (36.4%), bifocal (12.7%).

At tumour diagnosis, 28/55 patients (50.9%) displayed endocrine dysfunctions: among them, 57.1% were affected by DI, 57.1% by central AI, 50% by central hypothyroidism, 28.5% by GHD, 10.7% by HH, 10.7% by gonadotrophin-independent PP. These patients had predominantly germinoma (74.3%) or suprasellar IC-GCT (63.9%). Patients underwent biopsy (46/55), surgery (8/55), chemotherapy (42/55) and radiotherapy (50/55). At the last follow up, endocrinopathies were diagnosed in 37/55 patients (67.3%): among them, 30/37 (81.1%) developed AI, 30/37 (81.1%) GHD, (78.4%) DI, (73.0%) hypothyroidism, (62.2%) HH. None of the pre-treatment endocrinopathies resolved. The new endocrine disorders arose at a median of 15.15 months (range 1.3–204.2 months) after the end of treatment. No cases of hypergonadotrophic hypogonadism due to chemotherapy-related gonadal toxicity were reported in our cohort. Overall survival (OS) rate was 80%. No statistical difference in OS was found between patients with and without endocrine sequelae ($p=0.37$).

Conclusion: Our study confirmed that endocrine disorders were frequent in patients with IC-GCTs at diagnosis. Additional endocrinopathies can occur decades after completion of treatments and require long term monitoring. Although survival rate was not affected by the presence of endocrinopathies in our cohort, close lifelong surveillance is mandatory to provide the best care for these patients.

P2-349

Machine learning to detect the Klinefelter syndrome endocrine profile

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Introduction: Klinefelter syndrome (KS) is the most common sex-chromosome disorder and cause of infertility and hypogonadism in males. However, KS remains an underdiagnosed condition with the majority of expected cases escaping clinical diagnosis and follow-up. Generally, the mid-puberty endocrine profile associated

with KS is characterized by elevated levels of gonadotropins due to diminished testosterone feedback.

Objective: To devise a machine learning model to identify cases of KS amongst healthy controls based on inter-individual endocrine profiles, and test its predictive value.

Methods: The current project used hospital records of hormone levels in $n=15$ genomically confirmed and untreated cases of KS (47,XXY) in the age interval 6–13 years. Sex and age-adjusted hormone z-score equivalents of serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), anti-Müllerian hormone (AMH), dehydroepiandrosterone sulfate (DHEAS), sex hormone-binding globulin (SHBG), 4-androstenedione, testosterone and 17-hydroxyprogesterone constituted the current ‘endocrine profile’. The random forest machine learning algorithm was trained and applied to classify cases of KS relative to the endocrine profiles of $n=107$ healthy, prepubertal (testicular vol. <4 ml) and age-matched boys. The machine learning model was trained using 75% of the total observations and subsequently applied to classify the remaining test data using the ‘randomForest’ and ‘caret’ packages in R.

Results: Classification performance of the machine learning model exhibited an accuracy of 0.97 (95% CI, 0.96 to 0.98), Kappa of agreement of 0.92 (95% CI, 0.89 to 0.94) and average sensitivity of 0.97 and specificity of 0.96. Corresponding confusion matrices confirmed the generally correct classification of KS and healthy subjects. Serum levels of FSH for age were the best singular hormone to classify KS, but this marker exhibited an accuracy of merely 60% in this respect. Clustering between healthy and KS endocrine profiles were also observed by principal component analysis (PCA), where LH and FSH levels primarily contributed to the variance between the two groups.

Conclusion: Machine learning applied to biochemical data was able to make valid predictions to accurately classify cases of KS in this relatively small retrospective cohort. The model may be improved by addition of anthropometric (e.g. height-for-age) and other biochemical markers with relevance for the KS phenotype.

P2-350

Nuchal Skinfold Thickness in Pediatric Brain Tumor Patients

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Background: Severe obesity and tumor relapse/progression have impact on long-term prognosis in pediatric brain tumor patients.

Methods: In a cross-sectional study, we analyzed nuchal skinfold thickness (NST) on magnetic-resonance imaging (MRI)

follow-up monitoring as a parameter for assessment of nuchal adipose tissue in 177 brain tumor patients (40 World Health Organization (WHO) grade 1–2 brain tumor; 31 grade 3–4 brain tumor; 106 craniopharyngioma), and 53 healthy controls. Furthermore, body mass index (BMI), waist-to-height ratio (WHtR), caliper-measured skinfold thickness (cSFT), and blood pressure were analyzed for association with NST.

Results: Craniopharyngioma patients showed higher NST, BMI, WHtR, and cSFT when compared to other brain tumors and healthy controls. WHO grade 1–2 brain tumor patients were observed with higher BMI, waist circumference and triceps cSFT when compared to WHO grade 3–4 brain tumor patients. NST correlated with BMI, WHtR, and cSFT. NST, BMI and WHtR were associated with increased blood pressure. In craniopharyngioma patients with hypothalamic involvement/ lesion or gross-total resection, rate and degree of obesity were increased.

Conclusions: NST could serve as a novel useful marker for regional nuchal adipose tissue. NST is highly associated with body mass and waist-to-height ratio, and easily measurable in routine MRI monitoring of brain tumor patients.

P2-351

Growth hormone deficiency in 52 children with brain Magnetic Resonance Imaging Abnormalities

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Growth Hormone (GH) deficiency is the most common pituitary hormone deficiency in children. Magnetic Resonance Imaging (MRI) of the brain detects structural pituitary anomalies associated with GH deficiency. The prevalence of MRI abnormalities in patients with GHD, ranging from 25.9–100.0%. The Growth Hormone Research Society currently recommends that an MRI of the brain, with particular attention to the hypothalamic–pituitary region, should be carried out in any child diagnosed with GHD.

The aim of this study was to ascertain the abnormality that is the best predictor of severity and type of GHD amongst the different MRI findings.

This is a retrospective study of 52 patients followed in our center: The available radiological, clinical and laboratory records of these children with confirmed GH deficiency by dynamic testing who had malformative anomaly in MRI brain were reviewed.

Of the 52 patients in this study, there were 34 boys 65 % and 18 girls 35 % with a sex ratio of 1.88. Isolated GH deficiency (IGHD) was diagnosed in 30 (57.7%) and multiple pituitary hormone deficiency (MPHD) in 22 (42.3%) patients. For all patients, Regular follow-up of growth might have allowed earlier diagnosis in the children with growth hormonal and radiological characteristics. The anomalies found were pituitary hypoplasia in 32 cases, aplasia of the anterior pituitary in 3 cases; patients with pituitary stalk interruption syndrome (PSIS) in 17 cases. All children with aplasia of the anterior pituitary had MPHD (100%), while 21 % had hypoplasia of the anterior pituitary and 70% had pituitary stalk

interruption syndrome (PSIS). The average age at diagnosis of pituitary hypoplasia is 9 years with extremes ranging from 2 years to 17 years. The growth under GH treatment was similar in the patient groups and did not vary according to the pituitary MRI findings. The annual growth was evaluated as well as the chronology of the appearance of the associated pituitary deficits.

The types and incidence of MRI abnormalities of the sellar region differ significantly between the IGHD and MPHD groups. The progressive worsening of endocrine impairment throughout childhood justifies periodic follow-up to check for additional hormonal deficiencies.

P2-352

Patients with PWS and related syndromes display differentially methylated regions involved in neurodevelopmental and nutritional trajectory

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Background: Prader-Willi syndrome is a rare genetic neurodevelopmental disorder caused by a paternal deficiency of maternally imprinted gene expression located in the chromosome 15q11–q13 region. Previous studies have demonstrated that several classes of neurodevelopmental disorders can be attributed to either over- or under-expression of specific genes that may lead to impairments in neuronal generation, differentiation, maturation and growth. Epigenetic changes that modify gene expression have been highlighted in these disorders. One recent study focused on epigenetic analysis and compared patients with PWS with patients with other imprinting disorders. No study, however, has yet focused on epigenetics in patients with PWS specifically by comparing the mutations associated with this syndrome.

Objective: This study investigated the epigenetic modifications in patients with PWS and patients with PWS-related disorders caused by inactivation of two genes of the PWS chromosomal region, *SNORD116* and *MAGEL2*. Our approach also aimed to compare the epigenetic modifications in PWS and PWS-related disorders.

Methods: We compared genome-wide methylation analysis (GWAS) in seven blood samples from patients with PWS phenotype (5 with deletions of the PWS locus, one with a microdeletion of *SNORD116*, one with a frameshift mutation of *MAGEL2* presenting with Schaaf-Yang syndrome), as well as two control patients.

Results: The analysis identified 29,234 differentially methylated cytosines, corresponding to 5,308 differentially methylated regions (DMRs), which matched with 2,280 genes. The DMRs in patients with PWS were associated with neurodevelopmental pathways, endocrine dysfunction, and social and addictive processes consistent with the key features of the PWS phenotype.

Conclusion: The PWS is associated with epigenetic modifications with differences in *SNORD116* and *MAGEL2* mutations, which seem to be relevant to the different associated phenotypes.

P2-353

Clinical course of primary empty sella in children: a 10-year single-center experience

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Background: Various studies, mostly conducted in adults, evaluated the hormonal axis in primary empty sella (PES), and reported different forms of pituitary deficiencies. We report our 10-year experience of pediatric cases with PES, investigating the pituitary function, associated impairments, and responses to treatments.

Materials and Methods: We reviewed 10,560 cranial and 325 pituitary magnetic resonance imagings (MRIs) performed in our university hospital between January 2010 and December 2020. Cases with additional abnormal MRI findings, history of cranial surgery or radiotherapy, autoimmunity, long-term use of chemotherapeutic or immune-suppressive agents, or incomplete diagnostic evaluation were excluded. Clinical, radiological, and laboratory evaluations were recorded. The results are reported as median (interquartile range, minimum-maximum).

Results: The study included 16 patients [8 girls, 8 boys; median age 12.4 years (8.3, 4.3-17)]. The median size of the pituitary was 2 mm (0.8, 1.2-3). Based on age-dependent pituitary height measurements, fourteen (88%) subjects showed pituitary gland hypoplasia. Five cases presented due to short stature, two had both pubertal delay and short stature, and one had pubertal delay. Eight cases had presented with neurological symptoms including headache, tinnitus, tics, and dizziness. Two of the seven short subjects had normal growth velocities for age with IGF-1/IGFBP-3 levels >0 SD score. The remaining five short subjects had growth deceleration and/or target height discrepancies with low to normal IGF-1/IGFBP-3 levels. All these patients failed to achieve an adequate growth hormone (GH) peak in GH stimulation tests; thus, GH therapy was initiated. The patients with pubertal delay showed normal pubertal responses to gonadotropin-releasing hormone stimulation test. Five of the patients had a baseline cortisol level below 10 mcg/dL. All of them showed normal cortisol responses to stimulation tests. None of the patients had hyper- or hypoprolactinemia, hypothyroidism, or diabetes insipidus. There was no statistically significant association between the size of pituitary gland and the severity of hypopituitarism ($p=0.472$).

Conclusion: The high incidence of pituitary dysfunctions ascertain that this entity should not be considered as a normal variant, instead should be evaluated carefully with appropriate basal and dynamic hormonal testing to identify the varying hormonal dysfunctions.

P2-354

Relation between specific pubertal growth and breast maturation - a longitudinal study in healthy girls

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Background: Few studies have investigated in detail how the pubertal breast maturation in girls is related to the pubertal growth spurt in a longitudinal setting. The golden standard for assessment of secondary sex characteristics for girls includes breast development (B1-B5)¹. The different maturation stages follow the increasing estradiol production from the ovaries also giving rise to the pubertal growth spurt. The QEPS-growth model makes it possible to conduct detailed analyses of pubertal growth and separate total growth into specific pubertal (P-function) height gain and basal/prepubertal growth (QES-functions)^{2,3}.

Objective: To investigate the relationship between the development of breast maturation in healthy girls and their pubertal growth spurt. To visualize the individual variation in the relation between breast maturation and the attained specific pubertal height gain.

Method: The study group included 32 healthy girls who were longitudinally followed during puberty with 1-4 yearly visits, including height measurements and assessments by trained paediatric endocrinologists of breast maturation, by the method of Tanner¹. Maturation was assessed 2-9 times for each girl. Analyses of growth patterns were done with the QEPS-growth model^{2,3}. Pubertal heights were expressed in both cm and by QEPS-growth estimates, i.e. how many % of the specific P-function-pubertal growth that was attained at each visit. Breast maturation was related to % of the specific P-function-pubertal gain attained (P%).

Results: As expected, with increasing stages of breast maturation the specific P-function-pubertal height gain increased, and each girl followed an individual trajectory. However, the individual variation was considerable as seen by the range in the Table below:

Pubertal Stage	Mean P-percent	SD	Range	Mean age (years)	SD
B2	32	21	4 – 83	12.0	1.07
B3	57	15	25 – 82	13.0	1.18
B4	82	10	65 – 96	14.0	1.33
B5	94	6	82 – 100	15.7	1.95

Conclusion: The specific pubertal gain in height has for the first time been analysed and visualized in relation to breast maturation during puberty in girls. We found a clear relation between breast maturation and specific pubertal height gain, demonstrating the validity of the QEPS-model in this new research question. Each

girl followed her trajectory, with broad inter-individual variation in breast maturation versus P%, of the specific P-function-pubertal height gain.

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P2-355

Did Central Precocious Puberty Increase in COVID 19 Pandemic?

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Background: The timing of puberty in children is occurring at an increasingly early age. During the COVID19 pandemic period, children experienced changes such as epidemic stress, sedentary life, and weight gain.

Aim: To make a retrospective evaluation of the incidence of newly diagnosed central precocious puberty (CPP) during the first months of COVID-19. And to compare these corresponding data with the previous year.

Methods: The files of 57 patients who were started GnRH analogue treatment with a diagnosis of CPP between April 1-July 1 2019 (group 1) and April 1-July 1 2020 (group 2) were retrospectively analyzed. We collected and evaluated the auxological, clinical, endocrinological and radiological data in all groups.

Results: 27 patients in group 1 (26 female, 1 boy) and, 30 patients in group 2 (28 female, 2 boys) were diagnosed CPP. The mean ages at the time of diagnosis for Group 1 and 2 were 8.43 ± 1.27 and 7.87 ± 1.11 years, respectively ($p=0.026$). The mean bone ages at diagnosis for Group 1 and 2 were 9.71 ± 1.85 (3.8-13) and 8.72 ± 1.56 (5.5-12) years, respectively ($p=0.024$). The mean ages of treatment initiation for Group 1 and 2 were 8.94 ± 0.88 (6.8-9.9) and 8.07 ± 1.11 (4.8-10) years, respectively ($p=0.001$). The mean birth weights for Group 1 and 2 were 2950 ± 1100 (2300-3400) and 3180 ± 717 (870-3820) grams, respectively ($p=0.012$) (The SGA case number for Group 1 and 2: 4 and 2). The stage 3 breast development at the diagnosis time was found 57% in Group 1. The stage 2-3 breast development at the diagnosis time was found 64% in Group 2 ($p=0.009$). Family history, follow-up time, weight SDS, height SDS and BMI SDS values, pubic hair staging, basal LH, basal E2, peak LH values to LHRH stimulation and ovarian volumes at the beginning of treatment were found to be similar in all groups, but the uterine length was higher in Group 2 ($p=0.09$).

Conclusion: During the COVID 19 pandemic period, it was found that the age of initiation of CPP treatment was earlier. However, no significant factor, such as obesity, was found to be effective on CPP. In our single center experience, COVID 19 did not have a significant effect on CPP. It was thought that the evaluation of these issue with larger series is needed.

P2-356

Delayed diagnosis of paediatric intracranial germ cell tumour (IC-GCTs)

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Introduction: Delays in diagnosis of IC-GCTs in the paediatric age have been frequently reported, affecting outcomes and prognosis.

Aims: This study analysed clinical features of children with IC-GCTs treated at two European tertiary centres in the last 25 years. We retrospectively reviewed time lag between symptoms onset, radiological findings and definitive diagnosis of IC-GCT.

Methods: Presenting symptoms were assessed for each patient. Diagnostic intervals were classified as: total diagnostic interval (TDI), defined as the interval between symptom onset (including retrospective recall of symptoms) and definitive diagnosis of IC-GCT; patient interval (PI), between symptom onset and initial referral to a healthcare specialist; system interval (SI), between specialist evaluation and first brain MRI. They were compared to recurrence and survival rates (median follow-up of 78.9 months from diagnosis).

Results: We collected data of 55 pediatric patients (67.3% males, median age at diagnosis 12 years, IQR 9-16) of which 63.6% had germinomas, 14.5% teratomas, 12.7% mixed GCT and 3.6% yolk sac tumour. 10.9% of cases were metastatic at diagnosis. IC-GCTs were suprasellar (41.8%), pineal (36.4%), bifocal (12.7%). The most prevalent presenting symptoms were related to raised intracranial pressure (RICP) (43.6%); however, by the time of tumour diagnosis, 50.9% of the patients had developed endocrine dysfunctions. All pineal GCTs manifested with RICP, whereas all suprasellar GCTs with endocrinopathies. TDI ranged from 0 to 58.5 months. Eight patients (14.5%) with thickened pituitary stalk were diagnosed with IC-GCT after a median neuroradiological follow-up of 27 months (range 0.25–50). Pineal GCTs had the shortest TDI compared with other locations ($p<0.001$, median 1 months). TDI>6months was observed in 47.3% of patients and was significantly associated with endocrine symptoms at diagnosis ($p<0.001$) and not correlated with age, histology and metastatic disease at diagnosis. SI did not differ significantly among age groups and presence/absence of endocrinopathies. The longest PI (median 18 months, range 8-26.5) was found in those aged >11 years, in which suprasellar germinoma occurred more frequently (75%, $p=0.052$). Five-year progression free survival and overall

survival rates for all patients were 83.6% and 80%, respectively. Patients with TDI>6months showed the tendency towards lower rates of relapses (HR 0.35; $p=0.072$). TDI>6months was not associated with different mortality rates (HR 0.39; $p=0.15$).

Conclusion: Approximately half of our patients displayed a TDI>6months, mostly when endocrine deficiencies were presenting symptoms. Nevertheless, we did not find significant negative impact of delayed diagnosis on progression-free and overall survival.

P2-357

Gonadotropin-releasing hormone analog treatment in children with idiopathic central precocious puberty: a pharmacovigilance study in a pediatric population

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Background: Central precocious puberty (CPP) results from premature activation of hypothalamic-pituitary-gonadal axis, which leads to an increased release of gonadotropin-releasing hormone (GnRH). GnRH stimulates the development of secondary sexual features, rapid bone maturation and growth. GnRH agonists (GnRHa) represent the gold-standard therapy in CPP children and their use is responsible for pituitary GnRH receptors down-regulation, luteinizing hormone (LH) and follicle stimulating hormone (FSH) suppression up to gonadal sex hormones blockade. Several pharmaceutical formulations of GnRHa, such as buserelin, histrelin, leuprolerin, triptorelin and goserelin, are available and used clinically. The treatment is generally safe and well tolerated. However, several studies reported side effects, including bruising, pain, injection reactions and sterile abscesses. Furthermore, flushes, headaches, and nausea were observed and are classified as minor menopausal-like side effects.

Study Design: The present study is intended to: a) identify which side effects were featured in CPP patients; b) discover possible correlations between clinical and radiological parameters and side effects. 85 female patients (median age 7.35 ± 0.67) affected by CPP were enrolled in this retrospective study, carried out from 2018 to 2020. The enrolled patients were treated with leuprolide (46 patients) or triptorelin (39 patients) and minor menopausal-like side effects appearance during therapy was investigated. **Moreover, clinical parameters and radiological changes were monitored to evaluate the possible relationship between GnRHa treatment and side effects appearance.**

Results: Overall 40 (47,1%) of the studied patients reported minor menopausal-like symptoms. Although the bone age was significantly lower in symptomatic patients ($p=0,004$) than in those asymptomatic, no significant differences were observed between symptomatic and asymptomatic patients in chronological age ($p=0,16$), weight ($p=0,20$) and height ($p=0,29$) before treatment. In

addition, symptomatic patients showed a higher ovarian volume and breast growth (BG) than asymptomatic females ($p=0,005$), whereas no significant differences were detected in peak-stimulated or basal LH, FSH and somatomedin C levels between the two groups of patients. Concerning the drug used, 23 patients treated with triptorelin and 17 patients with leuprolide reported symptoms ($p=0,043$). The patients treated with triptorelin or leuprolide showed headache (33,3% vs 15,2%), mood swings (20,5% vs 17,4%), increased appetite (20,5% vs 17,4%) and nausea (2,6% vs 10,9%). Symptoms were managed with analgesics or over the counter (OTC) medications so that it was possible to keep GnRHa treatment.

Conclusion: Our results suggest the need of implementing pharmacovigilance activity in pediatric patients treated with GnRH agonists in order to optimise and personalise the treatment.

P2-358

Pubertal induction in girls with hypogonadism: preliminary prospective data of efficacy in patients with/without initial overnight estrogen replacement

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Background: Pubertal induction in girls with hypogonadism through estrogen replacement therapy (ERT) aims at the development of secondary sexual characteristics, cognitive functions, uterine growth and maturation, bone mass accrual and linear growth. To date, the best induction regimen, capable of assuring both physiological gradual progression through Tanner stages and effective uterine development, is still to be established.

Patients and Methods: we prospectively followed 19 hypogonadal girls (16 with hypogonadotropic hypogonadism and 3 with premature ovarian insufficiency) pre-pubertal (Tanner stage B1) at baseline (mean age: 16.9 ± 2.8 years, range: 11.7-24.8 years), for at least 12 months (range 1.0-4.2 years) after ERT start (transdermal 17 β oestradiol patches). Eleven out of 19 patients started with overnight ERT for six months (0.07-0.1 mcg/kg/day). In all patients, ERT was gradually increased every six months. Progesterone replacement was started in 10 girls at Tanner stage 5 or bleeding occurrence. Auxological, biochemical (17 β oestradiol), pelvic ultrasound and bone age assessment data were collected every 12 months from ERT start.

Results: mean tempo at Tanner stage B3 was 1.2 ± 0.4 years, being negatively correlated with ERT dose/kg at start ($p=0.01$). Mean tempo at Tanner stage B4 was 2.0 ± 0.5 years, being higher in patients with initial overnight ERT ($p=0.02$). Mean tempo at Tanner stage B5 or bleeding occurrence was 2.4 ± 0.7 years, being

positively correlated with uterine maturation (uterine length > 65 mm, $p=0.02$). Mean adult height (AH) was 171.3 ± 6.1 cm (1.24 ± 0.94 SDS WHO), not statistically different from mid-parental height (MPH-AH -0.6 ± 1.4 SDS WHO, $p=0.2$). Uterine maturation was achieved by 71% patient at the end of induction, with final uterine length positively correlated with ERT dose/kg at progesterone introduction ($p=0.02$). No difference was found in uterine length between patients who underwent to initial overnight ERT and others.

Conclusions: our data indicate that (i) initial overnight ERT, resembling the nocturnal activation of hypothalamic-pituitary-gonadal axis and increasing mean tempo at Tanner stage B4, assures a gradual pubertal progression along with an adequate uterine maturation; (ii) delaying Tanner stage 5 achievement and bleeding occurrence seems to be beneficial in terms of uterine maturation. Further multicentric data are needed to confirm these evidences and the possible role of initial overnight ERT replacement.

P2-359

Evaluation of pituitary/cranial imaging results of central-puberty precocious cases

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Introduction: The activation of the GnRH pulse generator before the age of 8 years in girls and 9 years in boys results in central precocious puberty (CPP). The majority of cases of CPP in girls are defined as idiopathic since no organic lesion is found, whereas intracranial lesions are common in boys with CPP. Previous studies have shown that the height of the pituitary gland in the CPP cases is higher than in the normal children. We aimed to evaluate the pituitary gland volume by MRI in CPP children, and explore the intracranial lesions among children with CPP.

Materials and Methods: The study was performed with 50 patients (41 girls, 9 boys) children who had been diagnosed with CPP and receiving treatment with a GnRH analogue. The data of the patients recorded in the hospital's information administration system were retrospectively analyzed. Pituitary MRI was performed in every patient after the diagnosis of CPP. Pituitary gland volume was calculated using Di Chiro's formula ($1/2 \times \text{height} \times \text{length} \times \text{width}$). Pituitary gland volume in CPP children, compared with age/sex matched control subjects. In addition, if available, cranial MRI of patients with CPP were evaluated and recorded for the presence of additional intracranial abnormalities or space-occupying lesions.

Results: The mean chronological age at diagnosis was 7.1 ± 1.0 (2.4-7.9) years in girls and 7.4 ± 1.7 (3.7-8.8) years in boys. CNS imaging showed pathological findings in 17% (7/41) of the girl cases, and 55.5% (5/9) of the boy cases. While there was no difference between girl patients with normal and abnormal MRI in terms of age at diagnosis, height-SDS and BMI-SDS, it was found

that bone age and bone age/chronological age ratio was higher in the group with abnormal MRI. No difference was found between the two groups in terms of estradiol levels, however, basal LH and FSH levels were higher in girls with abnormal MRI. There was no statistical difference between male cases with normal MRI and abnormal MRI in terms of auxological and laboratory parameters. Pituitary volumes of girls aged 6-7.9 years and boys aged 8-8.9 years were found to be increased compared to the control group.

Conclusion: In this study, we found that CNS imaging showed pathological findings in 17% of the girl cases, and 55.5% of the boy cases. Pituitary volumes of girls aged 6-7.9 years and boys aged 8-8.9 years were found to be increased compared to the control group.

P2-360

In vivo magnetic resonance spectroscopy as a non-invasive tool for the identification of a sellar tumour in a boy with precocious puberty

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Aim: To highlight the role of in-vivo magnetic resonance spectroscopy (MRS), as a non-invasive tool that can clarify the specific etiology of a sellar tumour in a boy with precocious puberty.

Case Presentation: A 4-year-old boy was admitted due to repeated episodes of focal seizures with fixed gaze, head turn to the right, and postictal drowsiness. Parents reported episodes of inappropriate laughter ("gelastic seizures") in the previous year. The child was referred to the endocrine department for investigation of possible precocious puberty. Clinical examination was significant for testicular volume 4-5 ml bilaterally, penile length of 7.5 cm, and absence of axillary or pubic hair. Laboratory tests revealed increased gonadotropins and testosterone levels (FSH: 2.2 mIU / ml, LH: 1.65 mIU / ml, testo: 1.65 ng / ml). The levels of CEA, β hCG, AFP, 17-OH-PG, DHEAS, TSH, fT4, and cortisol were normal. Clinical and laboratory findings established the diagnosis of central precocious puberty (CPP). The combination of "gelastic seizures" with CPP in a 4-year-old boy raised the suspicion of a hypothalamic hamartoma. The MRI of the sella turcica region revealed a lobular mass of $2.82 \times 2.42 \times 2.4$ cm with slight heterogeneity, signal intensity similar to grey matter, with no contrast enhancement located in the hypothalamic-suprasellar-mamillary bodies region of the brain, extending to the wall of the 3rd ventricle and in contact with the anterior lobe of the pituitary gland.

The differential diagnosis of the radiographic image included hypothalamic hamartomas, gliomas, and craniopharyngiomas. To further investigate the CNS mass, an in vivo MRS of the brain was performed.

The metabolites that were detected were N-acetyl aspartate (NAA), creatine (Cr), choline (Cho), and myoinositol (MI), as well as lipids and macromolecules. Compared to the spectrum of healthy controls, the NAA / Cr quotient was lower (30% of normal), the Cho / Cr quotient was normal and the MI / Cr quotient was slightly elevated. These findings, in combination with the findings of conventional MRI, were consistent with the diagnosis of a hypothalamic hamartoma.

Conclusion: Hypothalamic hamartoma is the most common type of CNS tumour that causes CPP, especially in very young children, and is often associated with gelastic seizures. MRS is a state-of-the-art, non-invasive, imaging technique that compares the chemical composition of normal tissue to that of abnormal regions, by juxtaposing the frequency of measured metabolites. MRS, in combination with clinical evaluation and classic MRI, can provide identification of CNS masses, thus eliminating the need for an invasive biopsy.

P2-361

Rahman Syndrome: Hypopituitarism might be responsible for changing height pattern

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Objective: Histones have important structural and regulatory roles mediating the dynamic packaging of DNA. The dysregulation of histone modification leads to overgrowth syndromes, such as Sotos and Weaver syndrome. Recently heterozygous variants in *HIST1H1E*, which encodes linker histone H 1.4 has been associated with Rahman Syndrome, which is characterized by a very rare complex phenotype consisting of overgrowth, dysmorphism, and intellectual disability. Growth pattern is typical and shows overgrowth in early ages decreasing over time. Here we report a new case of Rahman syndrome presenting with a novel finding of hypopituitarism.

Case: A 11^{7/12} years-old-boy was referred for hypothyroxinemia with normal TSH. He was born at 36 weeks, with a birth weight of 3660 gr (+2.37 SDS) and length of 52 cm (+1.63 SDS). There was a complaint of tiredness, weight gain, hair loss, slowing of thoughts, and tendency to sleep for two months. On examination, his height, weight and target height were 158 cm (+1.46 SDS), 61 kg (+1.72 SDS) and 183.5 cm (+1.18 SDS) respectively. He had high anterior hairline, prominent forehead, sparse eyebrows, wide nasal bridge, hypertelorism, prominent cheekbones, dental erosions, simple auricles, fleshy hands and ears, pes planus, camptodactyly, kyphoscoliosis, pectus carinatum, and mild mental retardation. Repeated thyroid function tests and symptoms were consistent with central hypothyroidism. Evaluation for other pituitary functions revealed central adrenal insufficiency. Levothyroxine and hydrocortisone

replacements were initiated. Although the patient was growing well with IGF1 and IGFBP3 within normal limits, very low growth hormone (GH) response to clonidine and L-dopa stimulation tests (L-dopa and clonidine stimulated peak GH: 2.13 mcg/L and 3.06 mcg/L respectively) were noted. Pituitary MRI was normal. A whole exome analysis was performed and revealed a de-novo heterozygous 1bp duplication in *HIST1H1E* (p.Ala145Glyfs*51), which predicted a truncated protein. The duplication was located in the carboxyl-terminal domain where all previously reported variants have been located.

Conclusion: Our case is the first case of Rahman syndrome with complete endocrine evaluation and shows hypopituitarism as a novel manifestation of the disease. This finding might explain previously unexplained progressive decline in height percentile with age in Rahman Syndrome. Normal IGF-I and IGFBP-3 levels despite bona fide GH deficiency remains to be explained.

Key Words: Overgrowth, hypopituitarism, *HIST1H1E*, Rahman syndrome

P2-362

Congenital hypopituitarism: the role of genetics

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Hypopituitarism refers to the insufficient secretion of one or more pituitary hormones. If default is present at the time of birth is called congenital hypopituitarism (CH). Causes of this are perinatal pathology and genetic alterations.

The clinical presentation is heterogeneous. The diagnosis is made by clinical suspicion supported by hormonal determinations, brain imaging test (MRI) searching of structural defects and genetic study.

The development of the pituitary gland is a complex process regulated by specific transcription factors. Mutations in precursor genes result in different degrees of hypopituitarism, which may be associated genes are PROP1, POU1F1, LHX3, LHX4 and HESX1. In recent years, due to advances in genetic sequencing techniques, a large number of genes associated with etiology of CH have been known. The type of inheritance shows great variability.

We present the cases of two pairs of siblings affected by CH of genetic etiology.

Case 1: 24-month-old-male patient, under study for short stature, an imaging test (MRI) is performed, in which structural alteration of the pituitary area is observed (pituitary hypoplasia, absence of pituitary stalk and ectopic neurohypophysis). In the genetic study there was a heterozygous pathogenic mutation in the *GLI2* gene. His younger brother also shows short stature, the directed study was carried out, with a heterozygous pathogenic mutation of the same gene. The MRI showed the same structural alteration as his brother. The family genetic study revealed that the mother of both is a carrier of the pathogenic mutation.

Case 2: 21-month-old female patient, under study due to short stature and hypoglycemia. She had a history of congenital

strabismus. The imaging study shows a structural alteration of the pituitary gland and a disturbance in the gene FOXA2 in the genetic study (heterozygous pathogenic mutation). A study was carried out on his 7-month-old brother with short stature and hypoglycemia, with an alteration in the same gene and the same imaging at pituitary gland. The family genetic study revealed that the father of both is a carrier of the pathogenic mutation.

In both cases, the similar clinical presentation in the siblings allowed us to conduct a directed family genetic study of the affected genes. The most appropriate approach to the study of the genetic etiology of CH should be through massive sequencing studies, with caution at interpreting the results and approaching a possible family study and genetic counseling.

P2-363

Pedigree analysis is essential for clarifying oligogenic transmission in a family with congenital hypogonadotropic hypogonadism (CHH)

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Background: Congenital hypogonadotropic hypogonadism (CHH) is a rare disease with a complex clinical picture and genetic background. In up to 50% genetic mutations are found. The goal is to be able to provide a comprehensive prognosis and genetic counseling for this family with CHH.

Case Presentation: At the age of 16 years a boy with familial constitutional delay (adrenarche only with 15 years, no growth spurt, bone age 14 years) presented at our clinics with pubertal stage P2, G1 (left testis inguinal, right descended, small phallus < -2 SD), ax.1. Hypogonadotropic hypogonadism was diagnosed by LHRH and HCG testing. Within 3 years, the patient showed adequate virilization and an increase in testicular volume to 6 ml under his choice of gradually increased testosterone therapy. In addition, the patient had a cleft lip and palate and congenital deafness on the right and acquired deafness on the left from his 4th year of life, both caused by otosclerosis, necessitating a cochlear implant. Family history (our patient was son 3) was striking for many symptoms of complex CHH: Puberty was delayed in both parents and all 5 sons, cleft lip/palate was present in the father and the 4 youngest sons, oligotonia in the 3 last sons, cryptorchidism in the 3 middle sons, renal duplication in the 4th son, suspected hearing impairment in the 3rd and 5th son.

Results: Genetic tests showed a monoallelic *NOS1* mutation in the father and the three middle sons, consistent with an autosomal dominant mode of inheritance. Caused by the oligogenic mode of inheritance only our patient had CHH: He inherited the genetic background of delayed puberty of the father (*NOS1* mutation) AND the mother (other unknown mutation).

Conclusion: While *FGFR1* and *CHD7* have been reported as the most commonly mutated genes in CHH, a *NOS1* mutation has also been suggested to be pathogenic if oligogenic (Quaynor

Mol Cell Endocrinol. 2016). In light of the fact that studies are underway to causally treat gonadal insufficiency with a nitric oxide synthase inhibitor in a cryptorchid mouse model (DeFoor J Urol. 2004), knowledge of this mutation found is even more important for offspring of this family.

P2-364

Congenital hypogonadotropic hypogonadism associated with X-linked ichthyosis due to X-chromosome microdeletion identified by chromosomal microarray

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Objective: To assess diagnostic usefulness and accuracy of different tools in patients with Kallmann syndrome and ichthyosis due to X-chromosome microdeletion. **Materials:** congenital hypogonadotropic hypogonadism due to *KAL1* pathological variants manifest with micropenis, cryptorchidism, delay of puberty, and not associated with disorder of sex development. This condition can be associated with ichthyosis due to deletion of X chromosome region with genes *KAL1* and *STS* (steroid sulphatase gene). We report the clinical cases of 2, XY siblings with Kallmann syndrome associated with ichthyosis and different clinical features of the disease. The ichthyosis was diagnosed at birth in both of them. One boy was born with micropenis and bilateral cryptorchidism. At the age of 7 months, his height SDS was 0.28 SD, LH 0.001 IU/ml, FSH 0.4 IU/ml, AMH 0.58 ng/ml, testosterone 1.6 nmol/l. Uterus was absent on ultrasound. During hCG stimulation test (5000 IU) level of testosterone increased to 1.82 nmol/l. After 12 months of topic androgens use the length of penis increased up to 2.5 cm. Because of micropenis, unpalpable bilateral testes, inadequate testosterone level after hCG test, next generation sequencing (NGS) was performed to analyse 38 genes associated with disorders of sex development. It revealed the variant with uncertain significance in gene *MAMLD1*. His elder brother (patient 2) was admitted to the endocrinological department at the age of 12 due to hypoplasia of both testes combined with ichthyosis. His height SDS was 0.87 SD. Tanner stage 1. Penis length ~ 5.1 cm, both testes were in scrotum. D=S=0.45 ml (by ultrasound). Bone age was 11-12 years. LH 0.06 IU/ml. FSH 0.84 IU/ml, AMH 23.7 ng/ml, inhibin B 11 pg/ml. Due to ichthyosis, testes hypoplasia and younger brother with micropenis and bilateral cryptorchidism chromosomal microarray analyses were performed in both boys. Microdeletions in Xp22.3 region from position 6533602 to position 8791660 were identified in both sibs. This region include *KAL1* (OMIM 308700) and *STS* genes (OMIM 308100). The patients were diagnosed with contiguous gene syndrome. **Conclusion:** Congenital hypogonadotropic hypogonadism can be misdiagnosed with sex disorders due common features, such as to combination of micropenis and bilateral cryptorchidism. The majority of cases can be diagnosed with NGS. However, the results of NGS with the variants with uncertain

significance must be carefully interpreted together with clinical features. Clinical features analysis can help the clinicians to choose the best diagnostic tool, to diagnosis the disease and initiate the therapy timely.

P2-365

Gonadotropin Flare with Different Depot GnRH

Agonists: Comparative Analysis

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Central precocious puberty (CPP) is effectively treated by inhibition of GnRH signaling through GnRH receptor desensitization with depot GnRH agonists (dGnRHa), but the first injection is associated with a surge in LH and FSH (flare) that proportionally increases estradiol levels. When estradiol levels drop, usually within a fortnight, vaginal bleeding may be seen in a small number of girls.

Although dGnRHa that use higher, longer-acting doses are increasingly being used in girls with CPP, as they reduce the number of injections/year, the magnitude of the flare caused by each of them has not been compared.

One concern that pediatric endocrinologists may have when administering higher doses of dGnRHa is the possibility of greater flare with unwanted consequences such as vaginal bleeding.

Objective: To compare gonadotropin levels during the flare in the first dose of two dGnRHa preparations that differ in dose, intervals, and route of administration in girls with CPP.

Methods: 29 CPP girls from our center were included; n=17 received **Triptorelin 3.75 mg** intramuscular route monthly (**Trip 3.75**) and n=12 received **Leuprolide 45 mg** subcutaneous route biannually (**Leu 45**) as first dose of treatment (data of Leu 45 were obtained from TOL2581A trial). The patients were not randomized to treatment. LH and FSH levels were measured (by ECLIA) at 3 hrs (Trip 3.75 group) and at 4 hrs (Leu 45 group). Clinical characteristics and gonadotropins levels were assessed.

Results: Chronological age (CA), bone age (BA), BA-CA, breast Tanner stage, growth velocity (GV) and BMI were comparable between groups. No patients experienced vaginal bleeding. The median LH flare was 15.5(7.8-46.8) IU/L in Trip 3.75 group and 26.4(14.4-62.9) IU/L in the Leu 45 group (p=NS). The median FSH flare was 19.3(11.6-38.6) IU/L in Trip 3.75 group and 18(6.9-30.5) in Leu 45 group (p=NS).

	Trip 3.75	Leu 45 mg	p
CA(years)	8.2 ± 0.6	8. ± 0.5	NS
CA-BA (years)	1.7 ± 0.7	2 ± 0.65	NS
GV(cm/year)	8.1 ± 1.9	9.3 ± 2	NS
BMI	18.5 ± 2.4	17.8 ± 2	NS
BTs n(%)	3 17 (100%)	11 (90%)	NS

Conclusion: Similar LH-FSH flare was observed in both groups. Leuprolide 45 mg, long-acting, biannual administration did not induce a significant higher gonadotropin flare as compared to the monthly Triptorelin 3.75 mg. This result suggests that there should be no concerns regarding flare when using Leuprolide 45 mg to initiate treatment of CPP in girls.

P2-366

Hypothalamic obesity in children with craniopharyngioma

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Introduction: Lesional hypothalamic obesity is most frequently attributable to craniopharyngiomas.

The aim of our work is to describe the modalities of occurrence of this complication in a series of 27 children with craniopharyngioma followed in our center.

We carried out a descriptive retrospective study of 27 cases of craniopharyngioma in children followed in the endocrinology department of the CPMC over a period of 16 years.

Results: We found 6 cases of hypothalamic obesity called group 1 and 13 patients of normal weight called group 2, with 08 patients lost to follow-up. Group 1 was younger at diagnosis, with an average age of 6 years and 7 months, while the average age of group 2 was 8 years and 4 months.

A clear male predominance in group 1 whereas the sex ratio of the second group was 1: 1.

The initial BMI was correct in the majority of patients in all groups; varying between -1DS to +1 DS, only one case presented a BMI between +2 and +3 DS in group 1.

Hypothalamic-pituitary MRI revealed a purely suprasellar site lesion in 66.7% of patients in group 1; and in group 2 the suprasellar and suprasellar lesion had predominated with 69.2% and the purely suprasellar lesions were only represented at 15.4%. The size of the lesion was in 50% of cases between 20 and 40 mm in the patients of group 1 while the lesions objectified in the second group were larger because in 46.2% their dimensions varied from 40 to 60 mm.

The treatment consisted of first-line so-called total excisional surgery in all patients in group 1, and complementary conformational radiotherapy and yttrium. The average radiation dose was 53.4 Gy

In group 1 The BMI at the last check-up improved for only one case, the other patients had a BMI of between +2 and +3 DS, while the BMI of group 2 was correct.

Conclusion: The prevalence of hypothalamic obesity in our series is in line with the literature. The patients in group 1 were younger at diagnosis compared to group 2. They also presented with suprasellar developing craniopharyngiomas in 66.5% against only 15.3% in group 2. surgical management was less conservative in group 1 or first-line resection, considered to be complete, was performed in all patients. fact known as a risk factor for hypothalamic injury. In group 2 only 38.4% benefited from a surgical excision which was considered partial.

Duplication of Pituitary Gland-plus Syndrome presenting with a Transcranial Nasal Dermoid Cyst

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Duplicated pituitary gland in association with other midline craniofacial anomalies – also described as DPG-plus syndrome – is extremely rare. So far the only described endocrine associations are precocious or delayed puberty.

We describe the multifaceted management of a female infant with DPG-plus syndrome. Interestingly, the patient also presented with trans-cranial nasal dermoid cyst and a nasal dimple with protruding hair, which has not been described in previous cases.

Our patient, the first child of a non-consanguineous Caucasian family, was diagnosed with cleft palate and an unusual lump on the dorsum of her tongue immediately after birth. She was started on assisted bottle feeding and referred to the cleft palate surgeon. Before this appointment could happen, she was hospitalised twice with complaints of respiratory distress during feeding and in flat position. At 11 weeks of age, she was seen by the cleft surgeon, who identified a wide palatal cleft with a large nasopharyngeal mass partly filling the defect. He also noted a nasal dermoid cyst, a nasal dimple with protruding hair, hypertelorism, retrognathia and low-set ears. The patient's first MRI brain scan at 5 months of age revealed duplicated pituitary gland, thickening of the floor of the third ventricle (hypothalamic hamartoma), duplication of basilar artery, cleft in odontoid peg, large right nasopharyngeal teratoma intimately related to nasal septum, and trans-cranial nasal dermoid cyst extending through the nasal bones to just above the cribriform plate. A skull-base CT scan confirmed the midline cranial osseous defect. The patient was diagnosed with DPG-plus syndrome.

Resection of nasopharyngeal mass and tongue polyp was performed at 8 months of age, which remarkably reduced the patient's breathing and feeding difficulties. Histopathology revealed the nasopharyngeal mass to be a mature benign teratoma and the tongue polyp, a hamartoma. The cleft palate was repaired at 15 and the trans-cranial dermoid cyst and nasal pit were resected at 27 months of age. The dermoid cyst was lined by keratinised squamous epithelium and contained adnexal structures with no evidence of malignancy.

At 3 years of age, the patient shows normal growth, development and neurological examination. Baseline endocrine tests at 7, 16 and 27 months of age were normal. She will need long-term neuroendocrine surveillance, specifically for central precocious puberty and any recurrence of nasopharyngeal or intracranial pathology.

This case report adds significantly to the growing body of literature on the clinical presentation and complex management of children with DPG-plus syndrome.

Sterile Abscess Formation with Two Different GnRH Analogues: Three Case Reports

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Introduction: Gonadotropin releasing hormone analogs (GnRHa) have been used safely for many years in the treatment of central precocious puberty(CPP).Although rare; pain,swelling,erythema at the injection site are known local side effects in patients receiving GnRHa treatment and are temporary. Sterile abscess(SA) development is also one of the rare local side effects.We presented three cases of treatment failure due to the development of SA after GnRHa therapy.

Case Presentations: The patients who were followed up with CPP between 2018-2020 in our clinics were evaluated.We found the three sterile abscess(1.07%) of the 278 patients [receiving triptorelin acetate(TA) or leuprolide acetate(LA)].The laboratory and clinical characteristics of the cases are summarized in Table-1.In the first case, SA recurred despite the treatment was switched to the another preparation.We had to stop treatment in all cases.

Conclusion: Although SA is a rare side effect, it is very important as it causes patients to be left untreated.In our cases, the active substance of the drug accumulates in the localization of SA and cannot be absorbed, so it cannot enter the systemic circulation. Therefore, puberty cannot be suppressed.Also, often leaving a scar is annoying for patients and their families.We suggest that if a dose increase is required,SA may develop.For this, we recommend the injection site check.If SA develops, we recommend discontinuing the treatment and not insisting on treatment.

Table 1. Clinical and laboratory characteristics of the patients at admission

Cases	1	2	3
Age(years)	6 ^{5/12}	7 ^{2/12}	8 ^{7/12}
Complaint	Pubic hair	Breast development	Breast development
Weight SDS	2.38	1.62	1.8
Height SDS	2.66	0.38	1.23
BMI SDS	1.48	1.73	1.58
Breast&Pubic hair stage(Tanner)	III&III	III&I	III&III
Bone Age(years)	11	8 ^{10/12}	11
Mother'/Father' height(cm)	Not available (adopted)	149/170.6	160/171
Basal LH&FSH (mIU/L)	0.1&2	<0.07&2.41	9.41&7.79
E2(pg/ml)	<12.1	12.9	45.7
Peak LH&FSH after LHRH stimulation	24.2&17.57	9.27&14.6	-
Standard dose ACTH stimulation	Peak cortisol 10 mg/dl, peak 17OHP 42.2 ng/ml		
Pelvic Ultrasound	Pubertal	Pubertal	Pubertal
Tryptase(mg/l) (N:<11.4 ng/ml)	-	38.6	3.98
Diagnosis	CAH+CPP	CPP	CPP
Treatment	Hydrocortizone+LA	LA	LA
Which drug causes steril abscess	LA and TA	LA	LA
The last drug doses	7.5 mg/28 days	3.75 mg/28 days	7.5 mg/28 days
The timing of steril abscess	4. dose	12. dose	5. dose
Injection site change	Scar	Scar	Scar

P2-369**6-Month GnRHa Formulations Are a Good Choice During the COVID-19 Pandemic and Beyond**

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Introduction: Achieving/maintaining effective hormone suppression is fundamental in treating Central Precocious Puberty (CPP). CPP patients are vulnerable to late dosing as they cannot self-administer and require clinic/hospital visits for injections, currently exacerbated by COVID-19. In children, the hypothalamic-pituitary-gonadal axis may rebound faster than elderly oncology patients, so hormone escapes are possible with late dosing. Additionally, the stimulatory flare from GnRH agonists (GnRHa) increases risk of escapes with late injections. Longer duration formulations demonstrating hormone suppression through the dosing interval should be considered. 6-month formulations typically require two office visits/year with only two opportunities to be 'late'. A novel 6-month small-volume, subcutaneously administered GnRHa treatment for CPP approved in 2020 effectively suppressed pubertal hormones and pubertal progression. As large

numbers of CPP patients are not present in real-world databases, we present data below in prostate cancer (PCa) patients treated with drugs with the same active ingredient and similar mechanisms of action.

Methods: A retrospective analysis (1/1/07-6/30/16) of US oncology/urology hospitals, multispecialty practices, small group practices, and physician offices EMR of PCa patients receiving GnRHa injections (n=85,030) was conducted to evaluate the frequency of late injections and testosterone(T) >50/20ng/dL (target levels in PCa). Mean late doses/year for 1,3,4,6-month GnRHa doses were calculated by multiplying late dose proportion and number of doses/year. Late dosing was defined as occurring after days 33,98,129,195, respectively.

Results: 84% of GnRHa were administered later than scheduled. Number of late doses/year for 1,3,4,6-month GnRHa formulations were 5.4,0.8,0.8,0.6 respectively. 27% of T values exceeded 50ng/dL with late dosing compared to only 4% with early/on-time doses. 43% of T values exceeded 20ng/dL for late injections compared to only 21% for early/on-time injections.

Conclusions: 6-month GnRHa formulations require fewer visits for treatment, which will likely be preferred by patients and clinicians, especially during a pandemic. 6-month formulations had fewer late doses/year vs. 1,3,4-month formulations. Late injections in PCa patients were correlated with ineffective T suppression: T levels were >50ng/dL over 25% of the time. Late dosing increased the proportion of T >20ng/dL compared to early/on-time dosing.

Clinicians should ensure dosing is on time or consider using 6-month formulations that have less frequent opportunities for late dosing and demonstrate/maintain efficacy through the labeled dosing. This will give greater confidence in continued hormone suppression when late. Similar studies should be conducted to assess the impact of late dosing of GnRHa in CPP patients.

P2-370

Size Matters: CAG Repeat Length of the Androgen Receptor Gene, Testosterone, and Male Adolescent Depression Severity

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Background: There is a distinct increase in the prevalence of depression with the onset of puberty. The role of peripubertal testosterone levels in boys in this context is insufficiently understood. Moreover, the number of CAG repeats of the androgen receptor gene (AR) and the depression status (subclinical vs. overt depression) may modulate the role of testosterone, but this has not yet been studied in a clinical sample.

Methods: Cross-sectional data from 118 boys treated as in- or daycare patients at a single psychiatric hospital were subjected to higher-order moderation analysis in the multiple regression framework, accounting for multiple confounders of testosterone levels.

Results: There was a constant relationship between free testosterone and the severity of depressive symptoms irrespective of the number of CAG repeats in adolescents with subclinical depression (Beck Depression Inventory-II (BDI-II) score ≤ 13 ; $n = 45$). In adolescents with at least mild overt depression (BDI-II score > 13 ; $n = 73$), however, there was a significant negative relationship between free testosterone and the BDI-II score in patients with less than 19 CAG repeats and a significant positive relationship in those with more than 28 CAG repeats.

Conclusions: These results suggest that the effects of testosterone on mood in male adolescents with depression depend on the genetic make-up of the AR as well as on depression status. This complex relationship should be considered by future studies

addressing mental health issues against an endocrine background and may, moreover, contribute to tailored treatment concepts in psychiatric medicine, especially in adults.

P2-371

Is quail egg a potential endocrine disruptor?

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Aim: Quail egg (QE) consumption became popular among children for alleged health benefits. Based on our observation of premature thelarche (PT) in a few children who consumed QE, we investigated the relationship between QE and puberty by a clinical and an experimental studies.

Method: In the clinical study, a questionnaire was used to compare the frequency and amount of QE consumption (between 55 girls with PT ($n=55$) and 54 age-matched control girls who had well-controlled type-1 diabetes mellitus. In the experimental study, Female Sprague-Dawley rats were orogastrically given QE (300, 1000 mg/kg/day) or 17 β -estradiol (E2, 50 mg/kg/day) or tap-water (control) starting by postnatal 14th day and continued until 30th day. Anthropometric measurements and the age of vaginal opening were recorded, vaginal smears were analyzed. Following sacrifice, serum FSH and estradiol levels were measured. Histological examination of uterus and ovaries were performed. Data were compared using chi-square (patients) and one-way ANOVA (rats).

Results: QE consumption in the diabetic control girls was either mild (20.4%) or moderate (7.4%), while a heavy QE consumption (20%) along with moderate (21.8%) and mild (18.2%) intake was present in PT-girls ($p<0.01$). Uterine and ovarian weights of E2- and QE-treated rats were higher than those of the control group. Vaginal smear analysis and histological analysis confirmed elevated counts of vaginal cornified cells and high numbers of endometrial glands of uterus, indicating enhanced estrogenic activity in QE-treated ($p<0.05$) and E2-treated ($p<0.001$) rats, while FSH and estradiol levels were increased compared to control group of rats ($p<0.05-0.01$).

Conclusions: Both our clinical observation of a higher quail egg consumption in girls with PT and experimental data demonstrating increased uterine and ovarian weights, elevated serum estradiol and FSH levels, and cornification of vaginal epithelium suggest that quail egg needs to be further investigated as a potential endocrine disrupter in children.

Keywords: Quail egg, precocious puberty, premature thelarche, endocrine disruptor

P2-372

The impact of the Covid-19 pandemic on the UK National Hypothalamic-pituitary Axis Tumour (HPAT) multidisciplinary meeting

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Background: The HPAT multi-disciplinary meeting (MDT) was set up in 2011 with the aim to improve collaboration with other hospitals treating children with rare paediatric suprasellar brain tumours. It is a monthly remote meeting conducted virtually.

Objective: To evaluate the impact of COVID19 pandemic by comparing the number of meetings, cases (news/ previously discussed), diagnosis, attendees, specialties, centres and outcomes (review of diagnosis, investigation plan, management and follow-up) pre and post-covid.

Methods: Retrospective descriptive study conducted between January 2019 and April 2021. Data was collected from the minutes generated after each patient discussion.

Results: PRE-COVID (January 2019-February 2020): 12 meetings were held and 42 cases discussed (median 3/meeting, range: 3-5): 8 craniopharyngiomas, 6 prolactinomas, 6 thickened pituitary stalks, 5 Rathke's cysts, 5 astrocytomas, 2 teratomas, 2 germinomas, 3 non-functioning pituitary adenomas, 1 optic pathway glioma, 1 pars intermedia cyst, 1 pineal papillary tumour, 1 ectopic pituitary gland and 1 Cushing disease 32 were new cases (76%) and 10 previously discussed (24%). 119 professionals attended (median 9/meeting, range: 5-15) from 5 different specialties: 92 endocrinologists (77.3%), 9 oncologists (7.5%), 8 neurosurgeons (6.7%), 8 radiologists (6.7%) and 1 nephrologist. 12 centres participated (all from the UK). Diagnosis was reviewed in 18 cases (43%), investigation plan in 19 (45%), management in 19 (45%) and follow-up in 16 (38%).

POST-COVID (March 2020-April 2021): 11 meetings were held (March, April and May 2020 cancelled due to the pandemic) and 50 cases discussed (median 4/meeting, range: 3-6): 9 thickened pituitary stalks, 8 craniopharyngiomas, 8 prolactinomas, 4 Rathke's cysts, 3 pituitary adenomas, 2 Cushing disease, 1 germinoma and 1 astrocytoma. 43 were new cases (86%) and 7 previously discussed (14%). 227 professionals attended (median 21/meeting, range: 17-26) from 4 different specialties: 169 endocrinologists (74.4%), 30 oncologists (13.2%), 16 neurosurgeons (7.04%), 12 radiologists (5.2%). 19 centres participated including UK, Ireland and the Netherlands. Diagnosis was reviewed in 24 cases (48%), investigation plan in 33 (66%), management in 21 (42%) and follow-up in 24 (48%).

Conclusion: It is clear there is an increasing interest in participating in the HPAT MDT despite the current COVID pandemic. The number of cases presented, professionals engaged and centres involved has actually increased significantly during the COVID period. Therefore, a national, regular, virtual HPAT MDT is feasible and welcomed, facilitating dialogue amongst a wider specialist professional group and benefiting the management of the patients with rare hypothalamo-pituitary axis tumours.

P2-373

Evaluation of Clinical, Laboratory and Radiological Findings in the Differential Diagnosis of Premature Telarche and Central Puberty Precocious

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Introduction and Aim: Central puberty precocious (CPP) is defined as the development of secondary sex characters due to the activation of the hypothalamus-pituitary-gonad axis before the age of eight in girls. Premature telarche (PT) is defined as isolated breast development in girls without other findings of puberty. We aimed to evaluate the clinical, laboratory and radiological findings used in the differential diagnosis of PT and CPP.

Material and Method: The study included girls accompanied of breast development before age of 8 and diagnosed with CPP or PT. Patients' calendar age, bone age, bone age/calendar age ratio, anthropometric variables, puberty stages, LH, FSH and Estradiol levels, ovarian and uterine volumes were examined retrospectively.

Results: The study included sixty-five girls 53.8 % PT (n=35) and 46.2% CPP (n=30). Height SD values (p=0.008), basal LH, FSH and estradiol levels (p=0.029, p=0.008, p=0.011, respectively), right and left ovaries and uterine volumes (p=0.030, p=0.008, p=0.039 respectively) bone age (p=0.039), and bone age/calendar age ratios (p=0.024) were found different between two groups. The importance order of the parameters used in the differential diagnosis of CPP and PT was found as basal LH level, ovarian volume, height SD value, and estradiol level.

Conclusion: In our study, our patients with CPP were taller than their peers with PT, had higher LH, FSH and estradiol levels, larger ovarian and uterine volumes, higher bone ages and higher bone age/calendar age. We found that the most important parameter in diagnosis was basal LH level.

P2-374

Crooke Cell Adenoma as a Rare Cause of Recurrent Cushing Disease: A Challenge in Treatment and Follow-Up

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Introduction: Crooke's cell adenoma (CCA) is an aggressive subtype of corticotroph adenoma, it is usually large, frequently invades surrounding tissues, and is resistant to both surgery and radiotherapy.

Case Report: A 13-year-old girl, admitted with weight gain for more than 3 months. Her height was 147.5 cm (-1.5 SDS), weight 58.5 kg (1.1 SDS), BMI 26.89 kg/m² (2 SDS) and blood pressure was 100/78mmHg. Her physical examination revealed truncal obesity, buffalo hump, moon-shaped face, acanthosis nigricans, abdominal striae and Tanner stage IV puberty. Early morning fasting blood glucose, lipids and thyroid function tests were normal, but serum cortisol was elevated and had lost its diurnal rhythmicity. 24-hour free urine cortisol level was high: 193 ug/L (4-56). The serum cortisol level was not suppressible (20.1 ug/dL) by low-dose dexamethasone, but was suppressed to 1.09 ug/dL by high-dose dexamethasone test. A pituitary magnetic resonance imaging (MRI) did not reveal a discrete adenoma and bilateral inferior petrosal sinus sampling showed that the pituitary was the source of Cushing syndrome. The interpetrosal sinus ACTH gradient indicated ACTH to the right side. Transsphenoidal right-sided pituitary adenectomy was performed, and pathology result revealed Crooke cell adenoma. Postoperatively she had a normal pituitary reserve, with the exception of hypothyroidism and was commenced on thyroxine therapy. Three years later, she re-presented with rapid weight gain, menstrual cycle irregularity. In this time, her weight was 82.8 kg (3.0 SDS), height 156.6 cm (-1.09 SDS) and BMI was 33.7 kg/m² (3.2 SDS). Early morning ACTH and cortisol levels were 51.8 pg/mL and 23.9 ug/dL respectively. Her 24-hour urinary free cortisol level was 46.26 ug/L (3-43). MRI examination revealed postoperative changes and 5x5 mm adenoma on the right hemisphere of the hypophysis. Cabergoline treatment was initiated for the patient. However, there was no response to the treatment within 3 months and the operation was planned for the second time.

Conclusion: Crooke's cell adenoma is a rare cause of Cushing's disease, which is difficult to treat and has a high risk of recurrence.

P2-375

Salivary sex steroids as markers of puberty in boys during late childhood and adolescence

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Introduction: Salivary androgens represent a non-invasive marker of puberty that may have utility in population studies as well as in the clinical arena.

Objectives: To establish normal reference values of salivary androgens using LC-MS/MS and demonstrate the correlations between salivary androgens and pubertal development in boys.

Methods: School-based adolescent cohort study with two time points for collecting saliva samples two years apart. Five androgens (Testosterone; T, androstenedione; A4, 17-hydroxyprogesterone; 17-OHP, 11-ketotestosterone; 11-KT and 11β-hydroxyandrostenedione; 11OHA4) were analyzed in saliva samples using LC-MS/MS. In addition, self-reported assessment of puberty through the Pubertal Development Scale (PDS) was also collected at both time points. Receiver-operating characteristic (ROC) curves were used to determine the areas under the curves (AUCs), of each androgen as a predictor of self-reported voice maturation.

Results: A total of 1,166 saliva samples were available from 929 boys aged between 11-16 years at either baseline or follow up or both time points with the median age of 12.3 yrs (range 11.3-13.2) and 14.3 yrs (range 13.4-15.8) at baseline and follow up time point, respectively. Median salivary T increased from 7 pmol/L (10th, 90th centile, 5, 41) in participants aged 11-12 yrs to 122 pmol/L (21.6, 267.4) in participants aged 15-16 yrs and median salivary A4 increased from 53 pmol/L (26.2, 92.0) in participants aged 11-12 yrs to 144 pmol/L (50.7, 241.2) in participants aged 15-16 yrs. In a subgroup analysis of 147 saliva samples that were collected within 90 days before or after PDS, salivary T and A4 concentrations showed the highest correspondence with self-reported voice-breaking (One-way ANOVA $p < 0.005$). ROC curve analysis showed that a salivary testosterone of 82.7 pmol/L and a salivary A4 of 113.4 pmol/L provided a sensitivity of 77% and 74%, respectively and a specificity of 76% and 74%, respectively. Salivary T concentrations revealed the highest linear correlation with salivary A4 ($r = 0.75$; $p < 0.01$) while the other androgens showed a lesser degree of correlation with salivary T with 17-OHP ($r = 0.58$; $p < 0.01$), 11-KT ($r = 0.39$; $p < 0.01$) and 11-OHA4 ($r = 0.27$; $p < 0.01$).

Conclusions: In boys aged 11-16 yrs, an increase in salivary T and A4 is associated with self-reported pubertal progress including voice change. These two biochemical markers represent valid non-invasive biomarkers of puberty in population studies.

P2-376

Efficacy of cabergoline in the treatment of pituitary macroadenoma complicated in a 14-year-old girl

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Introduction: Pituitary adenomas in children are rare and account for 3% of intracranial tumors in the pediatric population (1), dominated by prolactinomas and corticotrophic adenomas, but plurisecreting adenomas are exceptional. We report a case of a 14-year-old girl with a pituitary macroadenoma with a

prolactin-predominant plurisecretory immunohistochemical profile revealed by an intracranial hypertension syndrome with a good therapeutic response to cabergoline.

Observation: A 14-year-old girl presented to the emergency department with asthenia and intracranial hypertension syndrome. Clinical examination revealed signs of central hypothyroidism and hypocorticism, an impuberism, with a growth delay (-2 SD for weight and height) and visual impairment. Laboratory investigations revealed thyroid, corticotropic and gonadotropic insufficiency contrasting with surprisingly normal prolactinemia confirmed by the absence of the hook effect, and IGF1 was low. Hypothalamic-pituitary MRI identified a pituitary macroadenoma measuring compressing the optic chiasm. Immunohistochemical analysis was positive for TSH, FSH, ACTH, and GH with obvious predominance of anti prolactin antibodies. Screening for multiple endocrine neoplasia type 1 was negative. The patient *underwent* specific oral drug *therapy* with *cabergoline* at 0.5mg weekly besides hormone replacement therapy. Clinical features and the visual acuity improved. Hypothalamic-pituitary MRI after 6 months of treatment with cabergoline, showed a reduction of at least 50 percent in measurable tumor size.

Conclusion: Pituitary adenomas in children are rarely described. They are often aggressive and affect growth and pubertal development. In 14% of cases a genetic mutation is found. Urgent and multidisciplinary management are required to minimize morbidity and mortality in this vulnerable group.

Reference

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P2-377

Use of Tolvaptan in a child with SIADH post pituitary surgery

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Introduction: Post-operative management of fluid and electrolyte imbalance after surgery for pituitary or suprasellar tumors could be challenging. Post-operative course could include diabetes insipidus (DI) (transient or permanent) or a classical triphasic response (initial phase of DI followed by a second phase of transient SIADH and third and final phase of permanent DI). Mainstay of management of SIADH in these patients involves fluid restriction. At times, treatment with hypertonic saline and diuretics might be needed but may not be sufficient to manage severe hyponatremia. Tolvaptan is a V2 receptor antagonist that blocks the action of ADH and could be of potential benefit in SIADH management. We report a 15 year old boy who developed severe SIADH following suprasellar surgery, which was successfully treated with Tolvaptan.

Case Report: A 15 year old boy with a medulloblastoma and metastasis in the sellar region underwent surgical resection of the metastatic mass. Post-surgery, he had water imbalance and a triphasic response in which initial phase of transient DI lasted for 3 days and was treated with desmopressin and additional fluids. This was followed by a phase of transient SIADH which was initially treated with fluid restriction and then with hypertonic saline and furosemide. Despite this, he had persistent hyponatremia and a single dose of Tolvaptan (15 mg) was given which showed improvement in the sodium concentration (126 mmol/L to 133 mmol/L) with a prompt recovery from SIADH (serum osmolality increased from 265 mmol/L to 303 mmol/L and the urine output increased from 0.2 ml/kg/hr to 4.4 ml/kg/hr). Overall, the SIADH phase lasted for 5 days after which he developed persistent DI which was managed with desmopressin.

Conclusion: Tolvaptan could be a potential treatment option for resistant SIADH in children and young people.

P2-378

The effect of 3 years of Gonadotropin-Suppressive Therapy in Girls with Early Puberty: Height Z Score in Relation to Mid-Parental height Z score

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Introduction: Early and fast puberty (EFP) in girls, defined as pubertal onset at age 8-9 yr., with an accelerated course, may cause compromised final adult height (FAHt). Treatment with a gonadotropin-suppressive agent is still controversial because the improvement in FAHt is equivocal and there may be a risk of overweight.

Aim of the Study: We analyzed the data of 24 girls with EFP treated with GnRH analog (GnRH) since Tanner stage 2-3, for 3 yr; and measured their clinical, hormonal and skeletal maturation for the period of treatment.

Results: Before GnRH therapy their (age = 7.5 ± 1.8 y) their HtSDS = 0.75 ± 1 and their bone age was advanced by 2 ± 1 yr. compared to their chronological age. The difference between their HtSDS and their mid-parental HtSDS (MPhtSDS) = 1.5 ± 0.9 .

After 3 years of using GnRH 3.75 mg IM monthly, (age = 10.9 ± 1.5 yr.) their HtSDS = 0.43 ± 1.6 and their bone age advanced by 0.8 ± 1 yr. compared to their chronological age. The difference between their HtSDS and their MPhtSDS = 1.1 ± 1.3 . Their breast Tanner stage was similar to that at the beginning of therapy. The BMI SDS increased from 1.25 ± 1 before treatment to 1.65 ± 1 after 3 years of treatment.

Conclusion: GnRH therapy for 3 years was successful in delaying the onset of a pubertal growth spurt, decreasing the rapid progress of their skeletal maturation, and increasing the potential for attaining final adult height comparable to or higher than their mid parental height. The treatment was associated with a mild increase in the BMI SDS.

P2-379**An Observational, Retrospective Study to Evaluate Long Term Safety and Effectiveness of Leuporelin in the Treatment of Central Precocious Puberty**

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Objectives: To describe safety and effectiveness of high (≥ 90 -180 $\mu\text{g/kg}$) and low (< 90 -30 $\mu\text{g/kg}$) dose leuporelin in treating central precocious puberty (CPP).

Methods: In this observational, retrospective study, effectiveness was evaluated based on regression or no progression of Tanner staging as the primary outcomes. LH, FSH, estradiol or testosterone suppression, and decrease in bone age to chronological age (BA/CA) ratio were secondary outcomes. Data from medical records were organized into a treatment phase in which subjects were treated with at least 9 continuous months of leuporelin (Enantone) and a follow-up phase up to the day of last follow-up data for the subject.

Results: During the treatment phase, all subjects (104 females and 4 males) were treated with Enantone. The mean exposure time was 22.3 months and 97.2% subjects received the maximum dose of 3.75 mg. 69.4% subjects recorded AEs, the most common being upper respiratory tract infection. No SAEs were related to Enantone. One male had sufficient data for evaluation and showed progression of Tanner stage; 79.7% (63/79) females showed regression or no progression. LH and FSH peak levels were suppressed in 98.1% (52/53) and 100% (53/53) while suppression of estradiol occurred in 74.8% (77/103) of females and testosterone was suppressed in 100% (4/4) of males. 89.6% (86/96) of subjects had decrease from baseline in the BA/CA ratio at the end of the Enantone treatment phase. In the follow-up phase, 44 (62.9%) subjects were no longer on CPP treatment had a mean follow-up duration of 8.75 months; another 26 (37.1%) subjects were continuing their CPP treatment with another GnRH agonist. There were 10 AEs reported, none of which were related to Enantone. Of the 2 female subjects who had sufficient data for evaluations of Tanner staging, the percentage of regression or no progression was 50.0% (1/2) at month 9 and 0% (0/2) at month 12. There was insufficient data for this evaluation in male subjects. For subjects who were no longer receiving CPP treatment, only observations on estradiol suppression in 1 female 9 months post-treatment and BA/CA ratio in 3/4 females at 9 months post-treatment and in 2/3 females at 12 months after treatment were available.

Conclusions: The safety profile observed was consistent with the known profile of leuporelin and no concerns were identified regarding long term administration. The majority of subjects received a maximum dose of 3.75 mg. Enantone appeared to have been effective in the treatment of CPP.

P2-380

Abstract Withdrawn

P2-381**Characterization of puberty development in a large cohort of patients with Noonan syndrome with molecular diagnosis**

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Introduction: Noonan syndrome (NS) is a relative frequent genetic disorder, mainly characterized by dysmorphic face features, congenital heart defects and short stature. Though delayed pubertal development has been described in both sexes, the physiopathological root remains unclear. This study aims at characterizing puberty development in Noonan syndrome.

Materials and Methods: The study population included 111 individuals with a molecular diagnosis of NS. Data on puberty development was retrospectively collected from medical records. The sample was torn into two groups according to the presence or absence of delayed puberty. The correlation between age of puberty onset or occurrence of delayed puberty with sex, genotype, use of recombinant growth hormone (rhGH), cryptorchidism, heart disease, height, body mass index (BMI), IGF-1 levels, and bone age before puberty was assessed.

Results: Delayed puberty was found in 25% patients with similar frequency in boys and girls. The table below summarizes features analyzed in each group. Height SDS before puberty were significantly lower on delayed puberty group. Besides, adult height was similar in both groups. No correlation was found between sex, genotype, use of rhGH, cryptorchidism, heart disease, BMI SDS, IGF-1 levels, and pubertal delay or age at start of puberty.

Conclusion: Delayed puberty is frequently observed in children with NS and resembles constitutional delay of growth and puberty seen in children with idiopathic short stature. The lack of correspondence between genotype and pubertal delay may show that this feature is linked to the RAS/MAPK signal transduction pathway in a general way.

	Delayed Puberty	Normal Puberty	p-values
Sex (F:M)	14 : 14	44 : 55	0.759
Pathogenic variant in PTPN11	16 (57%)	71 (71%)	0.217
Use of rhGH	15 (54%)	36 (36%)	0.155
Age at the start of puberty (y)			
Male	15.1 ± 1.0	11.7 ± 1.0	<0.001
Female	14.2 ± 1.4	11.1 ± 1.3	<0.001
Age of evaluation before puberty onset (y)	8.7 ± 0.5	8.9 ± 0.5	0.129
Height-SDS before puberty onset	-3.4 ± 1.6	-2.3 ± 0.9	0.003
BMI SDS before puberty onset	-0.5 ± 1.1	-0.3 ± 1.0	0.294
IGF1-SDS before puberty onset	-1.3 ± 1.4	-0.3 ± 1.2	0.090
Bone age delay before puberty onset	-2.0 ± 1.5	-1.4 ± 1.4	0.088
Time to complete puberty (T2 to T5) (y)	3.4 ± 2.1 (n=10)	3.9 ± 1.8 (n=30)	0.268
Adult Height SDS	-2.3 ± 1.1 (n=20)	-2.0 ± 0.9 (n=38)	0.179

P2-382

Pituitary tumors in children and adolescents: clinical and etiological profile

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Introduction: Pituitary tumors are rare in children and adolescents. The etiology is dominated by craniopharyngiomas. The main clinical presentation is the tumoral syndrome. These lesions often affect growth and pubertal development. The objective of our work is to study the clinical and etiological characteristics of pituitary tumors in the pediatric population.

Materials and Methods: This is a retrospective descriptive study involving 08 patients hospitalized for pituitary tumors in the Endocrinology-Diabetology-and-Nutrition Department of the Mohammed VI University Hospital Center of Oujda, in the eastern of Morocco. All patients underwent a full clinical examination, visual evaluation and hypothalamic-pituitary magnetic resonance imaging. The data collected were analyzed using SPSS 21 software.

Results: The mean age of the patients was 14.2±1.8 years with an M/F sex ratio of 0.5. Tumoral syndrome was the reason for consultation in 87.5% of cases. The delay between the onset of symptoms and the first consultation was 25.7±18.6 months. Amenorrhea was present in 20% of the cases, acrogigantism in one patient, and a short stature in 25% of cases.

The etiologies were dominated by craniopharyngioma in 50% of cases, multi-secreting pituitary adenoma in 25%; and Cushing's disease in 12.5% of cases.

The size of the pituitary process varied between 4 and 57 mm with radiological signs of invasion in 50% of cases. Visual impairment was reported in 62.5% of patients, with bilateral blindness in one patient. 75% of patients benefited from a pituitary surgery.

Discussion-Conclusion: The main etiology of pituitary tumors is represented by craniopharyngioma, followed by pituitary adenomas which are secretory; this is in agreement with literature data. The delay in management determines the visual prognosis, and long-term monitoring of growth and puberty is necessary.

P2-383

Langerhans Cell Histiocytosis with Isolated Central Diabetes Insipidus, Low Grade Fever and Sellar Erosion

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Introduction: The annual incidence of Langerhans cell histiocytosis (LCH) is 5 per million in admission with a diagnosis of isolated central diabetes insipidus (CDI) in children under the age of 15. Here, the process leading to the diagnosis of LCH at presentation with isolated CDI, imaging findings, and the sellar erosion, which has not been previously reported in the literature, will be discussed.

Case Presentation: A 4-year-5-month-old male patient was referred to our outpatient clinic with complaints of drinking too much water and urinating frequently for 2 months. Physical examination, complete blood count, and biochemical tests were normal. Water deprivation test was performed with a pre-diagnosis of diabetes insipidus in a patient with a urine density of 1001. After water deprivation test, the patient was diagnosed with diabetes insipidus with serum osmolality 303 mOsm/L and urine osmolality as 121 mOsm/L. Urinary osmolality increased by 330% after administration of 10 microgram of **desmopressin acetate nasal spray solution**. With these findings, the patient

was diagnosed with CDI and desmopressin treatment was initiated. Other pituitary functions were found to be normal. In the follow-up of the patient, it was observed that his body temperature risen to 38-38.4°C in the evening once a day, and fell spontaneously and did not persist. On physical examination, any focus to explain the fever was not found. In laboratory tests, increases in acute phase reactants (WBC:14.89x10⁹/L, CRP:76.8 mg/L, Sedimentation:70 mm/hour) and anemia (Hb:10 g/dL, MCV:66.5 fL, RDW:16.3%) were observed. A lytic expansile bone lesion in the mid-diaphyseal part of the left-clavicle was found on skeletal survey. On pituitary imaging, it was observed that the height of the pituitary anterior gland was slightly increased. The infundibulum was significantly thick and the bright signal of the neurohypophysis was not observed. On cranial MRI, widespread lytic-destructive bone lesions were observed in the bone structure forming the sella turcica, and the lateral wall of the left orbital. The patient, who had a pre-diagnosis of LCH, was directed to an external center for bone biopsy and it was learned that the treatment for the diagnosis of LCH was planned.

Conclusion: Presence of isolated CDI with low-grade intermittent fever should be a warning for the diagnosis of LHH. But the patients with CDI should be evaluated in terms of LHH, the most known underlying cause, regardless of the presence of fever.

P2-384

Basal LH as a screening test for diagnosis of central precocious puberty

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Introduction: Central precocious puberty (CPP) refers to the development of secondary sex characteristics before ages 8 and 9 years in girls and boys, respectively. It is either due to organic brain lesion or idiopathic. Conventionally, Gonadotropin Releasing Hormone (GnRH) stimulation test is a mainstay tool for diagnosis of central precocious puberty in pediatrics. However, it is time consuming and expensive. Therefore, this study was aiming to find an alternative simple diagnostic modality for diagnosis of central precocious puberty.

Methods: From Jan 2019 to Jan 2021, the medical records of 42 children with early secondary sex characteristics were reviewed including their age, height, weight, Tanner staging of secondary sex characters, bone age, imaging studies and hormonal profile. Basal serum LH and GnRH stimulation test were done for all patients. Receiver operating characteristic curves (ROC) were done to obtain the optimal basal in correlation to peak LH after GnRH stimulation.

Results: Among the study cohort, there were 17 children with CPP, 4 children with peripheral precocious puberty and 21 children with premature thelarche. The cutoff value of basal serum LH was 0.33 IU/L for diagnosis of CPP and differentiation between GnRH stimulation positive and negative results (P=0.001, area under the curve [AUC]=0.941, 88% sensitivity, 76% specificity, 71.4% positive predictive value, 90.5% negative predictive value).

Conclusion: Basal serum LH can be used as a valuable simple tool for diagnosis of central precocious puberty compared to the standard GnRH stimulation test.

P2-385

A Practical Method for the Evaluation of Childhood Hypophysitis: Pituitary Stalk / Basillary Artery Ratio

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Introduction: Childhood hypophysitis (CH) is an extremely rare entity that has difficulties in definition and displays a wide variety of symptomatology. The volume and shape of pituitary gland may increase in physiological periods such as puberty and pregnancy, it may also change in various neuroendocrine and psychiatric diseases. *It is important to distinguish physiological changes observed in the pituitary, especially in puberty, from hypophysitis.* For this purpose in this study four adolescent cases presented

Case1: A 13-year old girl has applied to our clinic with the complaint of fatigue. Her puberty was at Tanner stage 5. Serum ACTH, TSH and cortisol levels were found to be low. *The pituitary gland height was found 7mm (above +2 SD) at the infundibulum level. Pituitary Stalk/Basillary Artery ratio (PS/BA) was measured as 0.5mm in sagittal section, being within normal limits.*

Case2: A 14-year-olds girl has applied to our hospital with an adenoma in the pituitary, which has been detected on the MRI taken due to high prolactin levels in blood tests performed at an external center she applied due to overweight. Serum LH and estradiol values were observed to be high. *PS/BA ratio was measured as 0.77mm in sagittal section (0.54-0.74) regarding the patient's pituitary MRI. The pituitary gland height was measured as 8.5 mm, it was above +2 SD according to age*

Case3: An 12-year-olds boy was admitted to our clinic with a complaint of overweight. She was morbidly obese and his puberty was at Tanner stage 5. A pituitary MRI was performed when high ACTH, TSH and Prolactin levels were detected. *The pituitary gland height was found to be approximately 9 mm (above +2 SD) at the infundibulum level. PS / BA ratio was measured with 0.58 mm (0.48-0.72) within normal limits and was interpreted as pubertal pituitary enlargement.*

Case 4: A 17-year-olds girl was admitted significant weight loss and anorexia nervosa. Her puberty was at Tanner stage 5. In the pituitary MRI *the height of the pituitary gland was measured as 8mm, and its size was above +2 SD for age. PS / BA ratio was measured with 0.68mm within normal limits and was interpreted as pubertal enlargement.*

Discussion: These data are valuable in terms of suggesting that the *PS/BA ratio in non-contrast MRI* is useful in physiological and pathological distinction of pituitary disorders, as well as in determining the diagnosis, monitoring and treatment decision.

Blood Pressure in Girls with Central Precocious Puberty and GnRH Analog Therapy

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Objectives: Several case reports describe hypertension (HTN) in children treated with GnRH analogs for central precocious puberty (CPP). However, relevant data on blood pressure (BP) under GnRH analog treatment are scarce. We evaluated BP among girls with idiopathic CPP and early puberty (EP) before, during and after GnRH analog therapy, and examined associations of BP with clinical parameters.

Design: A retrospective longitudinal cohort study in a tertiary pediatric endocrinology institute.

Methods: Demographic, anthropometric, clinical and laboratory data were collected from electronic files of 112 girls treated with GnRH analog for idiopathic CPP (n= 81) or EP (n=31) (the study group), and 37 healthy pre-pubertal controls. BP measurements from regular clinic visits were expressed as percentiles adjusted for gender, height and age. Data at baseline, under therapy and off-therapy were compared.

Results: At presentation, mean BP values were above the 50th percentile in all three subgroups; mean values of the study group did not differ significantly from those of the controls. At diagnosis, 53 patients (47%) of the study group had normal BP values, 16 (14%) had elevated BP values and 43 (39%) had values within the range defined as HTN. The mean systolic and diastolic BP percentiles at first measurement under treatment remained unchanged. After treatment cessation, the mean systolic, but not diastolic, BP percentile was lower than baseline (n=47, p=0.006). In the study group, girls with baseline BP >90th percentile had lower mean birthweight (p=0.01) and a higher mean BMI-standard deviation score (p=0.01). Girls with baseline BP >90th percentile were not different from those with BP < 90th percentile in mean age at onset of puberty, height-SDS, Tanner stage, bone age SDS, peak LH, E2, DHEA-S or androstenedione levels at diagnosis.

Conclusions: At presentation, girls with CPP and EP had BP values similar to pre-pubertal controls. BP did not change during GnRH analog therapy, but the mean systolic BP percentile decreased off-treatment. The stability of mean BP percentile during treatment is reassuring.

Isolated central diabetes insipidus and periventricular nodular heterotopia in a 9-year-old girl

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Background: Periventricular nodular heterotopia (PNH) is a brain malformation caused by dysregulation of neuronal migration during cerebral development, resulting in nodular neuronal structures in the ventricular surface. Associated ectopy of the posterior pituitary has been reported in literature and is usually associated with deficiencies of the anterior pituitary. The occasion of an isolated central diabetes insipidus due to absence of the posterior pituitary has not been described in detail so far.

Case Report: We report a 9-year-old girl with regular physical and cognitive development. The parents reported progressive polydipsia and polyuria, noticed from the age of 6 years during a varicella infection. While reporting a water intake of 5-6L per day, the patient did not reveal growth abnormalities nor biochemical evidence for malfunction of the anterior pituitary lobe. Water deprivation testing confirmed the diagnosis of diabetes insipidus with failure to increase urine osmolality and low copeptin levels despite hyponatremia. Cerebral MRI showed symmetrical periventricular heterotopias and a missing bright spot of the neurohypophysis. Treatment with oral desmopressin 30µg reduced water intake to 2-3 liters per day. Whole exome sequencing in the patient did not reveal causative variants in known genes for PNH, diabetes insipidus or immunodeficiency and chromosomal microarray analysis was normal.

Discussion: Although PNH is associated with other structural brain abnormalities, isolated absence of the posterior pituitary is extremely rare. Single cases of EPP with PNH in non-SOD patients have been described, all featuring growth hormone deficiency as symptom of anterior pituitary lobe affection. Bilateral posterior PNH (BP-PNH) as described by Mandelstam et al. 2013, represents a distinct subtype of PNH, featuring noncontiguous and asymmetric lesions. Similar to the findings in our patient, no genetic cause of BP-PNH could be identified so far. While 10% of patients with BP-PNH were shown to feature posterior pituitary abnormalities, only one patient has been described with absent bright spot so far.

Conclusion: The case of a patient with isolated central diabetes insipidus underlines the importance of evaluation of pituitary function in association to PNH. A common genetic origin in the distinct sub-entity of BP-PNH remains to be determined.

P2-388

Central precocious puberty: clinical, etiologic and therapeutic features

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Introduction: Precocious puberty is defined by the apparition of secondary sexual features before the age of 8 years in girls and 9.5 years in boys. Central precocious puberty (CPP) results from a premature activation of the hypothalamic-pituitary-gonadal axis. The aim of this study is to review the clinical, etiologic and therapeutic features of this entity.

Patients and Methods: It is a descriptive retrospective study including 7 patients with central precocious puberty followed-up in the department of Endocrinology-Diabetology and Nutrition of Mohammed VI University Hospital Center, Oujda, in the eastern of Morocco.

Results: We have collected 7 patients, 6 girls and one boy. The mean age at admission was 7.4 years ranging from 3.7 to 9 years. The major symptom leading parents to consultation was breast development in girls and testis development in the boy. Pubic hair development was noted in 57.1% of cases. Four patients (57.1%) had an advanced height. An advanced bone age was found in 5 cases (71.4%). The diagnosis of central precocious puberty was confirmed using gonadotropin-releasing hormone (GnRH) stimulation test. The mean peak luteinizing hormone (LH) concentration was 27.9 mUI/ml with a maximal peak of 71.8 mUI/ml. Pituitary magnetic resonance imaging was abnormal in 2 cases (28.6%) including a case of hypothalamic hamartoma and a case of pituitary picoadenoma. Six patients were treated using GnRH agonists at a dose of 3.75mg of Triptorelin with a mean interval of 26.16 days between injections.

Discussion-Conclusion: Central precocious puberty is a rare disease with a clear feminine predominance such as the results found in our study. Its diagnosis should be made as soon as possible in order to decide upon the utility of GnRH agonists with the aim of preventing short adult stature and adverse psychosocial outcomes.

P2-389

Atypical Presentation of Pituitary Macroadenoma in an adolescent girl: Central Hypothyroidism and Attenuated Pubertal Growth Spurt

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Introduction: Hyperprolactinemia (HPrl) secondary to macroadenoma is a rare endocrinopathy in childhood but represents one of the most frequent forms of pituitary adenoma.

Case Report: A 12yr old girl was referred for assessment of progressive weight gain in the last 1.5 years. Despite trials of weight control by changing the dietary habit and daily exercise weight her BMI SDS increased from 1.2 to 2.2. This was associated with progressive fatigability and a decrease of her HtSDS from 0 to -1.2). There was no history of headache, visual deficit, nausea or vomiting, change in school performance or sleeping pattern, heat/cold intolerance, galactorrhea, polyurea, or polydipsia. She was born at term with a normal birth weight (3kg). Physical examination revealed normal vital signs and BP for age. She had HtSDS = -1.2, BMI SDS = 2.2, Mid-parental Height SDS = -0.17 and annual growth velocity = 3cm/year (-2SD). Her breast and pubic hair were at Tanner stage 3. She had normal neurological exams and normal eye movements with a normal visual field. Lab tests showed Low FT4 and relatively low TSH twice (12.6 and 9.2 pmol/L, TSH = 1.1 and 1.2 mIU/L respectively). Her peak growth hormone after clonidine provocation was 4.43mcg/L. The bone age was 13 years. Pituitary MRI showed: a well-defined intra and suprasellar mass lesion measuring about 2.2 x 1.7 cm seen at the left lateral and paramedian aspect of the pituitary gland, extending to the left cavernous sinus and encasing the cavernous ICA completely. The pituitary infundibulum deviated to the right side. The mass lesion was effacing the suprasellar cisterna and indenting the inferior aspect of the optic chiasm. The girl was started on levothyroxine and Cabergoline therapy. A trial of Growth hormone therapy was started then on hold after raised in IGF-1 to +2SD.

Conclusion: Attenuation of a pubertal growth spurt and pubertal progression and central hypothyroidism could be the presenting manifestations of pituitary macroadenoma in adolescents even without neuro-ophthalmic signs or galactorrhea.

	29/4/2019	24/10/2019	26/12/2019	28/01/2020
TSH (N:0.5- 4.3mIU/L)	1.06	1.18	0.3*	0.78
FT4 (N:12.9-20.6pmol/L)	12.6 (L)	12.1 (L)	15	9.2 (L)
IGF-1	263	185	512**	232
LH		1.2		0.8
FSH		2.9		3.4
Estradiol		56.6		53.6
Cortisol (Am)				233
ACTH (Am)				35
Prolactin (mIU/L)				56,487 (= 2655 ng/L)
Serum osmolality				288
Urine osmolality				795

*On Levothyroxine 50mcg and therapy hold for 1 week, ** on GH 0.05mg/kg/day

P2-390

A case of partially Empty Sella with hypopituitarism in a child

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Introduction: Empty Sella (ES) is a radiological finding which is due to herniation of subarachnoid space into sella turcica. It's partial, when <50% space is filled with cerebrospinal fluid (CSF) and complete, when CSF fills >50% with pituitary gland flattened to <=2mm. Actual occurrence is debatable and often noted incidentally during magnetic resonance imaging (MRI). However, it can cause pituitary hormone (PH) dysfunctions, most commonly growth hormone (GH) deficiency. We are reporting a case of partially empty sella with GH and cortisol deficiencies.

Case: A 15year old boy presented with delayed puberty and absence of secondary sexual characteristics (G1P1TV 2mL & 3mL). He had short stature with height (153.2 cm) below parental target, on the 2nd centile (target 25th to 98th) and weight (58.05kg) on 50th centile. Mother felt he had low stamina during sports and took longer to recover from illnesses. However, he did not have morning tiredness. His birth and past medical history were insignificant. Parents were nonconsanguineous and both were late developers. Mum needed oestrogen for pubertal induction. His baseline tests were normal including thyroid function, coeliac, full blood count, IGF-1. He had 2.66 years bone age delay and normal male karyotype. Hence, he had a primed insulin tolerance test (ITT). It detected a poor GH peak of 1.7mcg/L and cortisol peak of 293nmol/L (acceptable minimum 6.7mcg/L & 430nmol/L respectively). ACTH was within range (16.3ng/L, 0-46ng/L).

After diagnosing GH and secondary cortisol insufficiency, he was started on hydrocortisone (HC) replacement. His T2 weighted MRI pituitary revealed partially empty sella with asymmetrical pituitary (pituitary gland measuring 4mm cranio-caudally on right and 2mm on left). He responded well to hormone replacement. Eventually he progressed to puberty on his own (G2P2TV 5mL & 6mL).

Discussion and Learning Points: ES is a rare entity in the paediatric population and probably less reported. Primary ES can be idiopathic, developmental, due to ICP etc. Although it is five times more common in adult females, in childhood more reported cases are males. Secondary ES is commonly due to injury to the gland from surgery, tumour, or trauma. Presentation varies from incidental radiological findings to symptoms of hormone deficiencies. PH deficiency can be in up to 60% cases of ES with GH being most affected. Treatment consists of hormone replacement, close monitoring of evolving deficiencies and treatment of the secondary causes if present.

P2-391

Cushing's disease in paediatric patients: Diagnosis and evolution

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Introduction: Cushing's syndrome is rare in the paediatric population, affecting 0.89 per million children between the ages of 0 and 20 years. The causes of Cushing's syndrome of endogenous origin are dominated by pituitary causes in 70-95%, with a peripubertal revelation. We report the case of a child followed for Cushing's disease in the department of Endocrinology-Diabetology-Nutrition of Mohammed-VI University Hospital Center of Oujda, in the eastern of Morocco.

Observation: It is a 14-year-old female child, without any particular pathological history, referred to our department for secondary amenorrhea, weight gain and hirsutism. The clinical examination found an obese child with a BMI of 35.5 kg/m², large purple stretch marks and a puffy face. Biological assessment

revealed ACTH-dependent biological hypercortisolism. Hypothalamic-pituitary MRI revealed a pituitary microadenoma measuring 4 mm. The case was discussed in a multidisciplinary meeting including endocrinologists, neurosurgeons, radiotherapists, and oncologists, then the patient benefited from a selective microadenectomy with complete post-operative remission.

Discussion-Conclusion: Cushing's disease in children is a diagnostic and therapeutic emergency. Early diagnosis remains a challenge for the clinician in order to prevent the consequences of hypercortisolism especially on growth and puberty. It requires a rigorous evaluation as well as a codified management as soon as possible, following a multidisciplinary meeting. Transphenoidal surgery remains the only curative treatment.

Key-Words: Cushing's disease – children

P2-392

Late Puberty in Children

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Objectives: This retrospective and descriptive study aim to study the frequency of children who have a pubertal delay and who are followed at the Department of Pediatrics II at the Children's Hospital of Rabat.

Materials and Methods: Among 1850 records collected, 24 patient records that meet the criteria for inclusion. A delay in the appearance of sexual characters: the lack of breast development after the age of 13.5 years in the girl and the lack of increase in the size of the testicles beyond 14 years in the boy.

Results: 24 patients (9 Girls and 15 Boys) who have a pubertal delay, the sex Ratio is 1.66. Their average age of diagnosis is 15.9 years (extremes: 11-18.8 years). Patients were consulted for small size (-2DS,-3DS) and absence of secondary sexual characteristics. 74% of patients have a weight between -4DS and -2DS, 87% have severe statural delay (-4DS,-3DS). 66% of girls and 53% of boys are pre-pubescent (stage I) according to Tanner and 34% of girls compared to 47% of boys are stage II. The metabolic balance of gonadotropins shows a high rate of FSH in 7% of boys (33.7 mUI/ml) and in 56% of girls, 15% of boys and 22% of girls has an average value. Serum LH is 2mUI/ml in 67% of boys and 22.2% of girls. 77% (13/15) of boys have low testosterone. Estradiol levels are low at 100% (9/9) of girls. Cytogenetic analysis shows 17% (4/24) of patients have Turner syndrome with a karyotype with partial or complete deletion of one of the X chromosomes (45 XX0 or 45XXq), a patient has Klinefelter syndrome with karyotype 49 XXXXY. The radiological examination shows a chronological age-bone age difference ranging from 1 year to 6 years (average: 4.6 years). All our patients have a pubertal development delay and

a statural-weight delay, 60% of which have an AO-AC difference between 4 and 6 years.

Conclusion: This original work shows the frequency of pubertal delay in children and its origin is central due to abnormalities of the hypothalamo-hypophyseal axis (genetic syndromes with hypergonadotropin hypogonadism or hypogonadotropin) or peripheral by abnormalities of gonad function. The pubertal delay is associated with moderate statural inflection and bone maturation delay.

P2-393

First Morning Voided Urinary Gonadotropin Measurements for the Early Screening, Diagnosis and Follow-up of Central Precocious Puberty Patients

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Central precocious puberty (CPP) is one of the most common pediatric endocrine diseases with an ever increasing incidence. CPP is associated with the loss of final adult height, early menarche, psychological problems and an increased risk of developing diseases in later adulthood such as female reproductive system tumors.

The gonadotropin-releasing hormone stimulation test (GnRHST) is the gold standard for the diagnosis of CPP. However, the test is costly and time consuming to implement because the invasive method requires hospitalization and repeated evaluation with multiple serum sample collections, thus making the test not suitable for routine screening.

A simple and effective method for identifying CPP remains to be developed. Recent studies have demonstrated that the first morning voided (FMV) urinary Gn(U-Gn) has a strong correlation with serum Gn(S-Gn) and performed equally well in predicting a pubertal GnRH test result. It also performed equally well as the GnRHST in the differentiation of early puberty (Tanner stage 2) from prepuberty (Tanner stage 1) and decreased after

3 months of GnRHa treatment to levels below +2 SDs. Thus, the non-invasive FMV U-Gn measurement can reflect the gonadotropin secretion for a particular period during the day and suggest higher accordance with GnRHST compared with S-Gn, which suggests that FMV U-Gn may be an ideal indicator for CPP screening, diagnosis and follow-up. However, a uniform standard has not been agreed due to the lack of large cohort, multi-center clinical research data. Therefore, it is of great clinical value and scientific significance to study further FMV U-Gn concentration changes and cut-off values.

In the present study, 6,000 healthy children (aged 6-12 years) will be enrolled and classified at different Tanner stages in 11 centers in China to explore whether FMV U-Gn can be set at different cut-off values for predicting clinically established puberty (Tanner stage B/G 2) for boys and girls, and the ideal cut-off value will be determined. 400 precocious puberty (PP) patients will also be enrolled to determine if FMV U-Gn correlates with GnRHST results, and the sensitivity and specificity of U-Gn for diagnosis of CPP at different cut-off values will be evaluated to determine the ideal cut-off value. The CPP group will be followed up once every three months for a year to evaluate the value of FMV U-Gn in follow-ups of CPP patients.

Sex Differentiation, Gonads and Gynaecology or Sex Endocrinology

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P2-394

SRY negative 46XX male syndrome: case report

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Objective: To study the clinical characteristics of 46XX male syndrome case with negative SRY

Methods: To summarize the characteristics of one case of SRY negative 46XX male syndrome

Results: a 12-year-old boy came to our clinic for "breast development for one year". At the age of 1 year old, karyotype was done with the result of 46XX for hypospadias (penile-scrotal type). At the age of 2 years old, hypospadias repair and gonadal biopsy were performed. The pathological of gonad showed the both upper side of gonads were ovarian tissues, and a small amount of testis tissue was found on the edge of bilateral gonads. At the age of 11 years old, bilateral breast development was found with pain. The patient likes guns, cars. The child is G1P1. It is very difficult for the patient's mother to conceive and the father's sperm test is normal. Mother is 34 years old, and father is 36 years old. There was no family history of infertility. Physical examination: height 150.2cm (-1SD, according to the boy), weight 46.5kg (-0.2SD, according to the boy), fine skin, Tanner stage: bilateral breasts B4 stage, PH3, A2, penis size 5.5cm × 2.6cm, right testicle 4ml, left 8ml with soft texture. Lab test: E2 <10 pg/ml, T 1.92ng/ml, P0.10ng/ml, FSH 36.49 IU/L, LH 14.37 IU/L, SHBG 39.20nmol/L;

androstenedione 1.25nmol/L, DHEA 1.12umol/L, 17(OH)P 0.77ng/ml, AMH 2.18 ng/ml, InhibinB <10 pg/ml, E1 <8.10pg/ml. Normal electrolyte and hepatorenal function. Normal thyroid function, and normal ACTH, 8am cortisol. The bone age was 13.5 years. Color Doppler ultrasound of testis: the left side: testicular echo, size 2.3cm × 0.9cm; the right side: multiple round cystic structures, range 2.9cm × 1.1cm, no testicular echo. Chromosome: 46XX; SRY sequence (-); gene test for Sox9, Sox3, Sox8, Sox10, PGD2, FGF9, Dmrt1, DAX-1, FOXL2, Wnt4, RSPO1, CTNNA1, SF1 were all negative. Although the final gene test results are negative, we know from the published literature that the risk of tumor development in this kind of patients is very low, and sex steroids replacement therapy is needed in the adolescent development age. If the gender is identified as a boy, mastectomy is required. The child is unable to produce normal sperm, so he needs to use assisted reproductive technology to conceive the next generation.

Conclusion: children with SRY negative 46XX male syndrome have a low risk of tumor development and need sex hormone replacement therapy.

P2-395

Cognitive function and linear growth in Prednisone-treated children with salt-wasting congenital adrenal hyperplasia

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Introduction: Congenital adrenal hyperplasia (CAH) is a disorder with a wide spectrum of severity. Impaired cognition has been reported in patients with CAH, although the findings have been conflicting. It has been hypothesized that the major causes of the deficits are prenatal hormonal imbalances and/or excessive glucocorticoid treatment.

Objective: The objective of this study was to investigate cognitive function in children with CAH and to assess their anthropometric measurements who were diagnosed early in life and were under good hormonal control.

Subjects and Methods: This study was conducted on children with CAH at a tertiary center for pediatric endocrinology at Alexandria University Children's Hospital in Egypt. Anthropometric measurements were done for them.

Cognitive function testing was done by using the Stanford-Binet Intelligence Scale, Forth Edition. Vineland Adaptive Behavior Scale (VABS) was used in children that refused to interact in the Stanford-Binet Intelligence Scale.

Results: Forty-six children and adolescents (their mean age 7.33 ± 3.89 years) were included, 14 males and 32 females. None of their mothers received Dexamethasone during their gestation. 41/46 were diagnosed during the first 3 months of their life and 5 during the first year of life.

All children were on Prednisone therapy (3.72 ± 0.59 mg/m²/day) (equivalent to hydrocortisone dose = 14.82 ± 2.38 mg/m²/day) and fludrocortisone. Their doses were tailored to keep testosterone level (<9 ng/mL) and 17-OHP levels are < 600 ng/dl in the morning before medication.

34/ 46 had normal weight (>5 - <85 th percentile), 8/46 were overweight (85 - <95 th percentile) and 4/46 were obese $\geq$ 95 th percentile. Their mean height SDS (HtSDS) was -1.87 ± 1.43 SD and mean BMI was 20.3 ± 6.8 %.

Mild mental retardation occurred in 13.7 %, slow learning occurred in 25.5% and low average IQ occurred in 21.6 % of them. Moderate retardation was found only in one girl. There was no significant difference in IQ score between boys and girls ($t=0.481$, $p=0.634$).

Conclusions: Impaired cognitive function was observed in patients with CAH despite reasonable control of their androgens and 17- OHP levels. These results may reflect prenatal adrenal androgen excess, and the potential psychosocial consequences of the disorder.

P2-396

Combining big data science with clinics: Novel approach for understanding human sex development and its variants

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Background/Introduction: Whole exome sequencing (WES) revolutionized clinical genetics in patients with differences of sex development (DSD). However, our ability to interpret WES data is limited by our incomplete understanding of the mechanisms involved in DSD. Thus, we created a methodology that scores potential candidates based on single cells transcriptomics of human male gonadal cells and applied it to WES data from a cohort of genetically male (46,XY) DSD patients.

Methods: For each cell type in the male gonad, genes were ranked (R score) based on two variables: Single-cell RNA-seq expression in human fetal SCs and expression in sex development-unrelated organs (heart, lung, colon). Genes with scores higher than the mean were considered as candidate players for cell-type regulation. We then applied the R score as a filter to prioritize genes with rare variants identified in our cohort of unresolved 46,XY DSD cases. An interaction network of our candidates with known sex-development genes was used to highlight those candidates with multiple connexions with sex-development pathways for further studies.

Results: From the 13,000 genes expressed in gonadal cells, we were able to create ranking lists of the most relevant genes for each male gonadal cell type (Sertoli, Leydig and germ cells). Thanks to these rankings, we filtered the thousands of variants observed in

undiagnosed DSD patients, and selected high priority candidate lists of 100 genes for each cell type. Among the top-ranked candidates for further studies, we observed IGF1, KIT and IL-6, which are known to be involved in male gonadal regulation but have not been described in DSD patients.

Conclusion: This pipeline will ultimately advance basic knowledge in the regulation of human sex development. Moreover, our results highlight the value of integrating rich clinical data with cellular models and the need to generate multimodal data, serving as a proof of concept for developing powerful genetic analysis algorithms to ultimately overcome the difficulties in interpretation of next-generation data and eventually unravel the mechanisms governing human physiology.

P2-397

Vascular dysfunction and increased cardiovascular risk in hypospadias

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Background: Hypogonadism has been associated with cardiovascular disease. However, little is known about the cardiovascular impact of hypogonadism during development. Using hypospadias as a surrogate of hypogonadism, we investigated whether hypospadias is associated with vascular dysfunction during childhood and whether it is a risk factor for adult cardiovascular disease.

Methods: Our human study spanned molecular mechanistic to epidemiological investigations. Clinical vascular phenotyping (blood pressure, carotid intima-media thickness (CIMT), flow-mediated dilation, pulse wave velocity) was performed in 14 adolescents with hypospadias and 14 age-matched controls. Subcutaneous resistance arteries from penile skin from 27 young boys undergoing hypospadias repair and 37 age-matched controls were isolated and functional studies assessed by myography. Primary culture vascular smooth muscle cells (VSMCs) were used to assess: Rho kinase, redox signalling, nitric oxide (NO) and DNA damage. Systemic oxidative stress was assessed in plasma and urine (TBARS, 8-OHdG). Scottish linked hospital episode data identified 6,797 men with a history of hypospadias versus 8,073 controls matched for confounders.

Results: In adolescents with hypospadias, systolic blood pressure and pulse pressure were significantly increased, in association with increased CIMT SDS (1.6 vs 1.2 , $p<0.05$). Resistance arteries from boys with hypospadias demonstrated increased

vasoconstriction (Emax:137.9 vs 83.7, $p<0.001$) and reduced endothelium-dependent (Emax:77.3.4 vs 14.6, $p<0.0001$) and endothelium-independent vasorelaxation (Emax:39.5 vs 24.6, $p<0.0001$). Hypercontractile responses were ameliorated by fasudil (Rho kinase inhibitor), NAC (ROS scavenger) and melittin (Nox5 inhibitor). Activation of pro-contractile signalling pathways (Rho kinase activity; myosin light chain phosphorylation) were increased in VSMCs from affected boys, associated with increased Nox5-induced ROS generation, oxidative stress and downregulation of NO and antioxidant pathways. Men with a history of hypospadias had a 3-fold higher risk of arrhythmia (OR [95% CI] 2.8[1.4-5.6], $p<0.001$); 4-fold higher risk of hypertension (OR [95% CI] 4.2[1.5-11.9], $p<0.05$) and 2-fold higher risk of heart failure (OR [95% CI] 1.9 [1.7-114.3], $p<0.05$).

Conclusions: Hypospadias is associated with vascular dysfunction during childhood and predisposes to hypertension and cardiovascular disease in adulthood. Underlying vascular mechanisms involve perturbed Rho kinase- and Nox5/ROS-dependent signalling. Our novel findings delineate molecular mechanisms of vascular injury in hypogonadism, and identify hypospadias as a cardiovascular risk factor in males.

P2-398

Evaluation of genomic copy number variations in the etiology of syndromic patients with differences of sex development (DSD)

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Differences of sex development (DSD) occurs when the development of chromosomal sex, gonadal or internal/external genitalia is atypical. It has an incidence of 1:1000-4500 live born children. New chromosomal array technologies (SNP-array) can analyze the genome of the individual providing information of copy number variation (CNV) of specific chromosomal regions helping to identified pathogenic variants that could explain the etiology of the DSD. This study aims to analyze the presence of CNVs using genomic array platforms in DSD patients with syndromic feature in a cohort followed at the outpatient clinic of tertiary hospital. Two SNP-array platforms were used (Illumina® Infinium CytoSNP-850K BeadChip® and Affymetrics® CytoScan HD 750K).

Twenty-two DSD patients with syndromic features encompassing several systems, in addition to the genital abnormalities, were included in the study. A total of 229 CNVs were identified: 126 deletions, 66 duplications and 37 loss of heterozygous state. Reported CNV length varied from 2.8 Kb to 12.7 Mb. Nine CNVs in six different patients were considered pathogenic or probably pathogenic after *in silico* analysis. Two patients had the final diagnosis of 46,XX SRY + DSD associates with copy gain of 7 Mb Yp fragment. Two deletions, a 1.7Mb in 3q29 region in one patient and a 9 Mb in Xp22.33 in other patient, were revealed by the array

in addition to the Yp fragment. Four others pathogenic CNVs were found in three patients that can justify the syndromic features and genital ambiguity: a 11.6 Mb deletion at 10q25.3-26.2 in one patient; a 10.9 Mb deletion at 13q33.1 in other patient; a duplication (6.5Mb) and deletion (12.7) in chromosome 14q11.2-q12 and 21p11.2-q21.3, respectively in another patient. Genes related with gonadal development were deleted in one patient (*FGFR2* and *EMX2*) and in other patient (*EFNB2*). In one patient, a 12Kb deletion in chromosome 10 encompassing the *PITX3* was found responsible for congenital cataract.

The SNP-array technique allowed to establish the molecular cause of DSD in two patients 46,XX DSD SRY+ (10%). In three other patients, pathogenic CNVs that contained candidate genes related to DSD (10q25.3-26.2, 13q33.1-q34) and a contiguous gene deletion syndrome with atypical genital but without a known candidate gene (14q11.2-q12 duplication and 21p11.2-q21.3 deletion), were identified and may justified the presence of 46,XY DSD phenotype.

Copy number variation (CNV) of specific chromosomal regions containing pathogenic variants could explain the etiology of DSD.

P2-399

Self-reported Feelings of Adult Patients with Differences of Sex Development (DSD) Regarding Genital Surgical Procedures

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Introduction: DSD patients present varied degrees of atypical genitalia. The social sex assignment and the surgery decisions must be proceeded by a multidisciplinary team approach with the family. Surgeries should be only performed by experienced surgeons. The current trend is the early correction, but some patients and non-governmental entities argue that the surgeries should be delayed until the patient's consent.

Objective: To analyze the perspectives and feelings of adult DSD patients followed at a reference center in São Paulo regarding surgical approach.

Methodology: It was a transversal study. The patients were submitted to individualized semi-directed interviews to answer a questionnaire containing several questions regarding surgical procedures.

Results: The patients' mean age was 37 y. The proportion of male and female social sex was 40% and 60%. 80.6% were 46,XY, 11.9% were 46,XX and 7.5% have chromosome DSD. 68% of them

had atypical genitalia and 32% had female external genitalia. 89.5% of them concluded at least the high school. Partial gonadal dysgenesis and CAIS were the most frequent diagnosis. In 71% (33/46) of the patients the atypical genitalia were noted at birth. The median patient's age at first surgery was 4.5 y in masculinizing (n: 23) and feminizing surgeries (n: 24), and 16 y in isolated gonadectomy (n: 18). Among the patients submitted to surgeries, 54% of them were submitted only to one surgical procedure and 21% of them were submitted to more than three surgical procedures. When the patients were asked about the ideal time to undergo genitoplasty (n= 43), 78% of them chose childhood. Only two patients related that adulthood would be the ideal time for genitoplasty and only one patient decided not to undergo surgery (a CAIS patient who decided against gonadectomy). There was a reduction of the severe discomfort related to atypical genitalia from 86% before surgery to 46% after surgery ($p < 0.01$). 8.8% of the 46,XY DSD patients (6/68) presented gender dysphoria. The mean age of the patients was 49.6 y and the mean age at gender change was 25.5 y.

Conclusion: Most adult DSD patients considered childhood the ideal time to correct their atypical genitalia. The severe discomfort related to atypical genitalia presented by most of the patients was significantly reduced after genitoplasty. An early treatment and follow up with a multidisciplinary team may achieve positive results on surgical approach of the atypical genitalia in childhood with low prevalence of gender dysphoria in adulthood.

P2-400

Peripheral Precocious Puberty in girls affected by McCune-Albright Syndrome: safety and efficacy retrospective study on letrozole treatment

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Introduction: Precocious Peripheral Puberty (PPP) due to autonomous ovarian activation is the most frequent endocrinopathy in girls with McCune-Albright Syndrome (MAS). Main goals of treatment for PPP are to reduce signs of estrogen exposure, also improving final height, and mitigate secondary psychological influence of sexual hormones exposure. This retrospective study analyzes the long-term safety and efficacy of letrozole treatment in a cohort of girls with MAS-associated PPP.

Patients and Methods: Seven female girls affected by MAS showing signs of PPP were enrolled. A daily *per os* dose of 1.25-2.5 mg letrozole was administered. Subjects underwent serial anthropometric-clinical evaluation including history and physical examination, hormonal testing, bone age, and transabdominal pelvic ultrasound. Data were collected at five time points: at beginning (T0), ongoing (T1, 3 months; T2, 6 months; T3, 12 months) and (T4) at the time of discontinuation of the therapy.

Results: The mean age at PPP presentation was 2.4 ± 2.4 Years (0.2-8.0 years), the mean age of initiation therapy was 6.0 ± 2.3 years (2.7-9.3 years) with average duration of 2.6 ± 1.5 years (0.8-4.9 years). Thelarche regression was effective in 71% of

patients at T1, reaching 86% at T2. Bleeding episodes were almost completely remitted, since decreased from 57% at T0 to 14% at T1. The size of ovarian cysts and uterus decreased in 100% of cases, with a complete regression of the cysts in 57%. Growth velocity decreased in 71% of patients; bone age in relation to chronological age decreased in 43% of patients after 1 year of therapy and in 4/5 patients (80%) upon therapy discontinuation, while predicted the predicted final height z-score improved 2 girls. Central Puberty (CPP) occurred in 4 patients, so GnRH analogue treatment was associated. In the total person-year observing period of 27 years no side effects occurred.

Discussion: Letrozole therapy seems to be effective in reducing clinical manifestation of PPP in MAS girls and in our experience no side effects occurred. The benefits on skeletal maturation and growth are still controversial since bone age and growth velocity tend to decrease without clear effectiveness on height improvement. Further studies with additional patients who have completed treatment and reached skeletal maturity are needed to confirm the effect of letrozole on final height.

P2-401

Two sisters with primary hypergonadotrophic hypogonadism, pubertal progress and deletion of 61.5MB of Xq21.33q28 region

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Objective: To present the novel finding of hypergonadotrophic hypogonadism, pubertal progress and molecular alterations in two sisters with variable phenotype.

Case Presentation: Two Greek sisters were investigated. The eldest was referred for investigation of short stature, at the age of 9 and 5/12 years. There was no positive family history for short stature. Physical examination revealed no dysmorphic features, and she was prepubertal according to Tanner staging. She was diagnosed with growth hormone deficiency (peak GH 6 ng/ml, IGF-I 148.7 ng/ml) and she continues on growth hormone replacement therapy with good response to treatment and normal height at present (10%ile)

At the age of eleven years old she had breast development, however, laboratory investigation, revealed hypergonadotrophic hypogonadism, (FSH 31.24 m IU /ml LH 5.44 m IU /ml, estradiol 12.6 pg/ml). The karyotype was female 46, X, der (X) t (X; 20) (q21.32; p12.3). Her sister who, at the age of 10 years, was of normal height and prepubertal, was also investigated. She had elevated gonadotropins and the same karyotype as her sister. Ultrasound and magnetic resonance imaging of the uterus and ovaries in both sisters showed a similar picture. The right ovary was recognized with a cystic formation of 0.91 ml in the presence of an intact

follicle, while on the left, fibrous tissue was recognized at the site of the left ovary (0.16 ml). In the younger sister the left ovary was not recognized.

Array-CGH analysis detected a genomic pattern of female sex and the presence of: A) a size duplication ~ 8 megabases of the chromosomal region 20p13p12.3 (chr20: 60,747_8,117,942) that includes, according to the OMIM database 76 genes. B) a deletion ~ 61.5 megabases of the chromosomal region Xq21.33q28 (chrX: 93,622,826_155,226,073) which includes, according to the OMIM database, 102 genes.

The older patient at the age of 12.5 years had menarche. The laboratory results at this age were FSH 35.86 mIU / ml, LH 59.95 mIU / ml, Estradiol 173.9 pg / ml, antimüllerian hormone <0.01ng / mL.

Conclusion: We describe two sisters with unilateral hypoplastic ovary, hypergonadotrophic hypogonadism, normal mental status, and genomic pattern of female sex arr[hg19] 20p13p12.3(20:60,747_8,117,942) x3, Xq21.33q28(93,622,826_155,226,073) x1. To our knowledge, there are no reports of individuals carrying both findings. Regular monitoring of the patients is required in order to elucidate the evolution of the phenotype.

P2-402

Description of a new variant in the MAMLD1 gene in an infant with microphallus and hypospadias

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Introduction: The MAMLD1 gene is expressed in fetal and adult testes. It contributes to the development and formation of the male external genitalia in late stages of fetal organogenesis (week 8-12) and to testosterone biosynthesis. The pathogenic genetic variants of this gene determine a significant reduction in plasma testosterone concentrations, although they are not undetectable. Its most common phenotypic manifestation is hypospadias, also described in patients with microphallus with or without cryptorchidism.

Patient Description: 40 weeks gestation newborn with a microphallus of 1.5cm in length (nv:3.5cm ± 0.4) and terminal hypospadias with 3ml testes located in the scrotal bag. Normal anthropometry. At 6 days of life, a hormonal study was carried out with the following result: LH: 4.4IU/L (nv: 0.40-10.1IU/L), FSH: 3.8IU/L (nv: 0.6-7IU/L), Testosterone: 69ng/dl (nv:288-300ng/dl), IGF-I: 61ng/ml, and IGFBP3: 1.8g/dl. Normal thyroid and adrenal hormone profile. Karyotype 46, XY. Normal hypothalamic-pituitary magnetic resonance and testicular ultrasound with homogeneous echostructure and normal size testicles. At 1 month of age a 25mg dose of testosterone IM is administered. At 2 months of age the length of the penis is 2 cm with following hormonal profile: LH: 4.8U/L, FSH: 3U/L, testosterone: 49ng/dl, dihydrotestosterone (DHT): 0,1ng/ml (nv:0.25-0.99ng/ml), anti-

müllerian hormone (AMH): 77.2 ng/ml (nv: 97.9 ± 34.4ng/ml), inhibin B: 192pg/ml (nv: 209-321pg/ml). At the age of 4 months, a stimulation test with hCG 1000IU/dose is performed 3 times/week for 2 weeks without observing a significant increase in the concentrations of testosterone (111.1ng/dL), DHT (0.05ng/ml) or the length of the penis. The DSD massive gene sequencing panel identifies a hemizygoty pathogenic variant in the MAMLD1 gene (c.1738C>T:p.Gln580Ter)in exon3). Treatment with intramuscular testosterone 50mg every 3 weeks (2 doses) was started, showing a favorable response to treatment with an increase in penis length to 3.5cm.

Conclusions: Our patient presents a pathogenic variant in MAMLD1 not previously described in the literature that predicts "in silico" a truncated protein that could justify his genital phenotype. The existence of low testosterone concentrations during the infant's minipuberty stage and the absence of a significant increase in plasma concentrations of testosterone and DHT in the hCG test highlights the potential role of this gene in the biosynthesis of testosterone during the fetal stage and minipuberty of the infant. This case would be the first time that a decrease in DHT has been described in a patient with an abnormal MAMLD1. IM testosterone treatment is effective in these patients.

P2-403

Surgical aspects of the multicentric and interdisciplinary study in minors with different sexual development

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Introduction: After the evident socio-health transformation when facing intersexualities / entities with different sexual development (DSD), we wonder if clinical-care assistance has improved. Material and method Descriptive multicenter study by means of a retrospective review (2006-2019) of patients with a diagnosis of DSD in pediatric age. Interdisciplinary assessment through satisfaction surveys to families / patients. Results 67 patients were included. 27% were operated on, a total of 51 procedures, registering 18 complications. In the 22 cases with congenital adrenal hyperplasia, 16 procedures were performed, the majority (68%) for diagnostic purposes and 7 genitoplasties (32%). Median age of genitoplasties: 29 months, IQR 20.5-37 months. Registering 6 complications. 24 surveys were collected. Age Range: 1-20 Years, Fashion: 9-10 Years. Regarding the care process experienced, the information they had prior to diagnosis was nil-scarce in 87.5%. 75% and 54% consider the information received and the support in decision-making as good-excellent, respectively. Even so, the majority emotion was worry (62%) followed by fear or confusion. Evaluating the specialist teams, all classify endocrinology and surgical teams as good-excellent, as opposed to psychological assistance (55% bad-terrible and 45% good-excellent). Regarding the surgical

result, 1/3 of patients / family declared it excellent and 1/3 acceptable. 50% were good-excellent according to the surgeon. Conclusions: The post-surgical assessment is consistent according to the surgeon and family / patient. Major surgical procedures are scarce, the majority being procedures for diagnostic purposes. Genitoplasties have non-negligible complication rates. We advocate for psychological assistance as the main point of improvement.

P2-404

Is Inflammation the Major Driver of Polycystic Ovary Syndrome (PCOS)? A Proteomic Approach to Understanding PCOS in Adolescents and the Search for Novel Non-Invasive Biomarkers

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Background and Methods: PCOS is common and associated with significant comorbidity. However, its pathogenesis is complex and poorly understood. We have developed new methods for deep phenotyping discovery proteomic profiling of urine, aiming to identify disease mechanisms, drug targets and novel non-invasive biomarkers for PCOS in adolescents. Here, we present the baseline proteomic data from our prospective, longitudinal study (n=40). We undertook proteomic analysis (nano 2D-LC-QTOF MS^e) on a subset of 15 samples. We compared the urinary proteome of adolescents with PCOS (n=6), controls (n=6), and insulin resistance (IR) (n=3), to identify markers of PCOS as distinct from those of IR.

Results: We identified 3,793 proteins, of which, 314 were significantly and differentially expressed ($p < 0.05$) in the PCOS cohort in comparison to healthy controls, and 397 in the PCOS vs. IR analysis. Of these, 66 proteins overlapped and were differentially expressed in the PCOS cohort in comparison to both controls and IR, and as such are potential novel biomarkers for PCOS. These proteins had a median fold-change of -2.2 (range -16.6 – +1775.5) and eight were upregulated in the PCOS cohort. Gene ontology analysis revealed these proteins were mediators of complement, coagulation and apoptosis cascades, glucose homeostasis, pro-inflammatory cytokines, and cytoskeletal components, the latter important in folliculogenesis. Bioinformatic Ingenuity Pathway Analysis (IPA) of all significant proteins identified differential activation of 23 significant biological pathways in the PCOS cohort. The top five canonical pathways were the *coagulation system*, the *intrinsic prothrombin activation pathway*, *14-3-3-mediated signalling*, *remodelling of epithelial adherens junctions*, and *acute phase response signalling*. Almost half of all significant pathways (10/23; 43%) related to inflammatory/immunological responses and the

thrombotic/fibrinolytic systems. Nearly a quarter (n=5/53; 22%) were associated with glucose homeostasis/insulin resistance, hyperandrogenism, and neuroendocrine pathways. Whilst, one third (8/23; 35%) were involved in folliculogenesis, cytoskeleton reorganisation, remodelling, apoptosis and autophagy. IPA diseases and function analysis revealed the *inflammatory response* as the most significant biological process associated with PCOS in our study ($p < 0.001$).

Conclusions: To the best of our knowledge, this is the first study to utilise non-invasive matrices to map the proteome of PCOS in adolescents. We have identified 66 potential novel biomarkers, provided promising insight into the molecular pathways of PCOS, and demonstrated that inflammation could be a major contributory factor in the pathophysiology of this common condition. To confirm these findings, we are performing targeted multiplexed assays comprising 70 inflammatory proteins on our entire longitudinal cohort.

P2-405

Serum High Mobility Group Box 1 (HMGB1) levels are independently associated with glucose clamp-derived measures of insulin resistance in PCOS

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Polycystic Ovary Syndrome (PCOS) is one of the most common endocrine disorders among women of reproductive age, and is characterised by chronic inflammation and in most cases by insulin resistance besides ovulatory dysfunction and hyperandrogenism.

HMGB1 is a small protein with cytokine activity that can activate nuclear factor kappa light chain enhancer of activated B cells (Nf-kB), and signals through the Receptor for advanced glycation end products (RAGEs) and through the Toll like receptor family. HMGB1 is involved also with IR/hyperinsulinemia related diseases as diabetes type 2 and obesity, and its circulating concentrations have been reported to be higher in PCOS women with IR by us and in one previous study. The aim of the present study was to investigate the relationships between serum HMGB1 levels and clinical, endocrine and metabolic parameters of PCOS patients. Sixty women with PCOS, 30 with IR and 30 with normal insulin sensitivity (IS), and 30 healthy controls were included in the study. In these subjects, body fat was quantified by bioelectrical impedance; plasma HMGB1 levels were measured using a specific ELISA method (Tecan); and serum androgens were measured by liquid chromatography/mass spectrometry and equilibrium dialysis. In

PCOS women, IR was measured using the gold standard hyperinsulinemic-euglycemic clamp technique, combined with indirect calorimetry.

HMGB1 levels did not differ in PCOS women with respect to healthy controls (4.11 ± 3.22 vs 3.77 ± 2.50 ng/mL, respectively; $p=0.61$). Moreover, HMGB1 levels did not differ between PCOS phenotype subgroups. However, PCOS IR women showed higher levels of this protein as compared with PCOS IS (5.00 ± 3.53 vs 3.16 ± 2.59 ng/mL, respectively; $p=0.017$). In women with PCOS, HMGB1 levels were associated with several metabolic parameters, including IR measured by glucose utilization during the clamp ($\rho -0.37$, $p=0.005$). This correlation was preserved after adjusting for potential confounding parameters, such as age, fat mass and serum free testosterone. HMGB1 levels did not change during glucose-clamp induced acute hyperinsulinemia, either in the whole cohort of patients or in IR and IS subgroups analyzed separately. Both in the whole population under study and in PCOS women, HMGB1 levels did not correlate with anthropometric parameters, hormonal features and ovarian morphology.

HMGB1 blood levels showed an independent association with insulin resistance in women with PCOS. However, no associations with other typical features of the syndrome were found. Further research is needed to elucidate a possible role of this protein in the pathogenesis of PCOS.

P2-406

ZSWIM7 is associated with human female meiosis and familial primary ovarian insufficiency

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Background: Primary ovarian insufficiency (POI) affects 1% of women and is associated with significant medical consequences. In approximately 10% of cases, POI presents early with absent puberty or primary amenorrhoea. A genetic cause for POI can be found in up to 30% of women. Identified genes often relate to the complex biological processes occurring in fetal life which underpin normal ovary development and function in later adulthood.

Objective: We aimed to identify the genetic mechanism underlying early-onset POI in two sisters.

Methods: Exome sequencing and filtering using an autosomal recessive model was performed in the two affected sisters and their unaffected family members. Quantitative reverse transcriptase PCR (qRT-PCR) and RNA sequencing were used to study the expression of key genes at critical stages of human fetal gonad development (Carnegie Stage (CS) 22/23, 9 weeks post conception (wpc), 11wpc, 15/16wpc, 19/20wpc) and in adult tissue.

Results: The two sisters were from a consanguineous pedigree and presented with absent puberty and primary amenorrhoea. A diagnosis of POI was made on the basis of elevated FSH (94.8IU/L; 77.8IU/L), 46,XX karyotype, small ovaries on imaging, and no other obvious aetiology. Exome sequencing revealed only one homozygous variant co-segregating with the POI phenotype: a stop gain mutation in *ZSWIM7*, NM_001042697.2:c.173C>G, p.Ser58*. This variant is predicted to result in nonsense mediated decay and loss of the key zinc finger SWIM protein domain, precluding further functional studies. *Zswim7* is involved in homologous DNA repair during meiosis in mice. qRT-PCR demonstrated higher expression of *ZSWIM7* in the 15/16wpc ovary compared to testis, corresponding to peak meiosis in the fetal ovary. *ZSWIM7* was expressed in both the adult ovary and testis. RNA sequencing of fetal gonad samples showed that *ZSWIM7* has a similar temporal expression profile in the developing ovary to other homologous recombination genes known to be important for meiosis prophase I and which have been previously implicated in the pathogenesis of POI, including *MEIOB-BRCA2*, *STAG3*, and *RAD51*.

Conclusions: Disruption of *ZSWIM7* is associated with human meiosis and POI and can present with absent puberty. *ZSWIM7* is likely to be important for homologous recombination with roles in meiotic and potentially non-meiotic recombinational DNA repair pathways. These findings expand the number of genes associated with POI and demonstrate that a mechanistic understanding of POI can be gained from considering meiotic genes as functional partners.

P2-407

Is the recommended dual therapy for transsexual boys harmless?

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Objective: To study the impact of dual therapy on BMD and Inhibin B in a group of transsexual male adolescents who initiate treatment with advanced pubertal development.

Patients and Methodology: Retrospective study of 16 male minors who initiated treatment (Triptorelin and later Testosterone)

with complete pubertal development. Variables included: age, weight and height at baseline and at the last visit (calculated in SDS for assigned age and sex), BMD in L1L4 and total body (GE HealthCare's LUNAR Densitometer: in g/cm² and calculated in SDS for assigned age and sex), vitamin D and Inhibin B (Enzyme Immunoassay, normal range 25–325 pg/ml) as a marker of ovarian reserve. Statistical analysis with SPSS V25 software.

Results: Initial data: age 13.6±1.6 years, weight-SDS 0.96±1.7, height-SDS 0.1±1.4, BMD L1L4 1.12±0.18 g/cm² (SDS 0.5±1.3), BMD total body 1.06±0.08 g/cm² (SDS 0.84±1.03), Inhibin B 32.6±37.5 pg/ml. The determinations were repeated after 14±6 months of Triptorelin therapy (dose 60 µg/kg/4 weeks) and 13.2±8 months, after associating Testosterone (mean dose 113±52 mg/4 weeks). The results are shown in the table.

BMD values are normal at baseline and during therapy. BMD-SDS decrease progressively throughout the treatment. The mean initial level of Inhibin B is normal, seems to decrease during Triptorelin therapy and to normalize when Testosterone is associated, (differences are not statistically significant). Vitamin D levels remain low despite replacement therapy. Weight-SDS in the last visit is, on average, in the limits of overweight.

Conclusions: The physiological increase in BMD (g/cm²) at this age it's not observed but a significant decrease doesn't appear. Inhibin B doesn't undergo relevant modifications. Long-term studies are required to ensure the safety of dual therapy.

P2-408

Plexiform neurofibroma of the penis as an infrequent manifestation debut in a pediatric patient

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Background: Neurofibromatosis type 1 (NF1) caused by loss of function mutation in the NF1 gene; leads to the hyperactivation of RAS and its downstream mediators and contributes to tumour formation. The main manifestations of NF1 are café au lait macule, axillary and/or inguinal freckling. Neurofibroma plexiform is specific for NF1 and identified on the face and trunk. Urogenital presentation is infrequent in the penis. Identification of this lesion is essential because it carries a risk of malignancy in about 5%–10% of patients.

Case: We present a five-year-old boy who presented to us with progressive swelling of the penis since he was a newborn. He had no swelling in other parts of the body, without Urinary dysfunction and no history of neurological symptoms. Genitourinary examination revealed a penis length of 9 cm (greater than 2 SD for age) and a girth of 10 cm at the base level. Small lentigines at the tip and base of the penis. Unpigmented scrotum and testicular volume less

	Baseline	Triptorelin	Testosterone	p
Age (years)	13.6±1.6	14.8±1.3	15.8±0.9	-
BMD L1L4 (g/cm ²)	1.12±0.18	1.14±0.16	1.12±0.14	ns
BMD L1L4 (SDS)	0.5±1.3	0.26±1.5	-0.37±0.94	0.002
BMD total body (g/cm ²)	1.06±0.08	1.02±0.09	1.05±0.08	ns
BMD total body (SDS)	0.84±1.03	0.66±1.08	0.33±1.04	0.006
Inhibin B (pg/ml)	32.6±37.5	14.4±15.7	31.0±29.2	ns

	Baseline	Last Visit	
Age (years)	13.6±1.6	17.2±1.3	-
Vitamin D (ng/ml)	18.2±7.1	21.1±6.1	ns
Weight (kg)	-	70.6±19.9	-
Weight (SDS)	0.96±1.7	1.64±2.1	ns
Height (cm)	-	163.6±10.1	-
Height (SDS)	0.1±1.45	0.02±1.7	ns
Test Wilcoxon			

than 3 mL. After a dermatological evaluation, small café-au-lait spots observed on the right hip and posterior side of the left leg. The sister presented a hypopigmented spot on the hip skin and a café-au-lait spot on the right leg, and the father with reddish spots in the popliteal with a lymphatic appearance. A genital ultrasound showed lesions compatible with plexiform neurofibroma, and his hormonal profile, such as androstenedione, total testosterone, DHEA-S, 17-OHP and LH were within normal ranges. INVITAE study for RASopathies Comprehensive Panel and EPHB4 gene reported negative.

Conclusion: The genetic testing of NF1 would help to clarify the diagnostic process; however, this can be difficult for several reasons like phenotypes caused by mosaicism with mutations after fertilization; and are classified as segmental, generalized, or gonadal. The segmental type causes regions with pigmentary alterations, tumour growths, or both, limited to one or more regions of the body, precisely the diagnosis that we consider corresponds to our patient, even though genetic study (invitae) is reported as negative. It is essential to identify the diagnosis due to the increased risk of malignancy.

P2-409

Surprising X Chromosomes: Unusual Mosaicism

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Background: Among 46,XY individuals, androgen insensitivity syndrome (AIS) due to deleterious variants of the androgen receptor (AR) gene is one cause for a difference of sexual development (DSD). Typically, individuals with complete androgen insensitivity syndrome (CAIS) present with female external genitalia and palpable labial masses. Whereas most patients carry germline variants inherited in an X-linked manner, approximately 30% of patients manifest de novo variants. We describe an infant with phenotype-genotype incongruity associated with a variant in AR.

Case Presentation: This patient was referred to endocrinology at the age of 3 weeks for evaluation of atypical genitalia. The exam showed bifid scrotum, bilateral descended testes, scrotal hypospadias with chordee, and 1 cm phallus. Initial studies showed normal random growth hormone, cortisol, and 17-hydroxyprogesterone levels. Chromosome analysis showed 46,XY karyotype; FISH confirmed presence of the SRY gene. A pelvic ultrasound revealed absence of any Mullerian structures. Additional studies obtained at 2 months of age showed LH 1.78 IU/L, FSH 0.45 IU/L, testosterone 282 ng/dl (9.8 nmol/L), and DHT 65 ng/dl (2.2 nmol/L). Due to the infant's undervirilization, whole exome sequencing was performed. A rare pathogenic variant in the AR gene, c2104C>T, predicted to result in amino acid substitution p.Leu702Phe (rs155595851) was detected in 48% of the sequence reads, consistent with somatic mosaicism.

Discussion: The initial evaluation of this patient excluded hypopituitarism and defects in steroidogenesis from consideration. This AR gene sequence variant has been previously confirmed to be associated with CAIS. In this patient, somatic mosaicism for a pathogenic AR variant likely explains the inconsistency between his partially virilized phenotype and the sequence variant predicted to cause CAIS. Somatic mosaicism for a DNA sequence variant, resulting from post-zygotic changes during the early stages of embryo development, is emerging as a significant contributor to DSD. Identification of mosaicism is important for management and will help the medical team and the family discuss sex of rearing. For patients with mosaicism for a disease-causing variant, the proportion of cells with a wild type AR is likely variable and may ultimately influence androgen responsiveness and the patient's phenotype during adolescence and adulthood. Virilization at puberty has been reported in males with somatic mosaicism of AR (JCEM 2005; 90:106). Our patient showed some response to a testosterone trial and will receive another trial course of higher dose testosterone.

P2-410

Puberty delay in girls: etiological structure of the disease

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Objective: to analyze the structure of puberty delay in girls depending on the etiology of the disease.

Materials and Methods: 51 girls with puberty delay (14.2±0.82) were examined. Inclusion criteria: absence of secondary sex characteristics at 13; or absence of menarche by age 15 years or the absence of menarche during 3 years from the onset of estrogen-dependent puberty signs development. Exclusion criteria: age ≥18, ambiguous genitalia. Tanner stage, antropometric data, bone ages, genitometric parameters, LH, FSH, estradiol, testosterone, DHEA, inhibin B, AMH were provided. Stimulation tests using gonadotropin analog (n=24), cytogenetic (n=45), molecular genetic tests (n=7) and brain MRI with contrast (n=5). According to the results of complex examination and follow-up all the patients were divided into 2 groups depending on the onset of menarche: 1st group with permanent puberty delay (hypogonadotropic/hypergonadotropic hypogonadism) and 2nd group with transient puberty delay (functional hypogonadism/constitutional puberty delay).

Results: the permanent puberty delay was observed in 51% (26/51), which was caused by hypergonadotropic hypogonadism in 80.8% (21/26) and by hypogonadotropic hypogonadism in 19.2% (5/26, p<0.001) of girls. Transient puberty delay was diagnosed in 49% (25/51) which was caused by functional hypogonadism in 52% (13/25), by constitutional delay of puberty in 48% (12/25, p=0.778).

Among girls with hypergonadotropic hypogonadism Turner syndrome was diagnosed in 42.9% (9/21), disorders of sex develop-

ment 46,XY was diagnosed in 33.3% (7/21), disorders of sex development 46, XX in 23.8% (5/21). Moreover, the causes of disorders of sex development 46,XY included pure gonadal dysgenesis 46,XY in 57.1%(4/7), androgen insensitivity syndrome (complete form) in 42.9% of cases (3/7). Isolated hypogonadotropic hypogonadism diagnosed in 60% (3/5) while hypogonadotropic hypogonadism as a manifestation of hypopituitarism was diagnosed in 40%(2/5). Functional hypogonadism was caused by decompensation of type 1 diabetes mellitus in 46.2%(6/13), protein-energy malnutrition in 46.2%(6/13), celiac disease in 7.6%(1/13).

Conclusion: puberty delay structure in girls includes the equal proportions of transient and permanent hypogonadism cases. Hypergonadotropic hypogonadism is more often associated with permanent puberty delay (Turner syndrome, disorders of sex development, pure gonadal dysgenesis 46, XX, pure gonadal dysgenesis 46, XY, androgen insensitivity syndrome), while hypogonadotropic hypogonadism (isolated gonadotropin deficiency and hypopituitarism) is diagnosed in 1 out of 10 cases. Transient puberty delay as a result of constitutional delay of puberty in girls is observed as often as when it caused by functional hypogonadism due to somatogenic pathology (type 1 diabetes mellitus, protein – energy malnutrition, celiac disease).

P2-411

Rationale for a reduced dexamethasone dose in prenatal congenital adrenal hyperplasia therapy based on pharmacokinetic modelling

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Context: Prenatal dexamethasone (Dex) therapy is used in female foetuses with congenital adrenal hyperplasia (CAH) to suppress adrenal androgen excess and prevent virilisation of the external genitalia. The prenatal dexamethasone dose of 20 µg/kg/d has been used for decades in prenatal CAH. Despite the risks for the treated mother and potentially for the unborn child, no clinical study or evaluation had been conducted in order to determine a Dex dose with a scientific rationale.

Objective: To investigate a rationale of a reduced Dex dose in prenatal CAH therapy based on a pharmacokinetics-based modelling and simulation framework.

Design and Methods: Data from a published Dex study were used to develop a nonlinear mixed-effects model describing maternal dexamethasone pharmacokinetics (PK). In stochastic simulations (n=1000), a typical pregnant population (n=124) was split into two dosing arms receiving either the traditional 20 µg/kg/d dexamethasone dose or reduced doses between 5 and 10 µg/kg/d.

Target maternal dexamethasone concentrations, ensuring foetal hypothalamic-pituitary-adrenal axis suppression, were identified from literature and served as threshold to be exceeded by 90% of mothers at steady state.

Results: A two-compartment dexamethasone pharmacokinetic model was successfully developed and evaluated. The simulations, as well as a sensitivity analysis regarding the assumed foetal:maternal dexamethasone concentration ratio, resulted in 7.5 µg/kg/d to be the minimum effective dose and thus our recommended dose.

Conclusions: Based on our modelling and simulation results, the current experimentally used Dex dose seems 3-fold higher than needed, resulting in unnecessary high risks for treated mothers and foetuses. The clinical relevance and appropriateness of this reduced Dex dose during pregnancy will be tested in a prospective international clinical trial.

P2-412

45,X/46,XY Mosaicism: Phenotypic characteristics, Growth, and Gonadal features

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Introduction: 45,X/46,XY mosaicism is a rare sex chromosome abnormality. The aim of this study is to provide outcomes, namely growth, comorbidities and gonadal function in patients with 45,X/46,XY mosaicism.

Methods: This was a retrospective, longitudinal study conducted from January 2006 to January 2021 at a tertiary pediatric endocrine referral center. Patients' clinical presentation, karyotypes, height, hormonal profiles, imaging and histologic findings of the gonads were evaluated. Phenotypes were scored using external masculinization scores (EMS).

Results: A total of 12 patients (8 boys, 4 girls) with 45,X/46,XY mosaicism and its variants were included. 11 out of 12 patients presented with ambiguous genitalia. Median height SD score was -2.62 (range, -3.26 to -2.0) for females and -0.46 (range, 0.13 to -1.7) for males, both below genetic potential. 25% of patients had other abnormalities – cardiac and renal abnormality. Males in our cohort were undervirilized as the median EMS score was 4.5 [3.75 – 7.25]. During the course of follow up two patients underwent gender change. Two male patients had testicular microlithiasis. Mullerian duct remnants were identified 66% of the time. Histology of 14 gonads was available from patients who had undergone a gonadectomy or gonadal biopsy. All tissue samples from patients revealed abnormal gonadal histology. All intrabdominal gonads were streak or dysgenetic testicular tissue.

Conclusions: The 45,X/46,XY phenotype varies widely. Short stature and 45,X/46,XY mosaicism are associated. Management of each patient should be individualized according to the clinical assessment.

P2-413

Challenges faced by children and adolescents with Differences in Sex Development (DSD) managed at a tertiary care specialized university center in Sri Lanka

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Introduction: DSDs encompass a heterogeneous group of conditions associated with multiple medical and psychosocial challenges. There is a paucity of data from patients from relatively low resource settings, where difficulties faced and their management may differ based on the different socio-cultural background.

Objectives: To describe the underlying condition, presentation, medico-social issues, problems and challenges, and their management in a cohort of children and adolescents with DSD followed up at the University Paediatric Endocrine Clinic of the Faculty of Medicine, at the Lady Ridgeway Hospital for children, Sri Lanka.

Method: Clinical data of consenting patients with DSD registered at the clinic were collected onto data collection sheets during clinic visits and entered to an electronic database between 2018-2020. Ethics approval (EC- 18-092) was obtained from the Ethics Review Committee, Faculty of Medicine, Colombo.

Results: Among 111 individuals with DSD (mean age 12.5), 26 (23%) were children below 10 years of age and 85 (77%) were adolescents (aged 10- 22 years). Gender of rearing was female in 63 (57%) and male in 48 (43%). The commonest DSD type was 46 XY DSD (n=49, 44%), followed by 46 XX DSD 32% (n=34, 31%) and chromosomal DSD (n=15, 14%). Commonest underlying diagnoses were CAH (n=41, 37%) and Turner's syndrome in (n=14, 13%). Genetic diagnosis was available in 3 patients and majority of patients (n=56) lived outside the province where the centre was located in. More than half (n= 64, 58%) initially presented with ambiguous genitalia at birth and 9 (8%) had birth registered in the gender opposite that of rearing. 58 patients (52%) had undergone genital surgery either feminizing genitoplasty (n =3) or hypospadias repair +/- orchidopexy (n=20). Regarding issues faced by adolescents, spontaneous puberty was incongruent with gender of rearing in 3 patients, 5 had gynaecomastia and a quarter of all adolescents (n=21) needed pubertal induction. 10 patients (9%) had received pubertal suppression with GnRH analogs (7 to suppress precocious puberty, 3 to suppress secondary sexual characteristics incongruent with GR)

Discussion: The study elucidates the challenges encountered by patients with DSD of different age groups and the interventions provided at a relatively low resource healthcare setting. Whilst the patients had relatively good access to hormone replacement therapy, genital surgery and multi-disciplinary care; the lack of genetic facilities, legal support and absence of nearby centres remain prevalent issues hindering optimum patient outcome.

P2-414

A novel mutation of SOX2 gene in an idiopathic hypogonadotropic hypogonadism patient with olfactory bulb agenesis

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Abstract: Objective To enhance the understanding of the clinical phenotypes of patients with SOX2 gene mutations.

Method: A retrospectively analysis of the clinical manifestations and the laboratory results of a child diagnosed as idiopathic hypogonadotropic hypogonadism (IHH) by whole exome-gene sequencing and a review of relevant literatures.

Results: A 12-year-old boy clinically manifested short stature, mental retardation, a history of strabismus and gonadal dysgenesis, whose imaging examination showed no structure of the olfactory bulb. Whole exome-gene sequencing was performed and then identified the SOX2 gene de novo heterozygous mutation c.259A>G, p.Lys87Glu.

Conclusion: The SOX2 gene is involved in the development of the eyeball, the central nervous system, the olfactory bulb and the gonads. Mutations in this gene can lead to hypogonadotropic hypogonadism and olfactory bulb agenesis. The mutation site of this case has not yet been reported, and this is the first reported case of olfactory bulb agenesis in a SOX2 gene mutation patient, expanding the clinical phenotype of SOX2 gene mutations and the pathogenic gene pool of IHH. The whole exome-gene sequencing methods is helpful in the molecular diagnosis of such genetic heterogeneous diseases.

P2-415

Obesity, ovarian mass, vaginal bleeding and hypothyroidism in a 5-year-old female girl

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Introduction: Van Wyk-Grumbach Syndrome (VWGS) is a constellation of symptoms including precocious puberty without adrenarche, delayed bone age, ovarian cysts, and hypothyroidism.

Case Report: We report here a five-year-old girl who presented for evaluation of obesity, abdominal distension, vaginal bleeding, and abdominal distention. Her HtSDS = -1.3 and BMI SDS = 1.5. A large abdominal mass was palpable. She had no breast development or pubic hair. Her Investigations revealed TSH = 2288 uIU/ml and FT4 = 0.09 ng/dl, LH = 0.11 mIU/ml, FSH = 1.2 mIU/ml, and Anti TPO = 600 U/ml and anti-thyroglobulin antibody = 296 U/ml. Ct of the abdomen showed bilateral adnexal multi-locular masses. The right = 8x7.5x10.5 cm and the left = 4.5 x8.5 x 7 m. There were no enhancing solid components identified. There were a diffuse mural vaginal thickening and endo-vaginal collection and bulky uterus. L thyroxine was prescribed 75 mcg OD. After a month on thyroxine therapy, FT4 = 2.6 ng/dl, TSH = 2.43 mIU/ml.

Her ultrasonographic evaluation showed marked regression of the two adnexal lesions 9 right = 5.3 x 4.3 x 3.1 cm, and left = 4.4 x 3.5 x 2.9. The uterine body measured 4.7 x 1.7 cm.

Discussion: Significant regression of the ovarian masses occurred as early as 1 month after replacing thyroid hormone in this girl with VWGS. The etiology of her hypothyroid status was autoimmune. Given the presence of significant ovarian masses, a surgical emergency such as ovarian torsion or rupture must be ruled out. Even when the diagnosis of VWGS is confirmed, practitioners must be watchful to consider surgical intervention in the presence of uncontrolled vaginal bleeding, hemodynamic instability, or failure of regression of ovarian cysts with exogenous thyroid hormone replacement.

Conclusion: VWGS should be considered in the differential diagnosis of young girls with ovarian masses with vaginal bleeding and hypothyroidism. The prognosis is good with thyroid replacement therapy.

P2-416

Ovarian Juvenile Granulosa Cell Tumor in 9-Month-Old female Infant presented with Isosexual Pseudo Puberty: Case Report

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Background: In infants, less than 1-year JGCT is extremely rare, with very few reported cases in the literature.

Case Report: This 9-month old girl, presented with a day history of bloody vaginal secretions, with an increase in breast size bilaterally 2 months before presentation and growth of fine hair in the genital area. She had no skin hyperpigmentation, no skeletal abnormalities, and no dysmorphic features. On examination, the girl had no dysmorphic features. Her length = 75cm (1.66 SD), weight = 10.4kg (1.85SD), BMI = 18.07Kg/m² (0.92SD). Breasts (Tanner stage 2), with fine pubic hair. Her Initial laboratory investigations showed Androstenedione 6.8nmol/l (n=0.0-3.0), Dihydroandrostenedione sulfate 0.320umol/l (n=0.090-3.35), estradiol 1091pmol/l (0.0-132), FSH < 0.3 IU/L (n=1.2-12.5). LH < 0.3 IU/L (n=0.3-2.5), Anti-Mullerian Hormone (AMH) > 1714.0 pmol/L (n=0.1-38.6), Testosterone Level 2.2 nmol/L (n=0.0-2.2), Beta human Chorionic Gonadotropin 0.9 IU/L (n=0.0-5.0), Alpha-Fetoprotein 6 kIU/L (n=1-33) Serum Inhibin A 385pg/ml (n<4.7), and Serum Inhibin B 3805pg/ml (n < 111). Ultrasonography showed a well-defined round-shaped heterogeneous hypoechoic lesion 62.8ml in volume, 5.4x4.12x5.39 cm in dimension. No calcifications. Uterus developed 5.2x2.4x2.3 cm in diameter. Bone age was 1.8 years (+4.3 SDS for age and sex). MRI of the abdomen and pelvis was revealed a large solid lesion in the lower abdomen and pelvis related to the left ovary with significant gadolinium enhancement and minimal central necrosis. The uterus was enlarged. Findings were suggestive of hormone-producing sex cord-stromal tumor. Computed Tomography for the chest was normal.

Based on findings above total left salpingo-oophorectomy was done through an open abdominal incision, Smooth-surfaced ovoid encapsulated mass weighing 75g and measuring 100 x 50 x 40 mm with fallopian tube 50 mm long, attached. Solid yellow, nodular cut surfaces with no necrosis, hemorrhage, or cystic spaces. There is a small surface nodule near the Fallopian tube, 5mm across. Otherwise, the capsule is intact. The patient had no reported postoperative complications, no chemotherapy or radiation was administered. The patient sent home in the third postoperative day in good condition.

The histopathology revealed GCT, Juvenile type stage pT1a. Immunohistochemistry showed positive staining for inhibin A.

At 1 month follow up, no new concerns, repeated Hormonal test showed dropping of estradiol to 62pmol/l (0.0-132), and (AMH) to 9pmol/L (n=0.1-38.6).

Conclusion: These 9 months-old infants with JGCT presented with peripheral precocious puberty and advanced skeletal maturation. Surgical removal was curative with regression of all hormones to prepubertal levels.

P2-417

A case report of Non-syndromic 46, XX testicular DSD presenting as a genital ambiguity - Clinical, molecular and cytogenetic analysis

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Background: To demonstrate the etiology of 46, XX sex reversal by investigating the clinical feature and its relationships with chromosomal karyotype and the SRY (sex-determining region Y) gene.

Methods: A child with genital ambiguity with hypospadias and bifid scrotum consulted to our endocrine OPD for further management. Clinical data was noted, and Karyotype analysis of G-banding in lymphocytes and Fluorescence in situ hybridization (FISH) were performed. FISH analyses were conducted on both metaphase spreads and interphase nuclei.

The genomic DNA was isolated from EDTA whole blood. The isolated genomic DNA was checked for the presence of SRY and ZFY (Zinc finger chromosomal protein) genes to access the male factor via Polymerase Chain Reaction (PCR) followed by agarose gel electrophoresis.

Results: Examination of external genital showed bifid labio-scrotum sac, small phallus with ventral chordae with penoscrotal hypospadias. No history of consanguinity.

The biochemical test reveals normal electrolytes and renal function. His testosterone basal of 0.014 ng/dl, post HCG stimulation testosterone was 399ng/dl. Follicle-stimulating hormone was 1.32mIU/L (reference range: 0.26-3.0 IU/L) luteinizing hormone was 0.001 mIU/L (reference range: < 0.3 IU/L), and thyroid hormones, and serum cortisol were all within normal levels. 17 OH progesterone was 0.2ng/ml.

Ultrasound examination showed that patient's bilateral gonads were found lateral to the phallic shaft right and left gonads

measuring 1×0.5 cm and 0.5×0.47 cm respectively; no Mullerian structures were identified.

The karyotype was 46, XX. FISH analyses were conducted on both metaphase spreads and interphase nuclei which revealed a pair of X-chromosomes in all analyzed cells, ruling out mosaicism confirming conventional karyotyping results.

By PCR, the most common Yp loci, SRY, and ZFY were detected in the patient sample confirming the presence of malefactors.

Conclusions: Our case puts in a new case of 46, XX male subject with SRY-positive gene and further demonstrates that the presence of SRY gene and the absence of major regions in the Y chromosome should lead to masculinized phenotype with genital ambiguity.

Keywords: 46, XX testicular disorder of sex development (DSD), SRY-positive

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P2-418

46 XX, SRY negative testicular DSD presenting with VACTERL Syndrome

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Introduction: Sex determining region Y (SRY gene) located in chromosome Yp11.3, initiate gonadal differentiation into testes, which subsequently leads to development of Wolffian duct, male external genitalia, and regression of Mullerian duct. Not only SRY, SOX9, FGF9, DAX1, WT1, RSPO1, and SOX10 contribute for gonadal differentiation. Imbalance of expression of above genes in the absence of SRY leads to 46, XX testicular DSD. We describe a case of 46, XX testicular DSD presenting as VACTERAL abnormality.

Case History: Baby boy born as a first child to second degree consanguineous parents at term with the birth weight of 2800g. He had multiple congenital abnormalities. Which include imperforated anus, tracheo esophageal fistula, Tetralogy of Fallot, urogenital abnormality and ambiguous genitalia. Examination of external genitalia revealed prominent labioscrotal folds with pigmentation without rouge. Phallus was 1cm without palpable gonads in the perineal region. Ultrasound revealed bilateral undescended intra abdominal testes without identifiable Mullerian structure and ovaries. He also had complex urogenital sinus abnormality and left side dysplastic kidney. Karyotyping came as 46,XX SRY negative. He underwent loop sigmoid colostomy, esophagostomy and gastrotomy, vesicostomy and TOF repair. He is awaiting for esophageal reconstruction, refashioning colostomy, biopsy of intra abdominal gonads and orchidopexy.

Discussion: Majority of patients with 46,XX, SRY negative testicular DSD present with genital ambiguity (micropenis, hypospadias, and cryptorchidism) and infertility. Our patient had multisystem congenital abnormality suggestive of VACTERL syndrome. The SRY gene has a critical role in sex determination. SOX9, FGF9, and MAP3K1 genes play role in testicular development, RSPO1 and WNT4 genes involve in ovarian development. Dysregulation of above genes such as over expression of SOX9 and under expression of RSPO1 will lead to testicular DSD in the

absences of SRY. This child need lifelong follow up from multiple specialties. Genetic testing will help to find the exact etiology and appropriate further follow up.

P2-419

A late revelation of Sexual differentiation disorder 46XX due to 11 beta hydroxylase deficiency

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Introduction: Congenital adrenal hyperplasia due to 11 beta hydroxylase deficiency, is an autosomal recessive pathology that represents 5 to 8% of congenital adrenal hyperplasia.

The predominant symptoms of this disorder are androgen excess' features, including masculinization of female newborns and precocious puberty in male children. Approximately, two thirds of patients also have hypertension, which may or may not be associated with mineralocorticoid excess, hypokalemia, and metabolic alkalosis.

This observation reports the case of a child raised as a male, with congenital adrenal hyperplasia due to 11 beta hydroxylase deficiency, discovered as part of an exploration of a precocious pseudo puberty with high blood pressure and hypokalemia.

Observation: B.M is a 9 years old patient, from a second-degree consanguineous marriage, with an assigned male sex. B.M was brought up as a boy, he had a personal medical history of rheumatic fever and a similar case with his German cousin has been described. His height was 136cm (-1DS), Tanner was A5P5S1 with bilateral unpalpable testes.

BP: 170 / 120 mmHg. Karyotype test result was 46 XX, and laboratory examination showed: a high value for ACTH: 374pg/ml, testosterone: 4,3ng/ml delta 4-androstenedione: 126,4 nmol/l and

Deoxycorticosterone (DOC): 1448pg/ml. Ovaries and a uterus fundus, without abnormalities were found on USG examination. CT showed a homogeneous bilateral adrenal Hyperplasia. Trans-thoracic ultrasound: concentric left ventricular hypertrophy, minimal mitral regurgitation, minimal aortic insufficiency. Bone age study corresponded to 17-year-old male. The primary psychiatric expertise affirmed that the child is oriented towards the male phenotype and her parents chose to keep him as a male.

The orientation of child's sex will be reassessed after one year of psychiatric follow up. Removal of internal genitalia and wide hysterectomy before puberty will be, therefore, discussed.

Discussion: Late diagnosis of Congenital adrenal hyperplasia of the overrenal is a problem of sexual orientation so diagnosis and antenatal treatment are essential to avoid the virilization of the feminine sex fetus. So, the absence of testicles in the apparent scrotum and inguinal canal after physical examination is worth noting; had it been identified from the time of birth, it could have led to an early diagnosis and avoided the dilemma of dealing with a mismatch between chromosomal and assigned sex at a later age.

The challenge is to ensure good growth in the soil and soil between androgen hyperstimulation and corticoid therapy and to ensure a good quality of life.

Gonadal Tumor Risk, Bone Mineral Density, and Genetics, Clinical, Hormonal, and Psychosexual Aspects of a Large Androgen Insensitivity Syndrome Cohort

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Introduction: Androgen Insensitivity Syndrome (AIS) is the most common cause of Differences of Sexual Development (DSD) in 46, XY individuals. It is an X-linked genetic disease caused by allelic variants in the Androgen Receptor Gene (Xq11-12). **Methods:** Patients with clinical suspicion of AIS performed hormonal serum measurements (LH, FSH, estradiol, testosterone) and molecular sequencing of the AR gene, including exons and the 5'UTR region. Psychosexual variables (gender identity, gender role and sexual orientation) were evaluated through psychological questionnaires and tests. Histopathological and immunostaining of CD240 and OCT3/4 studies were carried out for all individuals submitted to gonadectomy. **Results:** This cohort is made up of 64 individuals: CAIS (n=25) and PAIS (n=39), from 46 different families. The inguinal hernia was the first clinical presentation in 35% of CAIS. Among the PAIS, 20 (52%) were assigned as females at birth, while 18 (48%) as male. Among PAIS, the degree of external genitalia virilization (Sinnecker score) influenced sex assignment ($p < 0.01$). Standing final height and weight were similar between PAIS and CAIS. The bone mineral apparent density (BMAD) by DXA was similar between individuals who had or not gonadectomy as well as between CAIS and PAIS. Furthermore, gender identity in adulthood, gender role at childhood, and sexual orientation agreed with sex assignment in virtually all cases of both PAIS and CAIS. No gender change was observed. Molecular diagnosis was obtained in 96% of CAIS and 87% of PAIS. Ten novel AR variants (4 in CAIS - 2 small deletions, one *missense* and one at splicing site and PAIS - 5 *missense* and two synonymous (both causing a new exonic splicing site leading to an aberrant AR protein). LH ranged from 9 to 48 UI/L (mean 19), testosterone from 190 to 1500 ng/dL (mean 438), without phenotype differences. Gonadal tumors were identified in 3 out of 25 (12%) among CAIS. There were two cases of Seminoma and a rare case of a borderline serous tumor. All CAIS tumors were identified after puberty. Among PAIS, there were 2 cases of NICG (at 3 and 19 years of age). **Conclusion:** Hormonal levels did not enable us to differ from PAIS and CAIS. Inguinal hernia is the commonest clinical presentation of AIS. External genitalia appearance in PAIS influenced sex assignment. The psychosexual development in AIS is usually aligned with sex assignment. There is a risk of gonadal tumors in CAIS, especially after puberty, which is not low enough to be ignored.

Radiological evaluation of children with atypical genitalia due to disorders of sex development (46, XY DSD) in a resource-limited setup

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Background: Disorders of sex development (DSD) comprises a heterogeneous group of conditions involving interference with normal sex differentiation and hormonal production in the embryo. Imaging is a very useful tool in assessing the patient's phenotypic sex through identifying the internal genital anatomy and the adrenal glands. Ultrasonography is a cheap and readily available tool. MRI has disadvantage of being expensive with long waiting lists especially in developing countries. We aimed to study the value of these 2 tools in the radiological evaluation of 46 XY DSD cases.

Methods: All 46, XY DSD cases referred to Endocrinology Clinic in Alexandria University Children's Hospital for evaluation of atypical genitalia over one year were included in the study. Parents signed an informed consent to participate in the study. Patients were subjected to full clinical assessment including external masculinization score (EMS) and blood testing for karyotyping, testosterone (T), dihydrotestosterone (DHT), Follicle stimulating hormone (FSH) and luteinizing hormone (LH). All cases had ultrasound pelvis and inguino-scrotal region and MRI abdomen and pelvis to assess internal genital organs, localize the gonads and measure the testicular volume.

Results: 24 new patients with XY DSD were recruited. The age of presentation ranged between 0.6– 14 years with a mean of 3.34 ± 1.85 years. Most of the cases were initially assigned as males (18 cases, 75%). Five alpha reductase deficiency was the most common diagnosis (12 cases, 50%).

Using ultrasonography, 20 cases had normal testicular volume for age (83.3%) while 2 cases (8.3%) had small testes. MRI findings match the ultrasonography in them. Gonads were non-detectable either clinically or by ultrasonography in 2 cases. One of them had male phenotype with bilateral cryptorchidism. MRI showed one atrophied gonad and the other was partially atrophied in the inguinal canal. The other case had female phenotype with bilateral cryptorchidism and MRI showed bilateral abdominal testes.

Conclusion: The diagnosis of XY DSD cases remains a challenge. Ultrasonography plays a major role in the evaluation of gonads and phenotypic gender. MRI should be reserved to cases when ultrasonography is non-conclusive especially in resource-limited setup.

17-hydroxylase deficiency and diabetes in a case with 46 XY female

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A 13-year-old patient was admitted due to delayed puberty. Ovary and uterus had not seen in USG and MRI. On physical examination; body weight: 57 kg (79 P), height 157.7 cm (45P), BMI: 22.9 (83P), TA: 120/80 mmHg. The patient was externally in female appearance and there was no puberty development. Labia minora was seen. The urethral and vaginal openings were in the vestibulum and bilateral gonads could not be palpated in the inguinal canal. Mother and father was cousin. Father has type 2 diabetes mellitus. USG was repeated. Uterus and ovaries were not observed in USG. In the proximal part of both inguinal canals, 20x7 mm sized testicular parenchyma-like appearances were observed. There was hypergonadotropic hypogonadism and high level of progesterone with adrenal insufficiency; ACTH 115 ng/L (7.2-63), cortisol 0.43 µg/dL, progesterone 8.45 µg/L (0.31-1.52). Hydrocortisone treatment with 20 mg/m²/day dose to the patient was started. 17-hydroxylase genetics were studied. The patient's karyotype was 46XY. In the genetic study, CYP17A1 (NM_000102.3) mutation was detected in both alleles (homozygous) c.1319G> (p.Arg440His). The patient was consulted with Pediatric Surgery. Bilateral orchiectomy was performed by laparoscopy. The tissue was macroscopically compatible with atrophic testicular tissue. Pathology report was immature testicular tissues and congested testicular structures. After the operation, estradiol 0.5 mg orally was started. In the follow-up, high level of blood sugar was observed 3 weeks after the operation. HbA1C was 8.5%, C-peptide 3.51 µg/L (0.9-7.1), insulin 13.05 mU/L (1.9-23), diabetes autoantibodies (-) in laboratory. Insulin and metformin treatment were started. Insulin treatment was discontinued later in the patient because of type 2 diabetes mellitus. The follow-up and treatment of the patient were hydrocortisone 20 mg/m²/day, estradiol 1 mg/day and metformin 1 g orally twice in a day.

Hypertension, hypokalemia and renin aldosterone suppression are present in 17-hydroxylase enzyme deficiency. 46XY cases with severe deficiency have a completely female external genital organ due to testosterone deficiency in intrauterine life. These cases are often diagnosed due to lack of secondary sex characteristics or amenorrhea in advanced ages. Since their sexual identity also developed as girls during this period, no gender change is made. There is a risk of gonadal malignancy due to the intra-abdominal testicles. In this case, we wanted to emphasize that 17-hydroxylase deficiency, which is rarely seen, is a cause of gender development disorder and to discuss the surprising developed diabetes mellitus in the follow-up.

Diagnostic Dilemma in a Patient with Central Precocious Puberty: Ovarian Steroid Cell Tumor

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Ovarian steroid cell tumors (OSCT) are rare sex cord-stromal tumors of the ovary and comprise <0.1% of all ovarian tumors. We herein report a case of an OSCT in a 9 year old girl patient who presented with central puberty precocious unresponsive to gonadotrophine relasing hormon analog (GnRH) therapy.

A 9 year old girl presented with breast development noticed 4 months ago and menarche 3 months ago. Her height was 141,5 cm (+1,3 SDS), body weight was 35,4 kg (+0,9 SDS) and body mass index was 17,6 kg/m² (+0,5 SDS). Her thelarche was Tanner stage 3, and pubarche was Tanner stage 2. She had dysmorphic face with frontal bossing and flat nasal bridge. She also had hypertrichosis and acnes. Laboratory results were as follows: follicle-stimulating hormone (FSH): 12,2 U/L, luteinizing hormone (LH): 8,1 U/L and estradiol: 93 ng/L. On admission pelvic ultrasonographic (USG) examination uterus was 56x20 mm, right ovary 34x16 mm, left ovary 35x16 mm, and a few millimetric follicle cysts were observed. Bone age was 12 years. Cranial magnetic resonans imaging (MRI) was normal. GnRH therapy (leuprolide acetate therapy 3,75 mg/28 days) was initiated due to centrally rapidly progressing puberty and early menarche. On her control examination 3 months later, growth rate was 6,7 cm/year, breast development Tanner stage 3, and hyperpigmentation of the nipples were detected. LH and estradiol were 4.4 U/L and 420 ng/dl (very high) respectively. She did not show any clinical improvement in the third month of treatment. Her pelvic USG repeated because of increase in estradiol; uterus was 65x36x24 mm, endometrium double foldable 10 mm, fundus/cervix ratio 1.5. Right ovary was 34x28x17 mm (8.5 ml) left ovary was 15x12x10 mm (0.9 ml). A solid mass 26x20x14 mm defined as homogeneous and hyperechogenic according to ovarian parenchyma, and hypervascular. The mass in the ovary was removed laparoscopically using the ovarian-sparing surgery technique. The histopathological examination revealed benign OSCT-not otherwise specified (NOS) composed of cells positive for inhibin, Melan A, GATA3, CD10, CD31, CD56 and negative for estrogen receptor, cytokeratin, P53, desmin, S 100, and placental alkaline phosphatase.

In conclusion, In this case peripheral puberty due to OSCT was combined with central rapidly progressing puberty. Estrogen-secreting ovarian masses may not be detected by USG when they are still small in size. Radiological imaging may be repeated, especially in rapidly progressing puberty cases showing clinical and hormonal progression despite treatment.

Dimensional approach to Gender Dysphoria in Nigeria: association with socio-demographics and psycho-sexual variables

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There is an exponential rise on the topic of Gender dysphoria (GD) on the internet, pubmed data, seminars and conferences. However, most of these discussions skewed toward the western populations. GD appears invisible or non-existence in Africa? Recently, GD has been conceptualized as a continuum of a bipolar disorder with varying degrees of dysphoric expression in between the poles. Hence, dimensional measure of assessment which is in keeping with nature's experiences is being advocated rather than the previous categorical approach of being present or absent. A total of 747 primary/secondary school students and university freshmen aged 10-24 years were studied using the 27-item gender identity/gender dysphoria questionnaire for adolescents and adults (GIDYQ-AA). Participants were divided into early, mid and late adolescents. The composite and domain scores were calculated using the criteria described by DeoGracias and comparison of the median scores were done using Mann-Whitney U-test and Kruskal-Wallis test as appropriate. Dunnett's post-hoc test was used for pairwise comparisons. There was a slight male preponderance (51.5%) and half of the participants (50.6%) were in the early adolescent period. The prevalence of self-identified transgender and self-reported non-heterosexuals was 0.9 and 18.6 percent, respectively. The participants as a group scored 4.56 out of a possible 5 in the gender dysphoria scale (indicating less gender dysphoric symptoms in this cohort). However, participants in mid- and late-adolescents had significantly lower scores in the gender dysphoria scale when compared with early-adolescents ($p = 0.009$). Sexual orientation and self-labelled identity did not differentiate participants in their scores in the GD scale ($p = 0.53$ and 0.31), respectively.

The findings of this study, although, preliminary, demonstrated a less gender dysphoric symptoms in Nigeria compared to the western population. Nevertheless, some degrees of GD was noticed in some participants revealing that it is still existent, perhaps its expressivity is hindered by stigma, the laws of the Nigeria government or lack of specific clinic to attend to their needs or a combination of these factors.

Puberty delay in girls: analyses of disease structure depending on clinical characteristics

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Objective: to evaluate the structure of puberty delay in girls according to clinical characteristics.

Materials and Methods: We included 51 girls with puberty delay (mean age 14.2 ± 0.82 years) into the study. Inclusion criteria: no secondary sex characteristics by the age of 13 years; or no menstruation by age 15 years or no menarche during 3 years or more from the onset of estrogen-dependent signs of puberty development. Exclusion criteria: age 18 years or more, ambiguous genitalia. According to clinical characteristics girls were divided into 3 groups: 1st group included girls with absence of secondary sex characteristics by age 13 years (mean age $\pm$ SD 13.6 ± 0.7 years, Tanner stage B1). 2nd group consisted of girls with no signs of further puberty progression by age 14 years or more (mean age $\pm$ SD 15.1 ± 0.8 years, Tanner stage B2-3). 3rd group included girls with absence of menarche onset by age 15 years or more (mean age $\pm$ SD 15.5 ± 0.5 years, Tanner stage B4-5). Tanner stage, antropometric data, bone age (with the help of Greulich-Pyle method), genitometric characteristics, LH, FSH, prolactin, estradiol, testosterone, DHEA, inhibin B, anti-Mullerian hormone serum levels were evaluated in all the girls. Gonadotropin stimulation test (GnRH), ($n=24$), cytogenetic ($n=45$), molecular genetic tests ($n=7$) and brain MRI with contrast agent were provided ($n=5$). According to the study design we analyzed girls with permanent puberty delay including hypogonadotropic and hypergonadotropic hypogonadism and girls with transient puberty delay caused functional hypogonadism and constitutional puberty delay.

Results: 1st group included 39.2% (20/51) of all patients, 2nd group consisted of 21.6% (11/51), 3rd group included 39.2% (20/51), relatively. Permanent puberty delay was observed significantly more often among the 1st and 2nd groups of patients (75% and 81.8%, relatively) in comparison with transient puberty delay (25%, $p=0.002$ and 18.2%, $p=0.003$, relatively) while transient puberty delay was more common among 3rd group (90% and 10%, $p<0.001$).

Conclusion: Such clinical features of puberty delay as primary amenorrhoea and complete lack of pubertal development were twice as frequent as the absence of puberty progression signs in girls in proper age. We revealed the association between permanent or transient puberty delay in girls and clinical signs of illness. Permanent puberty delay was observed more often among girls with the absence of secondary sex characteristics or puberty progression while transient puberty delay was observed more often among patients with primary amenorrhoea.

P2-426

Uterus agenesis in a patient with CATCH 22 Syndrome. Purpose of a case

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Introduction: The CATCH 22 syndrome or DiGeorge syndrome or velocardiofacial syndrome, is a frequent pathology with the worldwide prevalence estimated between 1 / 2,000 and 1 / 4,000 live births. The classic clinic is characterized by typical facial features (narrow palpebral fissures, bulbous nasal tip, small mouth and ears, malar hypoplasia) with functional insufficiency of the soft palate in about 75% of those affected, difficulties in learning, language and behavior, congenital heart malformations in more than 50%, some degree of immunodeficiency (secondary to thymic aplasia / hypoplasia), greater predisposition to develop an autoimmune disease such as hypothyroidism, neonatal hypocalcemia that usually remits with age, although it may recur. Other manifestations may include gastrointestinal, kidney malformations (multicystic agenesis or dysplasia), or deafness. However, the phenotype is much more variable and the clinical spectrum continues to expand. **CASE DESCRIPTION and COURSE:** Girl aged 7 years and 6 months at the time of the first pediatric endocrinology visit, diagnosed with CATCH 22 syndrome. Personal history: Controlled in cardiology due to intervened aortic ring, incomplete right renal duplication in pediatric nephrology follow-up, wearing hearing aids, velopharyngeal insufficiency in orofacial control by pediatric surgery and follow-up by pediatric neurology, normal immunological study without presenting serious infections. On physical examination in the first consultation, he presented Weight: 22Kg, height: 112.6 cm, TA 90 / 60mmHg, with a female velocardiofacial Sd phenotype and tanner stage 1, the rest of the examination was normal. In the control analysis, no alterations in phospho-calcium metabolism were observed (intact PTH 16 pg / mL [14 - 100], Calcium 9.2 mg / dL [8.4 - 11], Phosphorus 5.1 mg / dL [2.5 - 6]. evolution in consultation starting thelarchy at age 11. At age 14 Tanner 4-5 associating several episodes of hypogastric abdominal pain, no menarche. Faced with recurrent episodes of abdominal pain and the presence of primary amenorrhea, an abdomino-pelvic ultrasound was requested and a gynecology consultation objectifying: absence of uterus and both ovaries slightly reduced in size for age. **CONCLUSIONS.** In patients with 22q11.2 deletion syndrome, a multidisciplinary follow-up is required. Endocrine manifestations are the most frequent pathology after cardiac ones. From the endocrinological point of view, it is necessary to do a lifelong follow-up, controlling calcemia and thyroid function as the most frequently associated pathologies, but also to take into account the multiple manifestations that may present and be alert to the symptoms of primary amenorrhea since they are have described several cases of uterine agenesis in these patients.

P2-427

High throughput screening of DSD candidate genes with the help of the powerful model *Drosophila melanogaster*

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Drosophila melanogaster as a study model has already significantly contributed to the understanding of the mechanisms of many human diseases. So far *D. melanogaster* has rarely been exploited as a model for human sex development. Nanda et.al already demonstrated in 2009 that the *Drosophila* orthologue of *SOX9*, *Sox100B* is essential for testis development in *Drosophila*. Similarly, we could demonstrate that the fly homolog of *STARD8*, *cv-c*, that is suspected to be the cause of sex reversal in two 46 XY sisters, has similar location and function in the fly as its mammalian counterpart. *cv-c* mutant male flies had defects in formation of embryonic gonads and germ cells (GC) evading from their niche. These results indicate that the molecular mechanisms regulating dimorphic gonad development may be much more conserved over phyla than previously suspected. We thus established the fruit fly as a new alternative model to address the general consequences of mutations identified by WES in DSD patients.

We use the well-established Gal4-UAS system in flies for high throughput screening for novel DSD causing genes. Firstly, all genes that are known to cause sterility in flies (2576 genes) are predicted with the “DIOPT-DRSC Integrative Ortholog Prediction Tool” to have homologs and/or orthologues in humans (2449 genes) (duplicates are removed). After the already known DSD genes are excluded (126 genes), all other genes then orthologs that are predicted to rank “high” are excluded.

The remaining 1265 genes are subsequently knocked down in the germ cells (nos-Gal4) or the somatic gonadal tissue (mtd-Gal4) of the fly. The consequences on sex development will be rated by the female/male ratio of the F1 generation. The obtained fly strains will offer an ideal novel model to study in details the mechanisms underlying sex development and understand its defects.

P2-428

Case series: Use of tamoxifen in the management of gynaecomastia in three adolescent boys with 46 XY DSD

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Background: Management of gynaecomastia in adolescent males with Partial Androgen Insensitivity Syndrome (PAIS) remains a clinical conundrum. The main mode of treatment is mastectomy, while literature on pharmaceutical management is limited. This case series evaluates outcome of 3 children treated with tamoxifen.

Case 1: A 16-year-old-boy with genetically confirmed PAIS, presented with bilateral gynaecomastia at 11 years of age. He had severe under-virilization of genitalia at birth and stretched phallic length (SPL) remained at 2cm despite testicular enlargement and elevated serum testosterone levels. Tamoxifen 10mg daily was started at the age of 13 years. Pre-treatment palpable glandular breast tissue measured 8x10cm bilaterally with contours compatible with Tanner Stage-3. Tamoxifen therapy curtailed further progression of breast development, and substantially reduced granularity. Tamoxifen was continued for 3 years without significant side effects. Currently mastectomy is being contemplated due to persistence of gynaecomastia and considering patient's preference.

Cases 2 and 3: Two brothers with 46XY DSD (presumed PAIS), currently aged 16 and 14 years, born with micropenis and penoscrotal hypospadias, were also given a trial of tamoxifen.

Elder sibling presented with gynaecomastia at 13.5 years with bilateral testicular volumes of 6-8ml, SPL of 4.5 cm and elevated serum testosterone levels. By 14 years' breast tissue had increased to 5x5 cm bilaterally. Subsequently tamoxifen 10mg daily was started and continued for 2 years. In the first year of therapy, breast tissue reduced to 3x3 cm, and remained stable thereafter.

The younger brother was commenced on tamoxifen at the age of 13 years when he presented with bilateral gynaecomastia (right breast 3 x 4cm; left breast 2x2 cm). He has been on therapy for one year, with gradual regression of glandular breast tissue (right breast 2.5 x 3 cm, left breast non-palpable). At present, his testicular volume is 10-12cm bilaterally, with a SPL 3cm and pubic hair compatible with Tanner Stage 2. Both brothers report a reduction in psychological distress, lack of adverse effects and would like to continue therapy for longer.

Discussion: Treatment of gynaecomastia in PAIS, by irreversible procedures such as mastectomy, is best deferred until they develop a stable gender identity, and are mature enough to participate in informed decision making. Early use of tamoxifen appears to a viable interim measure to reduce progression of gynecomastia and provide psychological relief to affected adolescents.

P2-429

4-year-old female patient with mixed germ cell tumor and underlying Cowden syndrome

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Cowden syndrome (CS) is a cancer predisposition syndrome. The clinical hallmarks of CS are macrocephaly and mucocutaneous lesions. Several tumor types have been described, mostly malignancies of the breast, thyroid, endometrium, kidney and colorectum. The age of onset is extremely variable. So far, only two

case reports of children with ovarian tumors in the context of CS have been published, a granulosa cell tumor of a 16-year-old girl (Smpokou et al. 2014) and a bilateral endocrine-inactive dysgerminoma of a 7-year-old girl (Cho et al. 2008).

We report on a 4-year-old girl with an ovarian tumor in whom CS was identified as the underlying pathology. The patient presented for hyperandrogenemia with slight clitoral hypertrophy, premature thelarche, pubarche and accelerated growth with increased bone age. The initial testosterone level was 1.58 ng/ml, the oestrogen level was 18 pg/ml. Other causes of precocious puberty or adrenal androgen excess were excluded. Workup during the following months revealed normal MRI of the brain and adrenal glands, as well as normal the urinary steroid profile. Repeated pelvic ultrasound examinations were inconclusive. In the course of the disease, testosterone and oestrogen levels fell continuously to prepubertal levels. After referral of the patient to our center, an MRI of the pelvis was performed and a solid mass in the left adnexal area detected. The mass was resected in toto. Histologic examination revealed a mixed germ cell tumor with dysgerminoma and mature teratoma components, as well as structures suspicious for a hemangioma component. The presence of other clinical abnormalities such as lipomas, keratosis pilaris and macrocephaly led to the suspicion of CS, which could be genetically verified (c.406T>C, heterozygous missense mutation of the PTEN gene). The oncological follow-up for this patient was adopted accordingly.

To the best of our knowledge, this is the first case of mixed germ cell tumor associated with CS in children. In addition, the tumor biology showed a particular dynamic, transitioning from endocrine-active into -inactive.

P2-430

A comparison between Androstanolone and Testosterone Enanthate for penile augmentation in patients with idiopathic micropenis

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Introduction: Micropenis is defined as an anatomically correct penis that is abnormally short due to a defect in testosterone secretion or action. The length of the stretched penis compared to reference tables such as the Schönefeld curve is the best diagnostic criterion. Size less than -2.5 Standard Deviations (SD) defines micropenis. When the etiological assessment of micropenis does not reveal any abnormality, the diagnosis of idiopathic micropenis is retained.

Materials and Methods: We conducted a retrospective, descriptive and analytical study of 45 patients with idiopathic micropenis during the period between December 2014 to January 2021 in the department of Endocrinology-Diabetology-Nutrition of Mohammed-VI University Hospital, Oujda. The length of the penis was measured in millimeters on the dorsal side with a rigid ruler, from the pubis, after depressing the prepubic fat and causing

traction of the penis, to the tip of the glans. It was expressed in SD according to the Schönefeld reference curve. Idiopathic micropenis was considered when the penile size is < 2.5 SD and the etiology is negative. We compared the efficacy of two therapeutic choices (Androstanolone and Testosterone Enanthate) and their side effects. This group of patients was divided into two arms: the first treated with Androstanolone (n=25) and the second with Testosterone Enanthate (n=20). The outcome of the treatment included assessing the dimensions of the penis and the search for possible side effects at the end of treatment and at least 12 weeks later.

Results: The mean age of our patients was 9.7 years +/- 4.35. In the first arm: the average pre-therapeutic height was 2.9 Cm +/- 0.7 correspondings to (-2.7 SD) and after the cure of the micropenis, it attained 5.2 Cm +/- 1.03 (-0.7 SD) i.e. a difference in height of 2.4 Cm on average. In the second arm: the average pre-therapy size was 3 Cm +/- 0.9 correspondings to (-2.6 SD) and after the micropenis cure, it reached 4.85 Cm +/- 1.18 (-0.7 SD) i.e. a difference in the size of 1.8 Cm on average. The increase in penile size in the 1st arm was significantly greater than in the 2nd arm, p=0.008. Side effect analysis were absent in either arm.

Conclusions: The diagnosis of micropenis is purely clinical, based on the measurement of penile size. It is a simple symptom that can hide complex pathologies. Early management of micropenis is recommended to avoid sometimes dramatic complications, and androstanolone seems to be the most effective treatment without side effects.

P2-431

Combination therapy of hypogonadotropic hypogonadism with rFSH and hCG – case report

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Objective: assess advantages and disadvantages of the treatment of hypogonadotropic hypogonadism (HH) with rFSH and hCG.

Materials: We report the case of a 16-year old patient with complaints of no development of secondary sexual characteristics. Patient was 174 cm (SDS growth 0.25 SD, SDS growth velocity 1.62 SD, SDS BMI -0.4 SD, target height correction 1.01 SD) with Tanner G1 P1 (penis length was 5 cm). Laboratory studies included LH < 0.1 mIU/ml (0.8-7.6), FSH = 0/15 mIU/ml (0.7-11), testosterone 1.05 nmol/l (2.25-26.99), SHBG 115.5 (13.3-89.5), free testosterone index 0.9 % (15.5-102), inhibin B = 50.2 pg/ml (25-325). AMH=56.04 ng/ml (4.95-144.48). Bone age was 14 years (SDS = -2.1 SD). GnRH test with triptorelin revealed LH peak of 1.81 ME/ml and LH/FSH ratio was 0.85. On hCG stimulation (2000 IU/m2) total testosterone was 3.3 nmol/l. Testicular volumes by ultrasound were 1.1 cm3 and 1.04cm3. Olfactometry revealed mild hyposmia. MRI revealed no pathology. Karyotype was XY. Molecular genetic revealed no mutations. In 3 months of testosterone stimulation

(3 injections of 100 mg once in 30 days) Tanner stage was P3G1, testicular volume raised to 1.12 cm3, testosterone was 0.87 nmol/l, inhibin B was 64.1 pg/ml, LH peak on triptorelin test 0.68, LH/FSH ratio was 0.3. A patient was diagnosed with HH. Therapy with rFSH 75 ME in a week and hCG 1000 ME in a week started. hCG titrated to 3000 ME/week. After 2 years patient was 188 cm (SDS growth = +2SD, target height correction + 1.43 SD), bone age was 15.5 years, Tanner stage progressed to P5G5, US-proven testicular volume was 7.1 and 11.3 in 16 months of therapy. After 7 months of therapy testosterone already was 20.3 nmol/l, SHBG lowered to 44.2 nmol/l. Estradiol wasn't increased. AMH firstly raised at 4th month (172/2 ng/ml) and then lowered to 10.56 at 16th month. Inhibin B raised to 153.1 pg/ml. In 4 months after withdrawal the therapy patient started to complain of libido loss, depression. LH <0.2 mME/l, FSH <0.2 mME/l, testosterone 0.55 nmol/l, SHBG 79.4 g/l, inhibin B 114.2 pg/ml. Replacement therapy with rFSH and LH continued.

Conclusion: therapy of rFSH and hCG developed secondary sexual characteristics, raised testosterone with no estradiol increase. Testicular volume 8-10-fold increased, inhibin B increased three-fold. AMH raised and then lowered. Therapy helped to induct puberty according to increased testosterone so better fertility can be expected.

P2-432

46,XY DSD due to biallelic DHX37 gene mutations

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Background: DEAH-box protein *DHX37*, encodes an RNA helicase, is involved in ribosome biogenesis. Monoallelic mutations in *DHX37* gene have recently been identified in 46,XY differences/disorders of sex development (DSD) patients with nonsyndromic gonadal dysgenesis as well as testicular regression, while biallelic mutations have been associated with microcephaly and structural brain abnormalities.

Here, we present a patient with penoscrotal hypospadias and bilateral cryptorchidism, in addition to microcephaly, developmental delay and extreme myopia due to biallelic mutations in the *DHX37* gene.

Case Report: A 4.5-year-old boy was referred by pediatric urology due to penoscrotal hypospadias and bilateral cryptorchidism. He was born at 32th gestational week after an uncomplicated pregnancy, with a birth weight of 1115 g (-3.0 SDS). His parents were first cousins. He walked at 2 years of age and spoke his first words at 3 years. Mild secundum ASD and muscular VSD were detected in echocardiography. Surgery for correction of cleft palate was performed at the age of 2.5 years. He had severe myopia. At presentation to our unit, his height, weight and head circumference were 116.0 cm (-0.19 SDS), 15.7 kg (-0.92 SDS) and 48.0 cm (-2.28 SDS), respectively. Minor dysmorphic features such as micro-retrognathia, anteverted ears, long filtrum were observed.

He had penoscrotal hypospadias and bilateral cryptorchidism and stretched penile length was 3.8x0.8 cm. Scrotal ultrasonography revealed testes in the inguinal canal bilaterally. Total testosterone concentration was <0.07 µg/L and 1.74 µg/L before and after hCG stimulation. FSH:2.0 U/L, LH: <0.2 U/L, AMH:36.9 ng/mL were normal for age and sex. Karyotype analysis was 46,XY. A targeted next generation sequencing analysis revealed, c.703G>A (p.Val235Ile) and c.632C>T (p.Pro211Leu) variants in the *DHX37* gene.

Conclusion: Although monoallelic *DHX37* gene mutations are associated with 46,XY DSD, biallelic *DHX37* mutations may also cause 46,XY DSD in addition to concomitant neurodevelopmental disorders.

P2-433

Novel Mutation in an Iranian Family with 17-β Hydroxysteroid Dehydrogenase Type 3 Deficiency

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We report a large family with several cases of 46 XY and a new mutation in the 17-β-HSD3 gene. The proband was an 11-year-old girl and the first child of a consanguineous family. She was born by cesarean section with a height of 52 cm and a weight of 4200 grams. The external genitalia were completely female and had a short vaginal pouch. She had palpable gonads in her inguinal area and underwent bilateral gonadectomy at the age of two. Other physical examinations were normal. At age 10, she was referred to our clinic for more evaluation at the Hospital for the Sick Children in Qazvin, Iran. In pelvic sonography, uterine and ovarian were not seen. Her karyotype was 46, XY and her LH and FSH levels were elevated. We realized that three of the patient's aunts and one of the mother's aunts had the same phenotype; their karyotype was 46, XY and had symptoms of virilization because they had not had an orchiectomy before puberty. Our adult patients accepted female gender identity, married, and had female gender behavior but lacked fertility. Using whole exome sequencing, we identified a novel homozygous missense variation (c.731T>A, p. Ile244Lys) in *HSD17B3* gene. This alteration changes Isoleucine to Lysine in exon 10. This variation – which has not been reported before – is predicted to be a variant of unknown significance (VUS) based on computational analysis.

P2-434

A case of gender developmental disorder with difficulty in molecular diagnosis: new variant in NR5A1 gene

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“Steroidogenic Factor-1” (SF-1); It is encoded by the NR5A1 gene in 9q 33.3 and regulates the transcription of genes involved in steroidogenesis. It is reported that 46 of the variants in this gene constitute 10-20% of XY sex development disorders (DSD).

The patient admitted because of a swelling in the left groin at one month old. She was raised as female. Uterus was 12x2.5 mm in ultrasonography and the gonad in the inguinal region was evaluated as testis. She was Prader stage 3, single opening, phallus 1cm, bilateral 0.5x0.5cm ovoid gonads were palpated in the inguinal region.

Laboratory values were FSH: 8.99 mIU/ml (N: 0.16- 4.1), AMH: 16.59 ng/ml (N: 39.1 -91.1) Total testosterone: 50 ng/dl (N: 60 – 400). Serum electrolytes, glucose, ACTH, DHEA-S, 17-OH Progesterone were normal. hCG stimulation test was unresponsive. She was SRY (+) and XY was detected by QF-PCR. Male urethra, utriculus, and ureter orifices were observed in cystoscopic examination. With an initial diagnosis of partial gonadal dysgenesis; no mutation was found with the targeted Next-Generation Sequence (NGS) analysis (Trusight One) panel. The gender development disorder council decided to raise the patient as a male with the parents. Her identity was changed at the age of 1 year and corrective operations were performed. Heterozygous c.1161_1232delinsGGTGACAAATAAGCAG (p. His387GlnfsTer161) variant was found in the repeated analysis of the NR5A1 gene with Sanger sequence analysis of the patient, who was thought to have SF-1 deficiency clinically. It has been shown that the variant, defined as de novo, can disrupt the protein structure with modeling programs and is pathogenic according to ACGM criteria.

Mutations in NR5A1 can appear in a wide spectrum from hypospadias, uncertain external genital structure, anorchia, gonadal dysgenesis to infertility, and completely female external genital structure. Detecting ‘indel’ mutations with analysis programs is still a challenging field in next generation sequence analysis. Especially variants greater than 20bp and heterozygous as in this case increase the possibility of giving false negative results in the targeted next generation sequence analysis. In 46, XY DSD cases, even if molecular diagnosis is not made in the targeted NGS panel, repeating the molecular genetic analysis with Sanger sequence analysis in case of clinical strong suspicion may be necessary to make a diagnosis.

P2-435

Two pedigrees with congenital bilateral anorchia in one sibling and testicular torsion at adolescence in another: a shared genetic predisposition?

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Background: In bilateral anorchia or vanishing testes syndrome, testicular function is normal during the embryonic period, as shown by the absence of Müllerian remnants and of hypospadias. Although normally differentiated, the penis may be small due to decreased testosterone secretion during the fetal period. In a normally virilised boy with non-palpable testes, with or without micropenis, the diagnosis is established by undetectable plasma anti-Müllerian hormone (AMH) and absent Müllerian structures. The syndrome is thought to result from vascular obstruction and/or torsion. We report two unrelated families in which one sibling presented with bilateral anorchia diagnosed in infancy and one sibling with testicular torsion at adolescence.

Patients and Methods: retrospective case series. Setting: paediatric endocrinology units of two academic hospitals (Sainte-Justine, Montreal, Quebec, Canada and Hôpital Universitaire des Enfants Reine Fabiola, Brussels, Belgium).

Family 1 (Hôpital Universitaire des Enfants Reine Fabiola, Belgium): A 10-month-old boy was referred for bilateral cryptorchidism. His parents are healthy, non-consanguineous, of Spanish and Congo-Brazzaville origin. There was a family history of cryptorchidism in the paternal uncle and his son. The mother had taken paroxetine during pregnancy. The index case was born at term (38 weeks, 3240g, 47cm). Very small testes had reportedly been palpated in the neonatal period. At 10 months of age, physical examination was normal except for non-palpable testes. Plasma AMH level was undetectable and gonadotrophins were very elevated (FSH: , LH mU/L, respectively). At 14 years of age, an older brother presented with bilateral scrotal oedema (confirmed by ultrasound) and was initially treated with antibiotics. A right testicular torsion developed and bilateral orchidopexy was performed.

Family 2 (Sainte-Justine, Canada): The index case, a boy referred at 3-days of age for micropenis, has been reported previously (Stoppa-Vaucher et al, Clin Biochem 43: 1373, 2010). Subsequent to this publication, we learned that one of his brothers presented at age 15 years with three episodes of left testicular torsion that led to bilateral orchidopexy.

Discussion: Testicular torsion is familial in 10 % of the cases. Most cases of testicular torsion occur during adolescence. In these adolescents, an anatomical variant called the clapper bell anomaly renders the testis more mobile, predisposing it for torsion. By contrast, antenatal torsion does not seem to be associated with this anomaly. However, the present report of two families with congenital anorchia in one sibling and testicular torsion at adolescence in another suggests that both conditions represent a spectrum with a shared genetic predisposing factor.

P2-436

Importance of testicular biopsy for validation of diagnosis; cryptorchidism, analyzing prescrotal undescended testes

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Background: The hallmark of successful treatment of cryptorchid boys is fertility. However, reported incidences of normal spermograms for unilateral cryptorchid patients range from 83% to 22%.

Aim of the Study: Because, cryptorchid testis has always abnormal histology, performing testicular biopsy it is possible to differentiate between cryptorchid and a normal testicular histology thus validating obtained clinical diagnosis. We hypothesize that in a pool of patients with prescrotal testes a certain number of testes with normal histology could be found, thus explaining the wide range of fertility outcome in unilateral cryptorchid boys.

Patients and Methods: 301 cryptorchid boys having had orchidopexy and testicular biopsy performed by a single surgeon were analyzed. 15 % (45/301) of boys were found to have prescrotal located testes. Germ cell number and differentiation were estimated by analyzing at least 50 tubular cross-sections.

Results: Sixty-seven percent (30/45) of boys had a normal testicular histology for age [group A] while 15/45 (33%) [Group B] had a typical cryptorchid testicular histology with reduced germ cell number with 53% 8/15 belonging to high infertility risk group (no Ad spermatogonia and germ cell count <0.2/tubule). Left side was affected in 20 % group A and in 43% in group B. Patients age at orchidopexy was similar; 6.0 (95%CI.4.4-7.9) years (A), 6.6 (95%CI.5.5-7.6) years (B)

Conclusion: High percentage of prescrotal testes with normal histology underscores the need for testicular biopsy to predict patients fertility chances and more exact validate diagnosis; cryptorchidism. Fertility studies without testicular biopsy are subjected to overrepresentation of patients with normal fertility.

P2-437

Rare Genetic disorder associated with microphallid

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Term male baby delivered by elective c- section. On examination found to IUGR, hypotonic and microphallid less than 2 cms (stretched). Both testis were palpable. No other dysmorphic features noticed. Cranial ultrasound showed sub-ependymal cysts in the frontal region. Parents were concerned regarding his small penis.

He was referred to physiotherapy for his low tone and had genetic and metabolic work up done for his persistent low tone. The testosterone levels were found to be low for his age.

A diagnosis of 49xxxxx syndrome has been done by the genetics. Started on testosterone i.m injections on monthly basis for three months at the age of six months with a very good response.

Testosterone were re checked and found to be within the normal range for his age. At ten months of age the child tone has improved with normal growth.

P2-438

Congenital adrenal hyperplasia in detail: a multicentric and interdisciplinary study in minors with different sexual development

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Of the 67 included DSD patients, 33% were HSCs. 68% women and 32% men, with a total concordance between legal sex, current gender and chromosomal sex. Median age: 10.5 years, IQR 8-14. The most frequent clinical form was non-classical (NC) 45.5%, followed by classical with saline loss (CPS) 41%. The distribution of each clinical form according to the karyotype is significant ($p = 0.013$), the most frequent with XY karyotype is CPS and in NC forms all cases are XX. Median age at the start of the study: 2.5 months, IQR 0.75-42.5. In 68% the diagnostic process began before 12 months of age. According to gender, when comparing the medians, the results are not significant ($p = 0.187$). On the other hand, there is a higher median age in men with simple virilizing clinical forms (CVS), with 31.5 months. All cases were genetically defined, median age 1 month, IQR 0-5.2; a de novo mutation (I172N) was even identified. The clinical form with the earliest diagnosis was CPS, IQR 0-1.5 months. Detailing the associated pathologies, the following stand out: 12 uro-genital sinuses, 2 vesico-ureteral refluxes, no cases of testicular maldescent or TARTs, 3 ovarian bands, 3 cases of precocious pubarche, one case of acne and 3 hydroelectrolytic decompensations. No metabolic disorders or osteopenia were described. Regarding the treatment, in no case was prenatal treatment offered. 86.3% are under medical treatment, 23% with glucocorticoids in monotherapy. The NC forms are those with the greatest variability with 30% without treatment, 50% glucocorticoids and 20% mineralo-glucocorticoids, significant differences ($p = 0.005$). Three cases required psychopsychiatric treatment, one CPS and two NC. It should be noted that the only two patients who required hospital admission and pharmacological treatment of all DSD were two women with CAH, without a diagnosis of gender dysphoria. 16 surgical procedures were performed, 68% for diagnostic purposes and 7 genitoplasties. Median age of genitoplasties: 29 months, IQR 20.5-37. Registering 6 complications. Regarding the surgical result, 1/3 of patients / family declared it excellent and 1/3 acceptable. While 56% were good-excellent according to surgeon / a. Evaluating the specialist teams, all classify endocrinology and surgical teams as good-excellent, as opposed to psychological assistance (55% bad-terrible and 45% good-excellent). ConclusionsThe post-surgical assessment is consistent according to the surgeon and family /

patient. Major surgical procedures are scarce, the majority being diagnostic procedures. We advocate for psychological assistance as the main point of improvement.

P2-439

Sex assignment at birth: is it always easy?

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Introduction: Disorders of sex development (DSD) are a group of congenital disorders in which the development of chromosomal, gonadal, and anatomical sex is atypical and disharmonious. These DSD may constitute a medical emergency (a salt-wasting syndrome in congenital adrenal hyperplasia) or a social emergency due to the parents' anxiety generated by the difficulty of assigning the child's sex at birth. Providing urgent and adapted care defining the sexual orientation of the child remains challenging. The objective of this work was to describe the clinical, diagnostic, and therapeutic aspects of DSD at the department of Endocrinology-Diabetology-Nutrition of Mohammed-VI University Hospital, Oujda, in the eastern of Morocco.

Patients and Methods: A descriptive, cross-sectional study of 24 patients followed in the Endocrinology-Diabetology-Nutrition of Mohammed-VI University Hospital Center of Oujda.

Results: The average age was 6.2 ± 4.5 years. These patients were from a consanguineous marriage in 22% of cases. A delay of sex assignment at birth was found in 55.6%. The diagnosis of a defect in sexual development was made in the neonatal period in 55.6% of cases and in the pubertal period in 11.1% of cases. Sixty-six percent of the patients had external genitalia abnormalities and 22.2% had external genitalia defects associated with a growth delay. Genetic evaluation revealed a male chromosome formula (46, XY) in 65.5% and a female chromosome formula (46, XX) in 22.2%. A mosaic chromosome formula with a double cell population was found in 12.3%. The final diagnosis was partial gonadal dysgenesis in 22.2% of cases, mixed gonadal dysgenesis in 22.2%, 21-hydroxylase deficiency in 22.2%, testicular regression syndrome in 22.2%, and partial androgen insensitivity in 11.1%. The therapeutic management was multidisciplinary. Feminizing genitoplasty was performed in 22.2% of cases, hypospadias was cured in 33.3%, micropenis was corrected by dihydrotestosterone in 66.7% and gonadectomy was performed in 22.2% of patients. Patients with the classic form of 21-hydroxylase deficiency were treated with hydrocortisone and fludrocortisone. GH substitution was used in 22.2% of cases. Psychological support was offered to all patients according to their age and to all their relatives.

Conclusion: DSD is a rather rare entity. The diagnosis is generally made during the neonatal period when abnormalities of the external genitalia are observed. These pathologies require a rigorous diagnostic approach in which the blood karyotype plays a key role in order to distinguish between 46, XX DSD; 46, XY DSD patients and those with gonosomal abnormalities. Their management should be multidisciplinary.

Combination therapy of hypogonadotropic hypogonadism in boys with rFSH and hCG – case reports analyses

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Objective: To evaluate combination replacement therapy (CRT) with rFSH and hCG of hypogonadotropic hypogonadism (HH) in boys appropriateness and effectiveness.

Materials: 1 boy with isolated HH (№1) and 2 boys (№2,3) with HH caused by hypopituitarism (HP) included. Anthropometric data, Tanner; testosterone (T), LH, FSH, inhibin B, anti-Müllerian hormone (AMH), testicular volumes (TV), bone age (BA) evaluated in all patients. GnRH agonist (0.1mg), hCG test (2000/m2), brain MRI with contrast, molecular genetics provided. Regimens were the following: №1,2 received 3 testosterone injections 100 mg/month before CRT. №3 received 12 hCG injections 1500 IU/week. Then all patients received rFSH (75 IU/week) and hCG 1000/1500/3000 IU/week. Follow-up was 14.3±6.4 months.

Results: Before puberty HH was diagnosed in noone. №1 diagnosed with HH in 16 years due to complaints. №2 diagnosed with central hypothyroidism (CHT) in 11.9, growth hormone deficiency (GHD) and central hypocorticism (CHC) in 12.3. №3 diagnosed with CHT in 2.9 years, GHD in 3.4, CHC in 8. №3 had PROP-1 mutation diagnosed in 13.3. Before CRT №1 was 16-year-old boy, 174 cm (0.25SD, TH correction 1.01SD), Tanner 1, TV 1.07cm³ (<2nd perc), T 1.05nmol/l, inhibin B 50.2pg/ml, AMH 56.04ng/ml, BA 14 years (-2.1SD). After 24 months of CRT boy was 18-year-old, 188 cm (2SD, TH correction 1.43SD), Tanner 5, TV 9.14 (15th perc), T 16.05nmol/l, inhibin B 153.1 pg/ml, AMH 10.56ng/ml, BA 15.5 years (>-2SD). Before CRT №2 was 16.3-year-old, 172.5 cm (-0.24SD, TH correction 0.9SD, Tanner 1, TV 3.6 (<2nd perc), T 0.94nmol/l, inhibin B 114.5pg/ml, AMH 30.54ng/ml, BA 13.5 years (-2.6SD). After 21 months of CRT boy was 17.9-year-old, 184.5cm tall (1.48, TH correction 0.83SD), Tanner 4-5, TV 7cm³ (3rd perc), T 20.3 nmol/ml, inhibin B 131.8 pg/ml, AMH 6.01 ng/ml, BA no change. Before CRT №3 was 15.3 years, 165cm (-0.68SD, TH correction -1.03 SD), Tanner 1, TV 1.5cm³ (<2ndperc), T<0.087nmol/l, inhibin B 22.3pg/ml, AMH 22.17ng/ml, BA 14 years (-0.94SD). After 13 months of CRT boy was 16.3-year-old, 174.5cm tall (0.15 SD, TH correction 0.27SD), Tanner 4, TV 4.5cm³ (<2nd perc), T 18nmol/l, inhibin B 152pg/ml, AMH 17.58ng/ml, BA 14.5 years (-1.84 SD).

Conclusion: Late CRT initiation observed in case of isolated HH and in hypopituitarism which is due to the absence of micro-penis, cryptorchidism in all the patients. hCG was effective due to secondary sex characteristics development and pubertal testosterone and decreased AMH. rFSH was effective due to pubertal TV, increased inhibin B. HH caused by HP must be diagnosed by inhibin B and AMH. CRT must be initiated promptly.

Clinical case of premature ovarian failure in combination with blepharophimosis-ptosis-epicanthus inversus due to mutation in *FOXL2* gene

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Background: The *FOXL2* gene located on chromosome 3q22.3, and encodes FOXL2 protein. This protein transcriptionally modulates genetic programs required for early eyelid and ovary development and differentiation. Autosomal dominant mutations of the *FOXL2* gene is a cause of Blepharophimosis-ptosis-epicanthus inversus syndrome (BPES). Depending on the occurrence of premature ovarian failure (POF), there are two types of BPES in females: type I with POF, type II - with normal ovarian function

Clinical Case Description: Patient, 14 years 6 months old, complained of irregular menstrual cycle. On clinical examination, sexual development was Tanner 4, Me at 13 years old, the girl had 3 menses, with a last delay up to 8 months. Single terminal hairs along the white line of the abdomen, areola. The patient had epicanthus and narrowed eye slits of different sizes. She was operated on for congenital blepharophimosis in infancy. No one has similar problems in the family.

Blood Hormones: LH 4.7 U/l, FSH 3.2 U/l, estradiol 139 pmol/l, androgens: testosterone 1.3 nmol/l, DHEA-S 4.8 µmol/l. Pelvic organs ultrasound: endometrial thickness is 0.8 cm, yellow body cyst of the right ovary were revealed (echographic signs of a fluid formation with a diameter of 3.0 cm in the right ovary).

Dydrogesterone was prescribed. Hormones on the 4th day of the regular menstrual-like reaction of the cycle, LH 11.2 U / L, FSH 14.9 U / L, estradiol 69.5 pmol / L.

Medical examination after 3 months without treatment revealed hypergonadotropic hypogonadism (LH 36 IU/l, FSH 98 IU/l, estradiol 56 pmol/l). The level of antimüllerian hormone was measured - 0.9 (1.1-7.8). Considering the combination of blepharophimosis, hypergonadotropic hypogonadism, a defect in the *FOXL2* gene was suspected.

Method: *FOXL2* gene was analysed by Sanger sequencing.

Results: Heterozygous mutation c.264delC p.R89fsX149 in the first exon.

Conclusion: A clinical case of a patient with a *FOXL2* gene mutation has been described.

Persistent Müllerian duct syndrome presenting with bilateral cryptorchidism and obstructed inguinal hernia

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Background: Persistent Müllerian duct syndrome (PMDS) is a Disorder of Sex Development (DSD) caused by mutations in genes encoding anti-Müllerian hormone (AMH) or its type II receptor (AMHR2) with autosomal recessive transmission.

Objective: To report a case of transverse testicular ectopia (TTE), associated with PMDS, initially presented as an obstructed inguinal hernia.

Case Presentation: An 18- days- old male infant, with a known history of bilateral cryptorchidism, presented with a left-sided obstructed inguinal hernia. He was born at 38 weeks gestation with a birth weight of 3300 grs with no perinatal complications. On clinical examination he had normal penile length. Pelvic ultrasonography indicated two testes inside the left scrotum along with uterine tissue extended through the inguinal canal. The inguinal exploration revealed a hernial sac containing both testes and a uterus with fallopian tubes. During hernia repair surgery, all of the tissues were pushed back into the peritoneal cavity and biopsy samples were taken.

Endocrine evaluation revealed normal levels of gonadotrophins, testosterone, cortisol and 17-OH-progesterone (FSH: 1.96 mIU/ml, LH: 10.25 mIU/ml, testosterone: 1.26 ng/ml, 17-OHP: 2.5 ng/ml, cortisol: 7,5 µg/dl) and low levels of estradiol (E₂: 5.3 pg/ml). Serum AMH level was low: 160 pmol/l (normal range: 228-4280). Karyotyping confirmed a male gender (46 XY). The histopathological diagnosis confirmed the presence of Müllerian- derived tissues. Genetic studies revealed that our patient was heterozygous for two recessive mutations. The first one was a frequent deletion of 27 pairs of bases in the 10th of 11 exons of the gene, while the second one was a novel 2 base pair deletion mutation in the 6th exon. One year later and after confirmation of the diagnosis, removal of the Mullerian remnants and orchidopexy were performed.

Conclusions: PMDS is a rare congenital condition, usually presented as cryptorchidism with associated inguinal hernia. It is classified as a 46 XY DSD. The surgical approach of bilateral orchidopexy and hernia repair with or without removing Mullerian structures is the optimal treatment. The main therapeutic targets are the potential for fertility and prevention of malignant transformation. Gonadal biopsy and genetic testing should be carried out

in order to rule out other disorders. The diagnosis and treatment of neonates with DSD should be undertaken by a multidisciplinary team that consists of pediatric endocrinologists, urologists, surgeons, neonatologists, geneticists and psychologists.

5 alpha-reductase type 2 deficiency: a case report

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Introduction: In medical practice, sex assignment at birth depends primarily on the appearance of the external genitalia, which development begins as early as the fetal period and is largely dependent on dihydrotestosterone (DHT). Any discordance between the chromosomal, gonadal or anatomical sexes can lead to a disorder of sex development (DSD). 5 alpha-reductase 2 (5aRD2) deficiency is a very uncommon autosomal recessive genetic disorder that falls into the DSD 46 XY group, affecting the conversion of testosterone (T) to DHT. We report the case of a patient admitted for DSD whose investigations revealed a 5aRD2 deficiency, followed-up in the Endocrinology-Diabetology-Nutrition of Mohammed-VI University Hospital Center of Oujda, in the east of Morocco.

Case Report: An infant aged 10 months, from a first-degree consanguineous marriage, with a history of DSD in a cousin, was admitted in our department for DSD. The clinical examination revealed: genital tubercle measuring 02 cm with two orifices (the first is in normal position and the second is posterior and functional), and empty symmetrical and fused labioscrotal folds. Karyotype was 46XY. The endocrine evaluation showed a gonadotrophic axis in the quiescent phase. The exocrine and endocrine testicular functions were evaluated respectively by AMH: 87.9ng/ml (1.4-11.2) and hCG test which came back positive (T: 10.68 ng/ml). The diagnosis of 5aRD2 was based on a T/DHT ratio (after hCG test) = 12.27 (>8.5). Pelvic MRI showed the presence of testicles in the inguinal position. The patient benefited from a micropenis hormonal therapy using androstenedione gel, followed by correction of hypospadias and orchidopexy in two stages.

Discussion and Conclusion: 5aR2 deficiency is one of the causes of 46XY DSD. The phenotype of affected children can vary from an undervirilized male genitalia to a complete female phenotype. Following a review of the literature, the clinical presentation of this condition may be revealed by: clitoromegaly or micropenis, hypospadias, and cryptorchidism. The confirmation of the diagnosis is based on a high ratio of T/DHT after the hCG test (8.5 is considered the most reliable cut-off value), therefore, molecular analysis is the most effective diagnostic method. Treatment using DHT gel has satisfactory results on the correction of micropenis. Through this case, we understand the importance of 5aR2 in sexual differentiation, whose deficiency can lead sometimes to dramatic complications.

P2-444

An unexplained cause of unilateral gynecomastia in a 3-year-old boy

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Background: Pre-pubertal gynecomastia is characterized by the presence of palpable breast tissue in boys in the absence of signs of sexual maturation. Gynecomastia is common in normal males in the neonatal period, at early puberty, and with increasing age and pre-pubertal gynecomastia is a rare condition and can be associated with excessive aromatase activity or oestrogen-producing adrenal or testicular tumours.

Case Presentation: A 3-year-old presented with left-sided gynecomastia of 6 months' duration. He did not complain of headaches, visual disturbances or galactorrhoea.

He was born at term with normal birth weight and had an uncomplicated perinatal period. His development was age-appropriate and his growth parameters followed birth centiles. He did not have a history of liver or renal disease and was not on long-term medications. His mother did not use oestrogen-containing anti-ageing creams or oral contraceptives.

The height and weight were in the 3rd percentile. On examination, the child did not have Marfanoid features, eunuchoid body proportions or neurocutaneous manifestations. He did not have acne or hirsutism and his blood pressure was normal. He had breast stage III and I on left and right respectively. External genitalia examination was unremarkable with prepubertal testicles of normal consistency and absence of pubarche.

Results: Biochemistry revealed normal renal, liver and thyroid function tests. Prolactin was mildly raised 34.38 ng/ml, normal range 3.34 – 26.71) but had normalized when a month later. Basal gonadotrophins were prepubertal (FSH 0.63 IU/L, LH 0.17 IU/L) with detectable estradiol (40 pmol/L) and normal testosterone level (0.08 nmol/L, age-specific normal range 0.07-0.87). Repeated focussed ultrasound abdomen and testes by experienced paediatric radiologists did not reveal feminizing adrenocortical tumours or testicular masses or calcifications. Alpha-fetoprotein and beta-hCG levels were not elevated. Karyotype was 46, XX and did not demonstrate Klinefelter mosaicism.

Conclusion: Pre-pubertal gynecomastia is a rare condition and can herald sinister diseases warranting extensive investigations and repeated comprehensive evaluations.

P2-445

Could intramuscular testosterone differentiate between partial androgen insensitivity and 5 alpha reductase type 2 deficiency?

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Introduction: Disorders of sex development are challenging conditions for patients, parents and the interdisciplinary health care team. Sex assignment of these patients needs optimal hormonal profile and molecular diagnosis. This study aimed at finding a new tool for differentiation between partial androgen insensitivity and 5 alpha reductase deficiency especially when the molecular diagnosis is unavailable or highly expensive if available.

Methods and Subjects: Forty-four boys were included in this study through a year from Jan 2020 to Jan 2021. They were divided into **two groups:** partial androgen insensitivity (22 patients) and 5 alpha reductase deficiency (22 patients). All patients were assessed with emphasis on detailed history and thorough clinical examination including stretched penile length and glans diameter. Karyotype and hormonal profile were done for all of them. Imaging studies including ultra-sound for pelvic and inguinoscrotal region were done. All included boys received three intramuscular injections of testosterone enanthate 25 mg every four weeks as a preparation for masculinizing genitoplasty. Stretched penile length and glans diameter were measured again after injections. Moreover, the predicted side effects such as darkening of genital skin and appearance of pubic hair were monitored if they appear during treatment.

Results: The mean stretched penile length (SPL) before testosterone injections was 2.70 ± 0.72 cm, and after injections was 3.99 ± 1.05 cm. while comparing the effect of testosterone injections in the two groups of patients, there was statistically significant relation between the etiology of disorder of sex development and the effect of testosterone injections on penile length. Adverse effects like pubic hair and darkening of genital skin were noticed in only six patients (13.6%). Six boys needed to repeat the course of treatment to improve the penile length before the surgery.

Conclusion: preoperative testosterone injections can help the treating team to reach an accurate diagnosis as they can differentiate between partial androgen insensitivity and 5 alpha reductase deficiency especially when the molecular diagnosis is unavailable. Therefore, more clear decision of sex assignment can be reached.

Thyroid

P2-446

The efficacy and short- and long-term side effects of radioactive iodine treatment in pediatric Graves' disease: a systematic review

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Background: Graves's disease (GD) is the most common cause of hyperthyroidism. Maximal 30% of pediatric GD patients achieve remission with anti-thyroid drugs. The majority of patients therefore require definitive treatment. Both thyroidectomy and radioactive iodine (RAI) are often used as definitive treatment for GD. However, data on efficacy, and short- and long-term side effects of RAI treatment for pediatric GD are relatively scarce.

Methods: A systematic review of the literature (PubMed and Embase) was performed to identify studies reporting the efficacy, or short- and long-term side effects of RAI treatment in pediatric GD.

Results: Twenty-three studies evaluating 1,283 children and adolescents treated with RAI for GD were included. The treatment goal of RAI treatment changed over time, from trying to achieve euthyroidism in the past, to aiming at complete thyroid destruction and subsequent hypothyroidism in the last three decades. The reported efficacy of a first RAI treatment when aiming at hypothyroidism ranged from 42.8% to 97.5%, depending on the activity administered. The efficacy seems to increase with higher RAI activities. When aiming at hypothyroidism, both short- and long-term side effects of treatment are very rare. Long-term side effects were mainly seen in patients in whom treatment aimed at achieving euthyroidism.

Conclusion: RAI is a safe definitive treatment option for pediatric GD when aiming at complete thyroid destruction. When aiming at hypothyroidism, the efficacy of treatment seems to increase with a higher RAI activity. Prospective studies are needed to determine the optimal RAI dosing regimen in pediatric GD.

P2-447

Incidentally detected papillary thyroid cancer with elevated calcitonin in a 15 year-old female: a case report

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Thyroid cancer in children is not common but there is a tendency to increase requiring early suspicion and close monitoring of thyroid nodule. Papillary thyroid cancer (PTC) is the most common type of thyroid cancer and medullary thyroid cancer (MTC) is rare, MTC can be suspected if there is elevated calcitonin level.

A 15-year-6-month-old girl was admitted for generalized tonic seizure with fever. Initial Brain MRI showed a small oval diffusion restriction lesion in the midline of corpus callosum splenium. EEG did not reveal any epileptiform discharges. Urinary tract infection with acute pyelonephritis was proven with urine analysis, kidney ultrasound, and kidney scan. Initial blood test showed severe hypophosphatemia 0.9 mg/dL (2.7-4.5). Tubular reabsorption of phosphorus was 96% and parathyroid hormone (PTH), Vitamin D, and calcitonin levels were 72.7 pg/mL (10-57), 10.7 ng/mL (30-100), and 9744 pg/mL (0-10), respectively. After normalization of phosphorus to 3.7 mg/dL, calcitonin was decreased to 942 pg/mL, but it was still very high suggesting malignancy. Under the impression of MTC, thyroid ultrasonography was performed which revealed a lobulated taller-than-wide, 0.6*0.7*0.6 cm sized nodule, suggesting highly suspicious malignancy (K-TIRADS category 5). Her mother had also thyroid nodule, proven papillary thyroid cancer and right lobectomy was done. RET gene mutation was checked but no pathogenic variant was detected. 24 hour-urine VMA, catecholamine, metanephrine, and normetanephrines levels were within normal ranges. Fine needle aspiration was done and it showed atypia of undetermined significance. The patient was then consulted to general surgeon for thyroidectomy and the pathology turned out to be PTC in right lobe, with lymph node invasion (8 LN of 22 LNs). The TNM staging of cancer was T1N1MO. Post-operative parathyroid hormone and calcitonin levels became normalized (PTH 5.6 pg/mL, calcitonin 6.9 pg/mL). This case showed that PTC can not be ruled out although there is highly elevated calcitonin level.

Here we report a case of incidentally detected papillary thyroid cancer with elevated calcitonin in a 15 year-old female.

Methimazole-Induced Remission Rates in Pediatric Graves' Disease: a Systematic Review

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Objective: Comparison of studies on remission rates in pediatric Graves' disease is complicated by lack of uniformity in treatment protocols, remission definition, and follow-up duration. We performed a systematic review on remission rates in pediatric Graves' disease and attempted to create uniformity by recalculating remission rates based on an intention-to-treat analysis.

Methods: PubMed and Embase were searched in August 2020 for studies on patients with Graves' disease (i) 2 to 18 years of age, (ii) initially treated with methimazole or carbimazole for at least 18 months, (iii) with a follow-up duration of at least one year after cessation of methimazole or carbimazole. All reported remission rates were recalculated using an intention-to-treat analysis.

Results: Of 1,890 articles, 29 articles consisting of 24 patient cohorts, were included with a total of 3,057 patients (82.6% female). Methimazole or carbimazole was initially prescribed in 2,864 patients (93.7%). Recalculation based on intention-to-treat analysis resulted in an overall remission rate of 28.8% (829/2,880). Pooled remission rates based on treatment duration were 23.7%, 31.0%, 43.7%, and 75% after respectively 1.5-2.5 years, 2.5-5 years, 5-6 years (two studies), and 9 years (single study) treatment duration. Occurrence of adverse events was 419 in 2,377 patients (17.6%), with major side effects in 25 patients (1.1%).

Conclusions:

Using a standardized calculation the overall remission rate in methimazole treated pediatric GD is 28.8%. A few small studies indicate that longer treatment increases the remission rate. However, evidence is limited and further research is necessary to investigate the efficacy of longer treatment durations.

Congenital multinodular goiter causing acute airway obstruction in a newborn: a case report

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Introduction: Multinodular goiter is an extremely rare condition in neonates and can account for tracheal airway compression.

Case Report: A newborn girl presented immediately after birth with an inspiratory and expiratory stridor and a visible swelling in the neck. She was born term after an uneventful pregnancy with a birth weight of 3.26 kg. The mother had no known thyroid disease and had not used antithyroid or goitrogenic medication. She had a normal iodine containing diet throughout pregnancy. Ultrasonography and magnetic resonance imaging of the infant's neck showed a diffusely enlarged homogeneous thyroid gland with a left lobe volume of 11 cm³ (reference range newborns 0.4-1.7 cm³) and right lobe volume of 5 cm³ with evident narrowing of the trachea (approximately 50% compression with a rest lumen of 1 mm). Serum TSH and FT4 concentrations were normal, indicating euthyroidism. TSH-receptor antibodies, measured five days after birth, were negative in both mother and child. However, thyroglobulin concentration was extremely high (1870 ng/ml (reference range 10-250)). Family history revealed that the paternal grandmother had hypothyroidism without goiter from the age of 37 years and the father of this grandmother hyperthyroidism at an unknown age. Both grandmothers of the father had breast cancer around 60 to 65 years. Subsequent family history (up to the 3rd degree) was negative for cancer. Because of severe airway obstruction a left hemithyroidectomy was performed nine days after birth. Pathological examination of the left hemithyroid showed multinodular hyperplasia without signs of malignancy. Two months after hemithyroidectomy levothyroxine was started because of repeatedly low FT4 with normal TSH (lowest FT4 11.6 pmol/L (reference range 12.0-28.3), TSH 2.45 mU/L) without other pituitary hormone abnormalities. A targeted next generation sequencing panel, including 58 genes associated with thyroid dysgenesis, thyroid dyshormonogenesis and central hypothyroidism, was performed in blood. Additionally, *PTEN* and *DICER1* were analyzed in blood by sanger sequencing. No genetic abnormalities were detected. Genetic analysis in thyroid tissue is pending to detect possible somatic mutations. Eight and 17 months after hemithyroidectomy ultrasonography showed an increase in volume of the remaining right lobe to 14 and 22 cm³ respectively.

Conclusion: We report an infant with congenital multinodular goiter without thyroid dysfunction at birth. The goiter caused severe airway obstruction shortly after birth necessitating hemithyroidectomy. Congenital goiter may be encountered in neonates with congenital hypothyroidism due to dyshormonogenesis (e.g. iodine organification defects). Isolated congenital multinodular goiter without thyroid dysfunction is extremely rare.

Initial response to thionamide medication in young people with newly diagnosed thyrotoxicosis

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Objective: Patients with thyrotoxicosis can be treated with anti-thyroid drug (ATD) using a blocking dose with thyroid hormone then replaced (block and replace, BR). Alternatively ATD alone can be administered with the dose adjusted up or down according to prevailing thyroid hormone concentrations (dose titration, DT). We assessed the response of young people randomised to BR or DT during the first 6 months post-diagnosis.

Design: This was a multi-centre, phase III, open-label trial of newly diagnosed thyrotoxicosis patients randomised to BR/DT. The primary outcome of the trial was to compare biochemical control in the BR and DT groups beyond 6 months. In this study we present data in the BR and DT groups for the first 6 months post diagnosis.

Methods: Patients commenced 0.75mg/kg carbimazole (CBZ) daily with randomisation to either BR or DT. We examined baseline patient characteristics, CBZ dose, time to serum TSH/FT4 normalisation and BMI Z-score.

Results: There were data available from 80 patients (baseline) and 78 patients (61 female) at 6 months. Mean CBZ dose was 0.9mg/kg/day (BR) and 0.5mg/kg/day (DT). There was no difference in the time taken for patients to achieve non-suppressed TSH concentrations; 16 of 39 patients (BR) and 11 of 39 (DT) still had suppressed TSH concentrations at 6 months. Patients with a suppressed TSH had higher mean baseline FT4 levels (72.7 v 51.7 pmol/l; 95% CI for difference 1.73, 31.7, p value for difference=0.029). Time to normalise FT4 levels was shorter in the DT group (log rank test, p=0.049) with 50% attaining a normal FT4 at 28 days in DT (95% CI 25, 32) versus 35 days in BR (95% CI 28, 58). Mean BMI Z-score increased from 0.10 to 0.81 at 6 months (p<0.001), 95% CI for difference 0.57, 0.86 and was greatest in patients with higher baseline FT4 concentrations. 13 patients gained over 10kg in weight during the first 6 months.

Conclusions: DT-treated patients normalised FT4 concentrations more quickly than BR. This difference may reflect a number of factors including the simplicity of the DT regimen (one medication rather than two) with associated improved compliance. 94% of patients have normal FT4 levels after six months but 33% still have TSH suppression. The risk of excessive weight gain should be discussed in detail with families when ATD is commenced.

A girl with Trisomy 21 presents with Van Wyk-Grumbach syndrome. A rare diagnosis

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Background: Van Wyk-Grumbach syndrome (VWGS) is a rare diagnosis that should be suspected in children with signs of peripheral precocious puberty and hypothyroidism. It is characterized by multicystic enlarged ovaries, in the presence of long-term severe hypothyroidism. Treatment of VWGS consists of hormonal replacement with levothyroxine. Usually, ovarian cysts and increased ovarian volume subside within an average of 2 months but can persist up to 12 months after treatment.

Case Presentation: An 8yrs old girl with Trisomy 21, presented with recurrent vaginal bleeding for 3 days prior to admission. She was born full-term, with normal birth weight. Medical history was remarkable for occasional constipation episodes that were treated with dietary interventions. Immunizations were incomplete. Physical exam revealed bradycardia (74 bpm), apathy, sluggishness, as well as dry skin and eyelid oedema (initially underestimated due to the typical facies of the syndrome), suggestive of severe hypothyroidism. She was prepubertal. Pending laboratory confirmation, causes of vaginal bleeding such as trauma, possible abuse, foreign body insertion and urethral prolapse were excluded. Laboratory tests revealed TSH >1000 µIU/ml, T4 0.65 µg/dl, FSH 9.22 mIU / ml <3.80), LH < 0.1mIU /ml, E2 256 pg/ml, ANTI-TPO 521.30 IU /ml, ANTI-TG 361.70 IU /ml, B-hCG < 0.1mU/ml, PRL 1832 µIU/ml (58-471), confirming severe hypothyroidism. The combination of absence of breast tissue and very high estrogen levels were evocative of the presence of ovarian cyst that was verified by the abdominal sonogram that revealed bilateral ovarian cystic masses (V:26.69 cm3 and 14.38 cm3, right and left, respectively). The girl was diagnosed with VWGS and LT4 treatment was initiated, combined with LT3 for 2 weeks. Due to continuing bleeding, letrozole was added to treatment for 2 weeks. The patient responded with complete remission of symptoms and regression of the ovarian cysts one month after initiation of treatment.

Conclusion: It is very important to think of VWGS and investigate for thyroid status during the evaluation of ovarian cysts or isolated premature menarche. Early recognition can eliminate unnecessary extensive workup and/or surgery to remove ovarian cysts, as appropriate treatment with levothyroxine leads to complete remission of symptoms. Children with Down syndrome are more likely to develop hypothyroidism, so they should be screened annually.

Complications after pediatric thyroidectomy: lymph node dissection is a risk factor for permanent hypocalcemia

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Background: Thyroidectomy is a definitive treatment option in some benign thyroid disorders and the definitive treatment option for thyroid cancer. As postoperative mortality is extremely rare data on postoperative complications and long-term health consequences are important.

Objective: To evaluate the frequencies of short- and long-term complications, and their risk factors in pediatric patients (0-18 years) who underwent a thyroidectomy in a tertiary children's hospital.

Methods: A retrospective single center study was performed including all pediatric patients who underwent a thyroidectomy between January 2013 and February 2020.

Results: Forty-eight patients were included in this study (mean age 14.6 years, 37 females (77.1%)). Twenty-nine (60.0%) total thyroidectomies and 19 (40.0%) hemithyroidectomies were conducted. Twelve patients underwent a thyroidectomy because of thyroid carcinoma, thirty-six patients because of a benign thyroid disorder. After total thyroidectomy, rapidly resolved hypocalcemia was observed in three patients (10.3%), transient hypocalcemia in 10 patients (34.5%) and permanent hypocalcemia in six patients (20.7%). Permanent hypocalcemia was only seen in patients who underwent a thyroidectomy with additional lymph node dissection because of thyroid carcinoma (thyroid carcinoma: OR 43.73, 95% CI [2.11-904.95]; lymph node dissection: OR 76.14, 95% CI [3.49-458.98]). Transient and permanent recurrent laryngeal nerve injury was reported in four (8.3%) and one (2.1%) of all patients, respectively.

Conclusion: Permanent postoperative complications after thyroidectomy are rare in pediatric patients undergoing a thyroidectomy without lymph node dissection. However, in this age group permanent hypocalcemia occurs more frequently after thyroidectomy with additional lymph node dissection because of thyroid cancer. With respect to quality of life, especially of pediatric thyroid cancer patients, reducing this complication is an important goal.

Kinetics of FT4 serum concentrations in newborns and infants with congenital hypothyroidism during follow-up differ in the three severity groups

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Background: The goal of congenital hypothyroidism (CH) treatment is rapid normalization and maintenance of TSH and FT4 in the reference range. Recommended starting dose of levothyroxine (LT4) ranges from 10-15 mcg/kg/d. Hyperthyroxinemia can be accepted in the context of normal TSH and LT4 should only be reduced in case of symptoms or repeatedly increased FT4. The aim of this study was to quantify duration and maximum peak of FT4 levels outside the reference range for each CH severity group.

Methods: Retrospective longitudinal multi-center study. For specifying periods of hyperthyroxinemia in each CH severity group, pharmacometric simulation of FT4 kinetics based on a recently developed mathematical pharmacokinetics (PK) model characterizing FT4 dynamics in infants with CH was performed. CH severity groups were based on FT4 at diagnosis (severe <5 nmol/l, moderate 5-10 nmol/l, mild >10 nmol/l). Data are median [IQR].

Results: Longitudinal data of 56 CH-patients (71% females, GA 40.9 weeks [38.6,41.4]) diagnosed at postnatal day 7 [6,9] with 236 FT4 and 232 TSH measurements were included. A normalization method was used to merge FT4 values since different assay- and age-specific reference ranges were used.

Median starting doses for each severity group were lower than recommended by 2021 guidelines. Quantification of FT4 kinetics during follow-up by pharmacometric simulation of an average patient showed peak FT4 levels above target range at day 24, 24, and 27 for severe, moderate and mild CH, respectively. Time above age-specific FT4 target range for an average patient of the severity group was significantly shorter for severe vs. moderate (P 0.02) or mild CH (P 0.02) despite comparable number of consultations in the first 6 months (severe 4 [3,5], moderate 3.5 [2.5,4.5], mild CH 4 [2.5,5.5]) and no differences between severe and moderate CH in TSH at diagnosis nor starting dose.

	severe CH	moderate CH	mild CH
Patients	25	16	15
LT4 starting dose (mcg/kg/d)	10 [7.51,14.2]	8.91 [7.15,13.12]	7.06 [3.88,8.6]
Peak fold over FT4 reference range	1.45 [1.3,1.75]	1.55 [1.31,1.93]	1.39 [0.98,1.54]
Days above FT4 reference range	63 [47,89]	135 [59.5,158.5]	134 [82,152]

Conclusions: While fold of peak FT4 levels above target range were similar for all three severity groups, moderate and mild CH patients were significantly longer hyperthyroxinemic. From a pharmacological point of view, severity-based dosing during follow-up might be helpful to reduce duration of FT4 levels above reference range. Prospective data are necessary to confirm these preliminary findings.

P2-454

Thyroid dysfunction in small for gestational age infants: a need for second screening?

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Recently there has been studies which reported that SGA could be a risk factor for the development of delayed TSH elevation (dTSH) in preterm infant. To our knowledge, very few studies have addressed development of dTSH in SGA infants whose gestational age > 34. We included 76 SGA infants and 83 controls matched on sex and birth weight who showed normal results on the initial thyroid function screening test. On the following test for thyroid function, dTSH prevalence was significantly higher in SGA infants (15.8% vs 4.9%, $p=0.023$) and LT4 treatment was introduced more frequently in SGA infants (7.9% vs 0%, $p=0.012$), although known risk factor including lower gestational age, medical condition requiring ICU treatment were more prevalent in AGA infants. In SGA infants, mean age at the time of diagnosis of dTSH was 16 days and peak TSH concentration was noted at the age of 24 days. After multiple regression analysis, presence of VLBW, and exposure to steroid, SGA was still significant risk factor for the development of dTSH (OR = 7.451, 95% CI 1.61-34.5, $p=0.01$)

P2-455

Expression of Zinc transporter 8 in thyroid tissues from patient with immune and non-immune thyroid diseases

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Introduction: Recent studies have revealed the presence of zinc and the expression of zinc transporter (ZnT) family members in most endocrine cell types. It was demonstrated that ZnT family plays an important role in the synthesis and secretion of many hormones. Moreover, recently ZnT8 was described as a newly islet autoantigen in type 1 diabetes.

Materials and Methods: We studied the expression of ZnT8 transporter in thyroid tissues from patients with immune and non-immune thyroid diseases. The study was performed in thyroid tissues after thyroidectomy from patients with thyroid non-toxic nodular goiter (NTNG; $n=17$, mean age 15.8 ± 2.2 years) and cases with Graves' disease ($n=20$, mean age 15.6 ± 2.8).

In our study we investigated the expression of ZnT8 in human thyroid tissues from patients with immune and non-immune thyroid diseases using immunohistochemistry, Western Blot as well as immunofluorescence analyses. To the best of our knowledge, this is the first investigation which identified ZnT8 protein expression in human thyroid tissues, moreover, confirmed by three different laboratory techniques.

Results: Identification of ZnT8 molecule in the thyroid tissues revealed a higher expression of this protein in patients with Graves' disease (+++) in comparison to patients with NTNG (++). For positive controls with used tissue from patients with pancreatitis (+++). The elevated expression of ZnT8 in the thyroid tissue of patients with GD was observed mainly within the cytoplasm and cytoplasmic membrane in follicular cells and in C cells (membrane-cytoplasmic reaction) with proliferation features. The expression of ZnT8 molecule was detected in patients with Graves'

disease (+) in the lymphoid cells nuclei and in C cell groups. The tissue material was additionally subjected to Western blot analysis, which in GD patients showed the presence of ZnT8 in the band p41 (kDa). In patients with NTNG, the degree of expression of ZnT8 proteins was lower and referred to band 41 (kDa). This study showed predominant expression of ZnT8 in band 41 kDa in immune than in non-immune thyroid disorders and confirmed by additional immunofluorescence method. Each thyroid tissue sample obtained from our study patients underwent assessment for the presence of GAPDH using the Western blot method, which confirmed that the tissues were not degraded and indicated high-quality analyses.

In conclusion, expression of ZnT8 in thyroid tissues in patient with immune and non-immune thyroid disorders may suggest potential role of ZnT8 as a new thyroid autoantigen but it requires further study on a larger cohort.

P2-456

Hashimoto Thyroiditis: long term follow-up from childhood to young adulthood

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Introduction: The evolution of Hashimoto Thyroiditis (HT) has been investigated by several studies both in pediatric and adult age. However, there are limited data on the progression of the disease from childhood to adulthood

Objective: Aim of the study was to describe the evolution of thyroid function in children with HT from childhood to young adulthood.

Patients and Methods: The diagnosis of HT was defined by the presence of anti-thyroid peroxidase antibodies (AbTPO) and/or anti-thyroglobulin antibodies (AbTG), and the typical hypoechoic ultrasound pattern. Patients with chromosomal abnormalities were excluded. We reviewed the medical charts of 131 children (median age 10.5 (3.33-17.5) years, 104 females) seen for HT in 2006 at the Pediatric Endocrine Unit of the Pediatric Hospital Microcitemico in Cagliari. Personal, anamnestic, clinical and laboratory data reported during the first visit were collected as well as data referring to the follow-up and the last visit (median age: 18 (10.33-33.5) years). Then, we called back all these patients who had reached adult age by that time and for 50 of them we could collect data regarding their last endocrinological visit (median age: 25.25 (18.91-37.16) years, 39 female).

Results: Between the first and the last pediatric visit (median period of 7.33 (0.5-21) years), euthyroidism persisted in 82.5% of 80 patients with initial normal thyroid function. A progression toward subclinical hypothyroidism (SH) or overt hypothyroidism (OH) was observed in 5 and 11.25% of subjects, respectively. Amongst 33 patients with SH at first visit, 36.4% reverted to euthyroidism while 9.1% maintained their condition. Finally, 54.5% of

them showed an evolution of SH to OH. Between the last pediatric visit and the last endocrinological visit (median period of 7.42 (0.42-17) years), 70.4% of 27 young adults were still euthyroid, while 25.9 % developed OH. Considering the median interval (14.25 (11.75-21.5) years) between the first pediatric visit and the last available endocrinological visit, 58.6% of 29 euthyroid children and adolescents were still in this condition as young adults while 38% have developed OH. In contrast, 82.4% of the 17 patients with initial SH developed OH.

Conclusions: In this group of pediatric HT patients euthyroidism was maintained in 82.5% during the pediatric age, in 70.4% during young adulthood and in 58.6% after a long-term follow-up. In the same period euthyroidism and SH progressed to OH in 38 and 82.4% of cases respectively.

P2-457

A case of complete atrioventricular block after initiation of methimazole in a patient with Graves' disease associated with Down's syndrome previously undergoing cardiac surgery

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Background: Arrhythmias associated with hyperthyroidism are mainly tachyarrhythmias, such as sinus tachycardia and atrial fibrillation. In comparison, hypothyroidism shows several electrocardiographic changes, including sinus bradycardia, low amplitude QRS complexes, QT interval prolongation. There are few reports of bradyarrhythmia with hyperthyroidism, and it remains unclear.

Case: The patient is a 13-year-old girl with Down's syndrome. She underwent surgical closure of ventricular septal defect (VSD) at the age of 7 months. She had a postoperative complete atrioventricular block (CAVB), which required temporary pacing, and currently has first-degree atrioventricular block. She had been diagnosed with thyrotoxicosis at a nearby pediatrician since losing 6 kg of weight for 4 months. Her free T3 was > 20 pg/ml, free T4 was > 5.0 ng/dl, TSH was <0.03 μ IU/ml, TRAb was 23.9 IU/ml, and sonography showed diffuse swelling of the thyroid gland and increased blood flow. She was diagnosed with Graves' disease and started methimazole (MMI) 15mg/day. On the third day after initiating MMI, she suddenly lost consciousness and was diagnosed as CAVB and referred to our hospital. Continuous intravenous infusion of isoprenaline was started, and her heartbeat stabilized and her state of consciousness improved. At the time of admission to our hospital, the free T3 and T4 levels were 13.2 pg/ml and 5.47 ng/dl, respectively, with a marked improvement trend. MMI was continued, and 50 mg of potassium iodide (KI) was added. On the fifth day of hospitalization at our hospital, she was implanted with a permanent pacemaker, discontinued isoprenaline. After that, she has tapered off MMI and KI and currently continuing with MMI 5mg every other day.

Discussion: This case presented a patient with Graves' disease associated with Down's syndrome who had first-degree atrioventricular block after surgery for VSD and had CAVB 3 days after MMI treatment. Bradyarrhythmias are extremely rare as a complication of thyrotoxicosis. Previous cases of thyrotoxicosis causing CAVB were associated with other coexisting factors, such as infection or coadministration of cardiac medications, as well as our case. Graves' disease associated with Down's syndrome is more responsive to treatment than non-Down's syndrome, and rapidly improved hyperthyroidism may result in relative hypothyroidism. We speculated that a postoperative atrioventricular block and rapid recovery from thyrotoxicosis were the cause of the CAVB in this case.

Conclusion: Bradyarrhythmia in the early stages of treatment should also be noted in the treatment of Graves' disease with atrioventricular block after cardiac surgery.

P2-458

Unilateral autoimmune ophthalmopathy as a first symptom in manifestation of autoimmune thyroiditis and systemic lupus erythematosus in an adolescent girl. Case report

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A seventeen-year-old girl came to outpatient clinic complaining of enlargement and pains in the right eye. She had a history of a mild weight loss, anxiety and blurred vision for the last few weeks. She was referred from another clinic for evaluation of suspected hyperthyroidism. There was no family history of toxic goiter or exophthalmos. Her grandmother had a papillary thyroid cancer.

On physical examination, the patient showed a significant increase in size in the right eye. Diffuse goiter, mild tachycardia and increased sweating were also noted. Thyroid function tests, TSH 0.01 (0.35-4.94 mU/L), T4free 24 (9-20 pmol/L).

TPO Antibodies >3000, anti-thyroglobulin antibodies > 1500, confirming autoimmune thyroiditis. Thyroid ultrasound revealed abnormal echogenicity, confirming autoimmune thyroiditis too. Coeliac screen was negative. TRAb test was positive, and Doppler ultrasonography demonstrated increased vascularisation of the thyroid gland. Methimazole and propranolol were prescribed. Ophthalmologic examination revealed lid retraction in the right eye. Thyroid hormone levels normalized after 3 weeks and TSH normalized after two months of treatment. In spite of the treatment the right eye was continuing to increase in size. MRI of the brain was performed to exclude the brain tumor; no signs of abnormalities were found. Methimazole dose was tapered over two months and ceased.

In three months the patient developed right knee joint pains and enlargement. Circulating autoantibodies, immune complex, and complement activation were found as hallmarks of Systemic Lupus Erythematosus. The level of Interleukin-6, 17, tumor necrosis factor- α , and Th1 chemokines were changed.

Oral prednisolone was prescribed for 1 month, followed by a dose reduction. The articular syndrome was stopped, and the nor-

malization of the size of the right eye was noted. TRAb was found to be negative at 5-month follow-up. The same ophthalmologist who followed her reported a full recovery of the ophthalmopathy at month 5. The patient was found to be still euthyroid at the end of 12 months of follow-up. The relapse of SLE symptoms were found.

Conclusion. The case report demonstrates the unilateral autoimmune ophthalmopathy as a first symptom of autoimmune thyroiditis and Systemic Lupus Erythematosus debut. The orally steroid treatment leads to the normalization of eye size and relief of the joint syndrome. In the follow-up of this patient, careful monitoring of the thyroid gland will be advisable.

P2-459

Incidence and etiology of primary congenital hypothyroidism in Flanders

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Background and Aims: In several European countries, the incidence of primary congenital hypothyroidism (PCH) seems to increase in the last decade, especially in countries that have lowered the newborn screening TSH cutoff. In Flanders, two centers manage since 2012 the newborn screening for PCH and these maintained the same TSH assay (Delphia, Perkin Elmer) and cutoff (15 mU/L). We studied the current incidence and etiology of PCH and initiation of thyroxine treatment in Flanders.

Methods: Birth data, results of hormonal measurements at screening and at recall, scintigraphy and ultrasound results at initial evaluation, and data on thyroxine treatment initiation were analyzed from newborns diagnosed with PCH screened between 2012 and 2017 in a single center (VCBMA), covering about half of the newborns in Flanders.

Results: During the study period, 167,653 live newborns were screened for CH, and thyroxine treatment was started in 40 (22 females [F] and 18 males [M]) newborns because of confirmed PCH (serum TSH > 20 mU/L at recall). The yearly number of treated newborns varied greatly (between 3 and 15 per year), but without a clear increase. A low serum FT4 (< 15 pmol/L) was present in 36 newborns. Median (range) gestation, birthweight SDS and length SDS were 40 (25-42) weeks, 0.00(-2.31- 2.57) and -0.14(-1.93-2.89). Based on scintigraphy (n = 29) and/or ultrasound (n= 32), a diagnosis of gland in situ, ectopy, aplasia and hypoplasia and no imaging was made in respectively 12 (5F), 15 (11 F), 10 (5 F) and 2 (0 F) and 1 (0 F) newborns. Thyroxine was started at a median (range) age of 10 (3-18) days (n = 35 before day 14). The thyroxine starting dose ranged between 25 (n=6) and 50 μ g (n = 10). Newborns with apparent aplasia had the lowest FT4 concentrations (median (range) 3 (0.4 -18) pmol/l) and received the highest starting dose (12.6 (7.6-20.4) μ g/kg/day) when compared with the other etiologies. One infant had a congenital heart disease and one had trisomy 21.

Conclusion: The overall incidence of PCH was 1 in 4191 live newborns. Abnormalities in thyroid morphogenesis were diagnosed in 69 %. No fetal growth differences were seen between the different etiologies, but a female gender excess was observed in the newborns with ectopy. Newborns with apparent thyroid aplasia received the highest dose. Thyroxine treatment was initiated before the age of 14 days in 87.5 % of the newborns.

P2-460

Re-evaluation of the prevalence of permanent congenital hypothyroidism in Niigata, Japan: A retrospective study

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Introduction: Although newborn screening (NBS) for congenital hypothyroidism (CH) in Japan started more than 40 years ago, the prevalence of CH remains unclear. Prevalence estimations among the NBS-positive CH individuals include those with transient hypothyroidism and transient hyperthyrotropinemia, and re-evaluation with increasing age is necessary to clarify the actual incidence. Thus, we re-evaluated the incidence of permanent CH.

Subjects and Methods: Of the 106,114 patients who underwent NBS in the Niigata Prefecture, Japan, between April 2002 and March 2006, 116 were examined further due to high thyroid-stimulating hormone levels (≥ 8 mIU/L) and were included in the study. We retrospectively evaluated their levothyroxine sodium (LT4) replacement therapy status from the first visit to 15 years of age.

Results: Exactly 105 (91%) subjects presented to our department for the first time. Of these, 72 (69 %) started LT4 replacement therapy on the first visit. Subsequently, 27 patients continued LT4 replacement until 15 years of age after multiple re-evaluations. In addition to the 27 patients receiving LT4 replacement at 15 years of age, 10 patients were transferred or died while on LT4 replacement therapy. Thus, the number of patients with permanent CH ranged from 27 to 37, and the permanent CH prevalence was 1 in 2,500–3,500 children. In addition, the transient CH or transient hyperthyrotropinemia prevalence was 1 in 1,700–2,100 children.

Discussion and Conclusions: Although this was not a nationwide survey, this is the first study to clarify the true prevalence of permanent CH in Japan. This study was strengthened by uniform

data, as a single institution managed almost all the CH screenings in the Niigata Prefecture and transient CH was excluded from long-term follow-up until the age of 15 years. In our study, approximately 60 % of the LT4 replacement patients discontinued treatment by 15 years of age. From these results, the prevalence of permanent CH in the Niigata Prefecture during this period was 1 in 2,500–3,500 children.

P2-461

Early reassessment in congenital hypothyroidism

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Introduction: 2020 ESPE guidelines recommend early reevaluation in primary congenital hypothyroidism (PCH) with thyroid in situ (TIS) and with levothyroxine dose lower than 3 mcg/kg/day.

Objectives: To consider infants percentage on levothyroxine that could benefit from early reassessment in our population.

Materials and Methods: Our Congenital Hypothyroidism screening program determine TSH and TT4 in dried blood spot (DBS) at 48 hours of life. A second DBS (DBS2) is indicated when the first is positive.

Multicenter retrospective study (05/2016-05/2020; 105,858 screenings) of all newborns ≥ 33 weeks and/or ≥ 1500 grams with TSH ≥ 10 mIU/L in DBS2. Serum TSH and FT4 were determined to make final diagnosis: PCH if TSH > 20 mIU/L and hyperthyrotropinemia (HT) if TSH 10–20 mIU/L. Levothyroxine dose was assessed at diagnosis, at 6 and 12 months. Differences were related to phenotype.

Results: Medium date DBS2 collected was 7 days (4–27). TSH was upper 10 mIU/L in 54 children: 5.1 positives/10,000 screenings (26 PCH/28 HT). Only 2 false positives. DBS2 and serum TSH correlation was adequate (r of Pearson = 0.941; p : 0.000). Serum confirmed DBS2 diagnosis in the 26 PCH but 15/26 HT changed diagnosis to PCH. Scintigraphy in 31/41 PCH: 21 dysgenesis, 3 hypoplasias and 7 TIS. Levothyroxine started in 45: 40/41 PCH and 5/11 HT. Differences in dose were found between dysgenesis, TIS and HT:

Values: median (range)	Dysgenesis/ hypoplasias n=25	TIS n=7	Hyperthyrotropinemias n=5
Serum TSH (mIU/L)	300 (73–779) ^a	82.9 (76.3–89.5) ^a	15.9 (9.5–1.6) ^a
Serum FT4 (ng/dL)	0.7 (0.2–1.2) ^{a,c}	1.7 (1.6–1.8) ^c	1.3 (1.2–1.5)
Gestacional age (weeks)	40 (37–42)	39 (35–40)	40 (35–41)
SDS-newborn lenght	0.2 (-2.0–1.9)	0.0 (-1.1–2.5)	-0.5 (-3.4–1.3)
SDS-newborn weight	0.4 (-2.0–2.0)	0.1 (-1.3–0.5)	-0.2 (-1.8–0.7)
Levothyroxine start (days)	7.0 (4.0–16.0) ^b	7.0 (5.0–15.0)	18.0 (10.0–44.0) ^b
Starting dose (µg/kg/day)	12.5 (2.9–17.0) ^{b,e}	6.5 (3.5–13.0) ^e	3.5 (3.0–6.0) ^b
6 month dose (µg/kg/day)	4.5 (2.0–10.0) ^{a,d}	3.0 (1.6–3.8) ^d	1.6 (1.1–2.7) ^a
12 month dose (µg/kg/day)	3.9 (1.3– 6.0) ^a	2.5 (1.3–3.1) ^a	2.0 (1.2–2.0) ^a

U Mann-Whitney: ^ap:0.000; ^bp:0.001; ^cp:0.002; ^dp:0.003; ^ep:0.004

Conclusions:

- DBS2 TSH and serum TSH had a good correlation
- Dysgenesis is the most common cause of PCH
- Early reassessment at 6 month of life could be consider in TIS and HT.

P2-462

Growth impairment in children with severe autoimmune primary hypothyroidism and pituitary hyperplasia without goiter

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Background: Prolonged severe hypothyroidism due to Hashimoto’s thyroiditis (HT) is a rare cause of pituitary hyperplasia (PH) in children. Loss of thyroxine negative feedback causes a TRH-dependent hyperplasia of pituitary thyrotroph cells resulting in adenohypophysis enlargement. A transdifferentiation of pituitary somatotroph cells into thyrotroph cells could explain growth failure in those patients. We report a case series of patients with growth impairment diagnosed with PH due to severe acquired hypothyroidism in which evaluation of anterior pituitary function at diagnosis was performed.

Cases: Ten Caucasian patients (6 females – 4 males) were evaluated in 4 Centre of Peadiatric Endocrinology because of growth arrest (in 70% of patients) or growth impairment. Median age, height and BMI at diagnosis of HT were 11 years (IQR 8 – 14.8), - 2.0 SDS (-3.58 – 0.78) and 1.12 SDS (0 – 3.1), respectively. Difference between the median values of height and target height was 1.5 SDS. Median bone age retardation was 2.5 years (0 – 5.1).

No goiter was documented. Brain MRI, performed to exclude intracranial expansive lesions, documented adenohypophysis enlargement in all of children. Median pituitary volume was 650 mm3 (504 - 1965). Hypothyroidism due to HT was confirmed in the entire cohort by biochemical evaluation (median and IQR: TSH 981 mIU/L, 236.6 – 1648; FT4 3.1 pmol/L, 0.5 - 6.2; antibodies to thyroid peroxidase 809 IU/ml, 88.8 – 4480; antibodies to thyroglobulin 352 IU/ml, 15.5 - 2040) and ultrasound evaluation [reduced (40%) or normal (60%) thyroid volume associated with diffusely hypoechogenic, coarse and heterogeneous parenchymal echotexture]. Levothyroxine treatment (2 mcg/kg/day, 1.5 - 3.5) was started.

Other basal hormonal evaluation demonstrated hyperprolactinemia (60%) and low concentrations of cortisol (40%). IGF-1 was lower than - 2 SDS in 50% of patients; those two patients underwent stimulation test growth hormone was subnormal. Furthermore, 70% of them had high total and LDL-cholesterol levels and 50% showed high triglycerides and transaminases levels.

Conclusions: Since thyroid hormones promote GH biosynthesis, in severe primary hypothyroidism GH deficiency could be expected proportional to the hypothyroidism degree. However, in some hypothyroid patients IGF-1 concentration may be within normal range even though they have growth arrest. This is the largest pediatric cohort with PH due to severe HT in which growth arrest was the most evident presenting sign. Atrophic HT phenotype might be correlated with this specific clinical presentation. Prospective studies are needed to evaluate pituitary enlargement and thyroid volume in patients with extremely high TSH without goiter.

The Use Of Intravenous Introduction Of Glucocorticoids In The Active Stage Of Graves' Ophthalmopathy In Childhood. Clinical Case

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Introduction: Graves' ophthalmopathy (GO) is an autoimmune inflammatory disease of the retrobulbar tissue and oculomotor muscles associated with Graves' disease (GD). The incidence of GO in children is 0.79–6.5:100,000 per year. Some studies indicate that in the treatment of the active stage of GO intravenous introduction of high doses of glucocorticoids is more effective and has fewer side effects compared to oral administration.

Clinical Case: A 17-year-old patient was observed with a diagnosis of GD in October 2016. When the patient was examined in the hormonal profile there were hyperthyroidism, a high titer of antibodies to the TSH receptor, in connection of which thyrostatic therapy initiated.

In dynamics since November 2018 there has been a pronounced increase in the total volume of the thyroid gland.

Firstly she was examined at the Endocrinology Research Center in October 2019. During the CT examination, pronounced exophthalmos of the orbits, thickening of the external rectus oculomotor muscle, tension of the optic nerves were revealed. As a consequence of the ophthalmological examination the diagnosis was established: OU-Graves ophthalmopathy of moderate severity is inactive. For the purpose of preoperative preparation four Diprosan 0.5 ml of peribulbar injections have been performed.

Upon re-hospitalization, according to the ultrasound scan of the thyroid gland the total volume of the thyroid gland was 167.1 cm³. Re-consulted by an ophthalmologist recommended peribulbar injection of Diprosan for 1 day before the surgery.

On December 12th 2019 thyroidectomy was performed.

A month after surgical treatment complaints of photophobia, lacrimation, redness of the sclera, and soreness in the area of the eyeballs resumed. The patient was examined at the place of residence: according to the results of exophthalmometry negative dynamics were revealed.

In connection with the current situation a collective decision was made on the feasibility of pulse therapy with methylprednisolone in a total dose of 2000 mg.

When performing MR control of orbits (1 month and 9 months after the end of pulse therapy): MR - picture of lipogenic exophthalmos without thickening of the oculomotor muscles. There was a progressive positive dynamic in the form of a decrease in exophthalmos, hydration of retrobulbar fiber. No adverse events were observed.

Conclusion: This clinical case of intravenous introduction of large doses of glucocorticoids demonstrated stable positive dynamics of the course of Graves' ophthalmopathy, the absence of adverse events, allows us to use this method in the treatment of the active stage of Graves' ophthalmopathy in children.

Atypical presentation of acute suppurative thyroiditis in a 6 year old child

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Bacterial infection of the thyroid gland (acute suppurative thyroiditis, AST) is a very rare condition, particularly in children, as the thyroid gland is extremely resistant to infection. AST presents with painful tender mass in the anterior neck and is usually associated with fever, sore throat, dysphagia and limitation of the neck movements. In the most cases the left globe is affected. Common laboratory findings are leukocytosis, elevated erythrocyte sedimentation rate (ESR), increased C-reactive protein (CRP) and normal thyroid function. Ultrasonography (US) shows in the early stages heterogeneous echogenicity of the affected thyroid lobe with hyperperfusion of the gland.

We report one 6 year old girl which presented with painless enlargement of the neck area for 2 days. She had no history of fever or sore throat. On palpation rock hard neck mass. Laboratory tests showed no increase of the white blood cell count (8,2/nl), CRP was 7,8 mg/l and ESR 23 mm/hr. The US revealed a 2,2 cm x 1,4 cm -sized hypoechoic lesion of the left thyroid lobe with inflammatory changes. Thyroid function testing was normal. Thyroid autoantibodies were negative. Serum Calcitonin was elevated with 14,2 µg/l (normal range <9,8 µg/l). In the following days the neck mass became larger with tenderness and erythema of the skin. The child remained asymptomatic. The US showed progressive enlargement of the lesion without abscess formation. The white blood cell count and CRP remained low, but the ESR elevated after one week to 47mm/hr. We performed a fine needle aspiration to identify infectious organisms and rule out malignancy. The cytology was negative for malignancy. Prevothella oris was detected on the culture antibiogram. The girl was treated with Clindamycin for 6 weeks. The ESR and Calcitonin levels returned to normal within 4 weeks after begin of the therapy.

AST is very rare in childhood but should be considered as differential diagnosis of neck mass. AST may sometimes present with atypical findings without pain, without systemic reactions and with only mild laboratory changes. The thyroid function remains mostly normal. Serum calcitonin levels can be elevated in infectious thyroiditis and are not associated with malignancy. AST can be successfully treated with appropriate antibiotics. Recurrent infections need further assessment of the presence of anatomical defects as pyriform fistula. In our case we decided for a "wait and see" strategy, as sometimes a persistent pyriform sinus tract may close as result of the previous thyroid infection.

Allan-Herndon-Dudley syndrome: case report of a rare disorder

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Introduction: Allan-Herndon-Dudley syndrome (AHDS) is an X linked disorder – mutation of monocarboxylate transporter 8 (MCT8) gene. It leads to a severe psychomotor retardation, significant hypotonia of the skeletal muscles, spastic or dystonic quadriplegia.

MCT-8 is responsible for the uptake of T3 by neurons of CNS. AHDS is characterized by increased T3 concentration, increased T3 / T4 ratio, TSH not depressed, even slightly elevated levels. Because of impossibility for the T3 entrance into the neuronal cells, clinical features of hypothyroidism become evident early at a critical stage of neuro-cognitive development in newborn period. There are currently described 132 families with AHDS in the world. In peripheral tissues, T3 can be transported into the cell by alternative transporters, resulting in peripheral hyperthyroidism, manifested by tachycardia, hypertension, loss of muscle mass and weight, malnutrition.

Currently no treatment is available to correct the peripheral thyrotoxicosis. The effectiveness of levothyroxine and/or anti-thyroid therapy is not proven. There is no any guideline for the management of these patients. Recently a paper was published by Groeneweg S. et al (2019) showing the effectiveness and safety of T3 analogue Triac in the phase 2 trial. Triac enters into the neuronal cells independently from MCT8 via an alternative channels, which serves as an exciting and uncommon opportunity potentially to improve the neurocognitive development.

Case Report: A child was followed by neurologists from the newborn period due to neuro-developmental delay. Newborn screening of TSH was normal, later TSH and fT4 evaluation found subclinical hypothyroidism. Due to stable subclinical hypothyroidism treatment with levothyroxin was administered, which was ineffective and the treatment was stopped. Objective examination showed muscular weakness, scoliosis, global development delay, dystonic opened mouth, no contractures. The whole-exome-sequencing was performed by neurologists, which revealed a novel homozygous mutation (c.972G>A) in the *SLC16A2/MCT8* gene. Last examination: bilateral esotropia, severe tetraparesis with contractures, neuro-developmental delay, no speech, weight - < 3%, height - 25%, head circumference - <3%. Thyroid status: TSH-9.22mUI/mL, FT4-8.83pmol/L (NR=12.3-22.2), T3-6.04nmol/L (NR=1.42-3.8). Symptoms of peripheral hyperthyroidism: tachycardia 115-197b/min by Holter-monitoring.

Conclusion: early diagnosis of AHDS by evaluating the whole thyroid profile and genetic testing gives an opportunity to avoid useless treatment and frequent hormonal tests in patients with neuro-developmental delays. With the Triac a new insight is suspected to have in a nearest future.

Hypothyroidism in context of 1q44 microdeletion syndrome and DOLK-CDG

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1q44 microdeletion syndrome has a variable clinical phenotype, with various degrees. DOLK-CDG is a rare condition with an autosomal recessive pattern. Neurological involvement is often noticed in both of these conditions. The association between 1q44 microdeletion syndrome and DOLK-CDG has not yet been reported on the same patient. Also, hypothyroidism was not reported for DOLK-CDG patients. Furthermore, DOLK-CDG has only been described in patients having the homozygous mutation linked with a low life expectancy.

We present a case of a 2-months-old female born to non-consanguineous parents with central mild hypotonia and febrile seizures. She was born at 39 weeks of gestation, with 3540 grams, 50 cm length, 34.5 cm head circumference, and Apgar Score 7. Newborn neurological examination was normal for the GA and so was the corpus callosum at TFUS. Amniocentesis and fetal MRI were recommended in the second trimester of pregnancy because dysgenesis of the corpus callosum was suspected. However, both investigations showed normally developed corpus callosum and borderline lateral ventriculomegaly.

Despite constant follow-up at the neurologist and regular kinesiotherapy, hypotonia persisted.

Around the age of 1 year due to delayed motor skills and language acquisition, failure to thrive, and mild facial dysmorphism, an interdisciplinary approach was considered appropriate. The patient was then diagnosed with hypothyroidism due to right thyroid hemiagenesis and substitution therapy with Levothyroxine was initiated, normalizing the TSH level and improving the clinical appearance of the child. The genetic and imagistic evaluation was further considered beneficial. WES revealed a likely pathogenic 1734kb-large one copy loss within chromosomal region 1q44. Two heterozygous variants of uncertain significance (Class 3) were identified in the DOLK gene. Parental karyotypes were normal. 1q44 microdeletion syndrome was confirmed using array-CGH. Brain MRI indicated mild lateral ventriculomegaly and a reduction in the thickness of the corpus callosum.

The pattern and severity of DOLK-CDG vary among affected individuals. 1q44 microdeletion syndrome is a newly described syndrome with various degrees of developmental delay. Thyroid hemiagenesis is a rare form of thyroid dysgenesis, with a prevalence of about 0.05-0.2% in the normal population.

In our case, a multidisciplinary and complex approach was needed, including a pediatrician, endocrinologist, neurologist, and geneticist. Long-term follow-up and treatment (substitution therapy with Levothyroxine, kinesiotherapy, and speech therapy) are essential.

P2-467

Graves Ophthalmopathy in Pediatric Age: Different Severities, Different Approaches

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Ophthalmopathy associated with thyroid disease is uncommon (incidence rate 1.7-3.5 cases/100.000 inhabitants) and even rarer in children and adolescents (0.79-6.6 cases/100.000 children); it is being more frequent in adolescents (68.2% of 11-18 years old) and females.

We present two cases of Graves' orbitopathy in two boys, with different therapeutic approaches.

Case 1: 7-year-old, referred to a Pediatric Endocrinology clinic due to hyperactivity, hyperphagia, hypersudoresis and diarrhea. Clinical examination showed bilateral exophthalmos, eyelid erythema and conjunctival hyperemia [clinical activity score (CAS) 3 and mild severity].

The laboratory evaluation showed TSH 0.01uUI/mL (0.4-5uUI/mL), free T4 0.75ng/dL (0.7-1.8ng/dL), free T3 4.65ng/mL (2.5-3.9ng/mL), TRABs 15.4U/L (normal<1U/L).

Thyroid ultrasound: enlarged thyroid, nodular appearance, suggestive of thyroiditis.

Orbital-CT: slight bilateral exophthalmos due to thickening of the lower and right internal rectus muscles.

He was treated with thiamazole 3.5mg/day (94,6ug/kg/day), propranolol 10mg/day and, after observation by ophthalmology, lubricating eye drops and selenium 100mg/day. Systemic and eye complaints improved.

In the last appointment, he had no exophthalmos and was euthyroid, with still positive TRABs (2.4u/L), under thiamazole 2.5 mg/day (30,5ug/kg/day).

Case 2: 13-year-old sent by Ophthalmology to the Pediatric Endocrinology consultation for control and weaning from corticosteroid therapy (prednisolone 50mg/day), started two months before for Graves' orbitopathy (CAS 6 and moderate severity); already under thiamazole 10 mg/day (170,6 ug/kg/day). He had bilateral exophthalmos, mild eye pain, conjunctival hyperemia.

The laboratory evaluation showed TSH <0.004uUI/mL, free T4 4.74ng/dL, totalT3 6.7 ng/mL (0.9-1.8ng/mL) and TRABs 198 U/L.

Thyroid ultrasound: enlarged thyroid with diffuse heterogeneous parenchyma.

Orbital-CT: bilateral moderate thickening of the internal, upper and lower rectus muscles.

After discussion with Ophthalmology, he was kept on corticosteroid therapy and the antithyroid dose was adjusted due to overt hyperthyroidism. Six months later, it was possible to slowly wean off from the corticosteroid therapy.

In the last visit he had no exophthalmos nor eye complaints, was euthyroid even though the TRABs were still positive (2.9U/L). He was treated with thiamazole 3.5 mg/day (50,8ug/kg/day).

The cases of these boys show that although the symptoms of orbitopathy in the pediatric population are generally mild and self-limited, but in specific occasions targeted treatments are necessary, so all children with thyroid pathology must be observed in ophthalmology.

P2-468

Thyroid function in preterm infants admitted to the neonatal intensive care unit: a single center study

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Background: A common cause of neurodevelopmental impairment in children is congenital hypothyroidism, but can be preventable with adequate screening and proper management. Preterm newborns are more likely to have thyroid dysfunction, with small for gestational age (SGA) being an additional risk factor. However, only few studies addressed the altered thyroid hormone concentrations in the first few weeks of life concluding that Thyroid-Stimulating Hormone (TSH) levels are higher in SGA newborns. As a result, we conducted a study to compare thyroid hormone levels and the incidence of thyroid dysfunction between the SGA and the appropriate for gestational age (AGA) infants.

Methods and Materials: This is a cross-sectional retrospective single-centered study conducted at Centre Hospitalier Universitaire Notre Dame des Secours (CHUNDS), Jbeil, Lebanon, between January 1, 2016 and November 31, 2020. The medical records including thyroid function test results, sociodemographic characteristics and clinical conditions of 260 preterm infants admitted to the Neonatal Intensive Care Unit (NICU) were reviewed.

Results: A higher percentage of infants who were SGA had abnormal thyroid function in general (31.8% vs 14.4%, p=0.002), and hyperthyrotropinemia in particular (18.2% vs 6.2%, p=0.004) compared to AGA infants. Moreover, infants who were SGA had significantly higher mean TSH levels compared to those who were AGA ($6.86 \pm 4.31^*$ vs $4.55 \pm 3.22^*$, p < 0.001).

Conclusion: Preterm SGA neonates had higher TSH levels and an increased incidence of thyroid dysfunction. Therefore, close follow up with periodic thyroid function testing, endocrinological and cognitive assessment is of significant importance in SGA infants presenting these features.

P2-469

Thyroid dysfunction in Beta-thalassemia patients

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Introduction: B-thalassemia is a hereditary chronic hemolytic anemia characterized by a defect in the synthesis of beta-globin chains, particularly common in the Mediterranean region, southern Asia, and the Middle East

Transfusion programs and chelation therapy have greatly extended the life expectancy of patients. This has led to an increase in the prevalence of endocrine complications, linked to iron overload

The hypothyroidism is one of the most commonly reported complications in patients with polytransfused beta thalassemia. Thyroid dysfunction is directly linked to the degree of iron overload.

Objectives: Describe the frequency of hypothyroidism in patients with polytransfused β -thalassemia. Study the linking between hypothyroidism and the ferritinemia rate, the average transfusion volume (MTV), the duration of transfusion therapy, splenectomy, and compliance with chelating therapy.

Method: It is a descriptive, analytical and mono-centric cross-sectional study which was carried out in the pediatric department of CHU Mustapha and which involved 87 patients (46 Girls and 41 Boys), followed for several years on a regular basis and treated by a transfusion regime (more than 10 transfusions) combined with a chelating treatment.

All patients were evaluated by a clinical history, a somatic examination, and then a determination of free T4 (FT4) and thyroid stimulating hormone (TSH).

Results: Primary hypothyroidism is present in 16 (18.4%) patients, this hypothyroidism is subclinical in 12 (13.8%) patients and obvious in 04 (4.6%) patients.

The average age of patients with hypothyroidism was 12 ± 5.3 years.

Hypothyroidism was observed in 11 boys and 05 girls. Hypothyroidism was asymptomatic in all β -thalassemia patients at the time of diagnosis, no patient had goiter, and no central hypothyroidism was observed.

There is a significant correlation between hypothyroidism and the ferritinemia level in our study.

Conclusion: Hypothyroidism in thalassemia develops as a result of siderosis of thyroid cells, usually seen in the second decade of life.

An annual assessment of thyroid function is recommended in polytransfused β -thalassemic patients from the age of 10 years. Recognizing and treating hypothyroidism early in thalassemia help improve the quality of life for these patients.

P2-470

Victim pathologies of the pandemic. Severe acquired hypothyroidism

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Introduction: In the last year, the pediatric services have seen a reduction of up to 50% of the consultations and 1/3 of the admissions to the hospitalization ward; However, the existence of other pathologies cannot be forgotten despite the current situation, such as hypothyroidism, diabetic ketoacidosis, short stature, precocious puberty, etc., as far as endocrinology is concerned. Difficulty in accessing primary care, non-contact visits, along with the fear of families to go to the health field, can lead to a delay in the diagnosis of important pathologies. According to INE 2020 (National Institute of Statistics), there is an increase in mortality in Spain not directly attributable to COVID19 infections. **CLINICAL CASE:** A 35-month-old girl referred to outpatient visits for thyroid dysfunction detected in a non-face-to-face primary care consultation. Moroccan family, first-born with normal somatometry and neonatal screening at birth. Age-appropriate growth growth up to 2 years. The family reports 8 months before, coinciding with the onset of the pandemic, that the patient is more tired, dry skin, hoarse tone of voice and significant hair loss. Later, she presented psychomotor retardation, failure to thrive and swelling of the face, a fact that alarmed the family and for which they decided to consult in primary care. He does not refer associated goitrogens. No family history of thyroid function alteration. A blood test is performed where an elevated TSH > 500mU / L, FT4 < 0.42 ng / dL, FT3 < 1.0 pg / mL, Thyroperoxidase, ATPO Ac 4 IU / mL, Thyroglobulin 63.59 ng / mL, Thyroglobulin (ATG), Ab 203 IU / mL. Urine test in normal ranges without proteinuria. In a patient with severe autoimmune acquired hypothyroidism, treatment with sodium levothyroxine is started and a thyroid ultrasound is requested to complete the study. **CONCLUSIONS:** As pediatricians we must be attentive to alarm symptoms, be careful in the telematic assistance that is offered and above all assess if this is the most appropriate, since the essence of the "Lex artis" can be lost, observing and exploring our small patients.

P2-471

Mitigating thyroid cancer risk in multinodular hyperplasia secondary to a 10q23.31 deletion (PTEN Hamartoma Tumour Syndrome)

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Introduction: The phosphatase and tensin homolog (*PTEN*) hamartoma tumour syndrome (PHTS) groups related multi-system genetic disorders linked to germline mutations in the *PTEN* gene. There is an increased risk of thyroid cancer in PHTS, with

some cases arising in childhood. Annual surveillance for thyroid cancer by ultrasound is recommended.

Case Report: A 15 year old female was referred to Paediatric Endocrinology by Clinical Genetics for thyroid surveillance given a 10q23.31 deletion involving the *PTEN* gene. She had significant developmental delay, with severe learning difficulties, a diagnosis of autism spectrum disorder (ASD) and seizures. Her father and brother were known to have the same *PTEN* deletion. Both parents had head circumferences above the 97th centile. Her father had undergone a total thyroidectomy for a large multinodular goitre. He also had a history of lipomas and a cerebral vascular malformation. Our patient was clinically euthyroid and had a normal thyroid examination. Her head circumference plotted on the 50th centile. She did not have any mucocutaneous lesions, lipomas or haemangiomas. Thyroid function was normal (TSH 0.68 mu/L (0.34 – 5.6), FT4 14.8 pmol/L (7.5 – 21.1)). A thyroid ultrasound scan revealed bilateral thyroid lesions predominantly cystic in nature, without microcalcification or cervical lymphadenopathy. The patient required a general anaesthetic for fine needle aspiration (FNA), which was performed on the largest lesion (15 mm diameter). Histology was inconclusive and reported mostly colloid. Annual ultrasound surveillance with likely FNAs versus definitive surgery was discussed at the oncology thyroid MDT. Following an in depth discussion with the family, the patient, who was not Gillick competent, underwent a prophylactic total thyroidectomy aged 16 years. She was commenced on lifelong levothyroxine. Histology reported multinodular hyperplasia.

Discussion: Learning points from the management of this individual are as follows. There is an estimated 35% lifetime risk of thyroid cancer in PHTS. Annual surveillance is therefore essential, however ultrasound findings in this clinical context may warrant an immediate FNA. Yet such a procedure may not be easily tolerated in these individuals, repeat FNAs may be required over time and whilst FNA can be diagnostic, accuracy in children varies. Therefore, the risks versus benefits of repeated general anaesthetic in order to perform an FNA, should sedation fail, need to be considered. Another consideration is the inevitable progression of multinodular hyperplasia making thyroid surgery more challenging with time. We therefore advocate an individualised approach to mitigating thyroid cancer risk in children with PHTS.

P2-472

Thyroid dysfunction and autoimmune thyroiditis in children with new-onset diabetes mellitus

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Introduction: Type 1 diabetes mellitus (DM) can be related with other autoimmune disorders. Thyroid dysfunction and autoimmune thyroiditis are frequently reported in DM. This study was performed to evaluate the prevalence and risk factors of thyroid dysfunction and autoimmune thyroiditis in children with new-onset DM.

Subjects and Methods: Children with DM and followed for more than 6 months in a single tertiary center were included in the study. Medical records were reviewed. Sex, onset age, initial

HbA1c, presentation of diabetic ketoacidosis (DKA), serum T3, free T4, and TSH levels, positivity of anti-GAD, anti -insulin, and anti-IA2 antibody (Ab) as well as anti-thyroid peroxidase (TPO), anti-thyroglobulin (TG), and anti-TSH receptor Ab were analyzed to find the prevalence and risk factors of thyroid dysfunction and thyroid autoimmunity at the onset of DM. Chi-square, Fisher's exact test, t-test, and logistic regression were used for statistics.

Results: A total of 103 subjects were included in the study (T1DM:T2DM 57:46). Initial presentation as DKA was found in 34% and it was more frequent in T1DM (T1DM:T2DM 56%:7%). Among 57 subjects with T1DM, low T3 and low free T4 were found in 51% and 19%, respectively and both were more frequently occurred in T1DM compared to T2DM. The presence of DKA was associated with low T3 and low free T4, respectively ($P < 0.05$). Thyroid autoimmunity was not associated with low T3 or low free T4. Anti-TPO Ab positivity and anti-TG Ab positivity at the onset of T1DM were 24% and 22%, respectively and both were 3% and 11% in T2DM. Anti-TPO Ab was significantly more frequent in T1DM compared to T2DM. Presence of anti-TPO Ab was associated with younger age of onset and positivity of GAD Ab or IA2 Ab in total DM. However, among T1DM, anti-TPO Ab positivity was not associated with onset age, GAD Ab or IA2 Ab positivity.

Conclusion: This study showed that low T3 or low free T4 was frequently observed at the onset of T1DM and it was associated with the presence DKA. Among T1DM children, anti-TPO Ab and anti-TG Ab were positive in 24% and 22%, respectively, and there was no correlation between the presence of anti-TPO Ab and anti-T1DM Ab in children with T1DM.

P2-473

A Rare Cause of Congenital Hypothyroidism: Brain-Lung-Thyroid Syndrome

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Introduction: Brain-lung-thyroid syndrome (BATS) is a rare autosomal dominant inherited syndrome that develops due to mutations in the NKX2-1 gene, which is a thyroid transcription factor, and is characterized by respiratory distress in the neonatal period, congenital hypothyroidism, and choreatetosis. Approximately half of affected patients have the complete triad, with 30% affected by the neurological phenotype (motor developmental delay, gait difficulties, choreatetosis, hypotonicity, ataxia, dysarthria, dystonia, thirst, hunger, sleep problems) and hypothyroidism, while about 13% only have the neurological phenotype. In cases accompanying pulmonary dysfunction; neonatal respiratory distress, asthma, and frequent lung infections can be seen. Herein, a case with a heterozygous mutation in the NKX2-1 gene is presented with interesting family characteristics.

Case: A three-month-old girl who was diagnosed with congenital hypothyroidism at the age of one month and started treatment was referred to our clinic for follow-up. She was born at term, weighed 3300 grams and developed meconium aspiration in newborn period. In her family history, it was learned that there were neurodevelopmental retardation in her mother and choreiform movement disorder in her mother and grandfather. While receiving levothyroxine treatment at admission; thyroid function tests were euthyroid, thyroid gland was in normal localization and thyroid volume was within normal limits on thyroid ultrasonography. In the first year of the follow-up, although drug compliance was sufficient and her course was euthyroidic, neuromotor growth retardation was noticed, and choreiform movements started at the age of two and a half years. Metabolic examinations, brain imaging, electroencephalogram, echocardiography and Array CGH analysis, performed to clarify to etiology, were normal. In whole exome sequencing analysis, c.703G>T mutation was found in exon 3 in the NKX2-1 gene in our case, her mother and grandfather.

Conclusion: NKX2-1 mutation should be considered in cases of congenital hypothyroidism accompanied by neurological and / or pulmonary findings or family history indicating that these systems are affected.

P2-474

Recurrent fractures in a child with Graves' disease

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Introduction: Graves' disease is the most common paediatric cause of hyperthyroidism. Although hyperthyroidism has been reported to cause a decrease in bone mineral density (BMD), its association with recurrent bone fractures is extremely rare.

Case: A 10-year-old male patient, who had a pre-existing 7-year diagnosis of autism spectrum disorder, presented to emergency with right leg pain that started after collision with an arm-chair. On initial examination, his body temperature was 36.6°C, heart rate 136 beats/min, blood pressure 113/66 mm Hg, weight 45 kg and height 156 cm (79th and 97th percentiles, respectively). X-ray revealed a fracture of right femur and he underwent surgery. Demineralization of bone was detected and endocrinology was consulted. His medical history included fractured right femur one year previously and right foot nine months previously. Family history was unremarkable. He had prominent thyromegaly with diffuse enlargement and soft consistency on palpation.

Initial Blood Tests were: calcium 9.8 mg/dl (8.5-10.5); phosphate 4.53 mg/dL (3.7-5.6); alkaline phosphatase 229 U/L (42-362); PTH 14 pg/mL (12-88); 25-OHD 20.7 ng/mL (20-80); TSH <0.01 µIU/mL (0.38-5.33); fT3 >30 pg/mL (2.6-4.37); and fT4 5.59 ng/dL (0.61-1.2). Complete blood count, liver, kidney function tests were normal. Auto-antibodies were positive: thyroid peroxidase Abs 2455 IU/mL (0-9), thyroglobulin Abs 7.8 IU/mL (0-4) and TSH Receptor Abs 8.38 IU/L (0-0.1). Thyroid ultrasonography showed a significant increase in thyroid gland volume and vascularization. A diagnosis of Graves' disease was confirmed. Methimazole,

propranolol and vitamin D therapies were started. Pre-treatment bone densitometry showed significantly low BMD: lumbar BMD (L1-L4) was 0.543 g/cm² (Z-score -2) and femoral BMD was 0.323 g/cm² (Z-score -4.8). Thyroid ophthalmopathy was not found on ophthalmological examination. Euthyroidism was achieved after three months of treatment and clinical signs of hyperthyroidism had improved. At one year follow up there were no clinical signs of hyperthyroidism and the patient remained euthyroid. Bone densitometry investigation ten months after diagnosis showed marked improvement: lumbar BMD (L1-L4) was 0.721 g/cm² (Z-score -0.6) and femoral BMD was 0.323 g/cm² (Z-score -2.8). He is currently at the first year after diagnosis and is euthyroid on 10 mg methimazole daily.

Conclusion: While this case demonstrates the importance of thyroid hormone on bone health and that untreated children with Graves' disease may present with fractures, it highlights the importance of considering hyperthyroidism as a possible diagnosis among the differential diagnoses of pathological bone fractures.

P2-475

Case study of 13- year-old boy suffering from papillary thyroid cancer in stage pT3aN1bMX

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Papillary cancer represents majority of thyroid malignancies in children. However prognosis remains very successful. In recent years, we use elastography, except biopsy and standard ultrasonography in thyroid lesions diagnostic. We present a case of a male patient at the age of 13 years, with a history of ADHD and school phobia who was referred to Endocrinology Outpatient Clinic due to partial empty sella syndrome. Family history of endocrinological disorders was negative. Physical examination revealed light stretch marks on hips, enlarged thyroid gland. Blood tests showed normal levels of tropic hormones. Thyroid ultrasound showed inhomogeneous, hypoechoic area (size: 15 x 17 x 19 mm) without vascularity in right lobe with hyperechoic area in the middle (size: 6 x 4,5 mm), multiple micro- and macrocalcifications. ROI1/ROI2=10. Above, on the border of isthmus and right lobe homogeneous hypoechoic lesion 7 x 7x 4 mm was present. Enlarged lymph nodes on the right side. BACC was performed- microscopic image answered to diagnosis of papillary thyroid cancer (Bethesda VI/VI). In Oncology Centre in Gliwice total thyroid resection with middle neck lymph nodes was conducted. Bilateral biopsy with lymph nodes examination demonstrated metastases. Surgical removal of group II-V lymph nodes was performed. Pharmacological treatment constituted L-thyroxine supplementation (100 ug), Calperos * 6 x 1000 mg, Alfadiol * 3 x 1 ug. Histopathological

investigation confirmed papillary carcinoma with metastases to middle neck and bilateral lymph nodes- pT3aN1bMX. Complementary treatment with radioiodine I131- 100 mCi was done. There was no active cancer in scintigraphy. Suppressive dose of L-thyroxine was instructed to maintain TSH level in 0,1-0,4 uIU/ml range.

In Conclusion:

1. Fine needle aspiration biopsy is a gold standard in thyroid lesions diagnostic.
2. Elastography becomes helpful technique in thyroid ultrasonography, which firstly simplifies to recognize suspect lesions with smaller degree of distortion to perform biopsy.
3. Treatment of advanced stages of papillary cancer requires surgical treatment and complementary therapy with radioiodine.

P2-476

Evaluation of general characteristics of children with hypothyroidism

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Aim: This study aimed to investigate retrospectively the demographic, clinical and laboratory data of patients followed up for hypothyroidism and to determine the incidence of persistent hypothyroidism.

Materials and Methods: A total of 209 patients with hypothyroidism were included retrospectively in this study. Demographic data, clinical features, laboratory results, thyroid volume, follow-up time, treatment drug were recorded. These patients were divided into three groups (subclinical hypothyroidism, transient and permanent hypothyroidism).

Results: Forty four% (94) of the patients were female and 55% (115) were male. The anatomical structure of the thyroid gland varied between hypoplasia, agenesis and normal structure and they were 1%, 8,1% and 90,9% respectively. The patients with the transient, the permanent and subclinical hypothyroidism were 29,7%, 58,9%, 11,5% respectively. On the day of admission of the patients median was 21 days. The median duration of treatment was 40 months. The mean body weight SDs was -0,69, the mean height was 57,8 ± 11,08 and body weight compared to the height was 113,5, and the birth weight was 2933 g. Both transient and permanent TSH levels were higher than those of subclinical patients and this difference was statistically significant ($p < 0.05$). Thyroid volume was higher in patients with transient hypothyroidism than those with permanent hypothyroidism, which was statistically significant ($p < 0.05$).

There were no statistically significant difference in TSH level in patients with transient and permanent hypothyroidism ($p > 0.05$).

There were no statistically significant difference in sex, delivery method, birth week and birth weight according to the type of hypothyroidism ($p > 0.05$).

Thyroglobulin levels of the transient, the permanent and the subclinical hypothyroidism were found cut-off 104, 34, 40.6, sensitivity 55.77%, 72.12%, 70%, specificity 100%, 84.21%, 75% respectively.

TSH levels of the transient, the permanent and the subclinical hypothyroidism were found cut-off 10.3, 10.5, 10 sensitivity 100%, 100%, 100%, specificity 88.4%, 75.96%, 25% respectively.

ST4 level of the transient, the permanent, the subclinical hypothyroidism were found cut-off 0.92, 0.93, 0.90 sensitivity 100%, 100%, 100%, specificity 100%, 100%, 100% respectively.

Conclusion: Determining the etiology and type of hypothyroidism plays an important role in the treatment and follow-up of patients. Hypothyroidism should be considered in every patient with growth retardation and mental retardation. When hypothyroidism is noticed in the early period, we believe that it is necessary to remain under close follow up and monitoring because the problems caused by hypothyroidism can be treated.

P2-477

L-T4 absorption test in 14-year-old patient with severe refractory hypothyroidism after total thyroidectomy

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Hypothyroid patients post-thyroidectomy require 1.6-1.8 mcg/kg/die of Levothyroxine (L-T4). A persistent TSH level above the upper limit despite a daily dose >1.9 mcg/kg/die is defined as "refractory" hypothyroidism in adults. Malabsorption and "pseudo-malabsorption" need to be investigated in case of therapeutic failure. L-T4 absorption test (LT4AT) is useful in distinguishing these two conditions but it has only been described in adult age.

We present the case of a 14-year-old girl affected by severe refractory hypothyroidism after thyroidectomy, despite apparently taking high dosage of L-T4. At 10 years of age she was diagnosed with autoimmune hyperthyroidism (FT4 >6 ng/dL, FT3 >7 pg/mL, TSH <0.01 mcU/mL, TRAb >40 U/L) and she started treatment with Methimazole (0.5 mg/kg/day). After 15 months of anti-thyroid drug, the patient still presented not well-controlled thyroid function values and an important thyromegaly. Therefore, at 12 years of age she underwent total thyroidectomy. The postoperative period was regular, except for transient hypocalcemia requiring calcium and vitamin D. L-T4 therapy was started at a dosage of 1.5 mcg/kg/day. One year after surgery, TSH values oscillated between 25 and 120 μ U/mL with low FT4 despite the treatment with progressively higher dosage of L-T4 (4 mcg/kg/day) and referred adequate compliance. Therefore, she was hospitalized in our pediatric department. Thyroid function test was performed at the entrance and after five days of L-T4 administration under the nurses' supervision. All causes of malabsorption were ruled out as well as medications impairing L-T4 absorption. Thus, we decided to perform LT4AT test. We administered L-T4 1000 mcg peroral

	1 st day	5 th day	0h	1h	2h	3h	4h	6h	24h	After 7 days
TSH (mcU/mL)	217	96.6	43.5	38.3	34.8	28.3	31.5	29	15.3	4.72
FT4 (ng/dL)	0.27	1.22	1.44	2.46	3.04	3.12	3.14	3.25	2.84	1.74
FT3 (pg/mL)	/	/	2.58	2.75	2.82	3.03	3.07	2.92	3.25	3.45

and collected blood tests (TSH, FT4, FT3) at baseline and at 1-2-3-4-6-24 hours after drug intake. The concentrations of TSH, FT3 and FT4 at different timepoints are reviewed in the following table.

The test showed a >2 time increase in basal FT4 levels and a normalization of the thyroid function at seven days, excluding L-T4 malabsorption. We suggested to restart L-T4 treatment under parents' strict surveillance with close monitoring of thyroid function tests.

A possible non-adherence to L-T4 therapy must be investigated while managing refractory hypothyroidism and LT4AT test could provide valuable information also in adolescence.

P2-478

A child with anti-thyroid arthritis syndrome

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Introduction: Anti-thyroid arthritis syndrome (AAS) is a rare complication that may occur in patients treated with anti-thyroid drugs. Presentation is variable and may include myalgia, arthralgia, skin rash, high fever, and polyarthritis. Herein, we present a girl diagnosed with AAS.

Case Report: A 9-year-old girl was admitted to emergency complaining of fever and arthralgia. She was the second child of non-consanguineous healthy parents. She had been diagnosed with Graves' disease (GD) 40 days earlier at another hospital. At GD diagnosis, thyroid function tests (TFTs) showed free thyroxine (fT4) and, free triiodothyronine (fT3) were elevated at 2.62 ng/dL (0.61-1.2) and 11 pg/mL (2.6-4.37), respectively, concurrent with suppressed thyroid stimulating hormone (TSH) <0.01 µIU/mL. Furthermore, TSH receptor antibody 2.62 IU/L (0-0.1) was elevated together with anti-thyroperoxidase antibody 655 IU/mL (0-9) and anti-thyroglobulin antibody 141 IU/mL (0-4). Methimazole was prescribed at 20 mg/day. Twenty days after initiation of methimazole, she presented with generalized arthralgia, fever, and rash while euthyroid. Methimazole was stopped by her parents. Subsequently, she was referred to the emergency department with a presumptive diagnosis of acute rheumatic fever (ARF). On physical examination, fever was 38.6°C, heart rate was 120/min, arthritis was detected in the right knee and left elbow and maculopapular rash was present on the trunk and lower extremity. In laboratory work-up, erythrocyte sedimentation rate (21 mm/hr) and C-reactive protein (43 mg/dL) were elevated. She had positive anti-neutrophil cytoplasmic antibodies, antinuclear antibody and

anti-histone antibody. Her complement levels were within normal range. The diagnosis of ARF was excluded because of normal echocardiography and no evidence of group A streptococcal infection. She was finally diagnosed with AAS.

Methylprednisolone (2 mg/kg) was initiated. After two days, TFTs indicated hyperthyroidism (fT4 2.28 ng/dL, fT3 6.61 pg/mL, TSH <0.01 µIU/mL) and methimazole was restarted (10 mg/day). Methylprednisolone was slowly tapered over two months. Arthritis, fever and rash completely resolved with steroids, with no recurrence after cessation of methylprednisolone. Currently (three-month follow-up), she is euthyroid on methimazole 5 mg/day.

Conclusion: To date, few pediatric cases of AAS have been reported. AAS patients were reportedly treated with radioactive iodine or surgery. As methimazole is commonly used in pediatric GD, in pediatric AAS and prior to radioactive iodine or surgery, a slow increase in methimazole with steroid and tapering the steroid slowly may be an alternative treatment approach.

P2-479

Thyroglobulin deficiency: a rare cause of neonatal stridor

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Background: Nonimmune neonatal goitrous hypothyroidism is a rare cause of neck mass and stridor. Retropharyngeal extension, described in 7% of cases of goitre spreading outside the thyroid bed, represents a diagnostic dilemma that requires a systematic multimodality imaging approach combined with hormonal and genetic analysis. We report the case of a one-week-old baby who presented with stridor and respiratory distress, without palpable neonatal goitre and whose biochemical profile suggested defective thyroglobulin synthesis. Case: A eight-day-old term male infant was admitted to the Neonatal Intensive Care Unit for assessment and management of persistent stridor. Clinical examination of his neck was normal. Microlaryngoscopy and bronchoscopy (MLB) revealed subglottic stenosis and neck MRI scan confirmed a large goitre with retropharyngeal extension. Following a borderline TSH result of 17 mU/L (normal range, NR <8mU/L) on neonatal screening, venous hormonal profile showed modest TSH

elevation (28.7 mU/L, NR: 0.35 - 5.50 mU/L) with low free T4 (6 pmol/L, NR 10.4 - 22.7 pmol/L), normal -high free T3 (9.2 pmol/L, NR 4.6 - 10.1 pmol/L) and undetectable serum thyroglobulin concentrations (<0.2 ug/L, NR 7.82-79.5 ug/L). Maternal thyroid function was normal and thyroid stimulating immunoglobulins were not detected in mother or neonate. Treatment with levothyroxine 11.5 mcg/kg/day was started to normalise serum TSH concentrations, thereby mitigating thyroidal trophic stimulation and goiter growth, however, due to persistent respiratory distress, intubation and ventilation were required. Isthmectomy was performed at 22 -days- old to facilitate extubation, since two weeks of medical treatment had not ameliorated goitre size. Histopathology and immunohistochemistry findings were consistent with defective thyroglobulin synthesis, although thyroglobulin sequencing results are still awaited. Levothyroxine dose was optimised, repeat MLB showed significant improvement of subglottic stenosis and follow up MRI scan showed reduction of the goitre size without any focal thyroid lesions. The baby was extubated on day 43 of life and discharged home on thyroxine 5.7 mcg/kg/day when he was two months old. Multi-disciplinary management was key in his progress and successful discharge. Conclusions: Dysshormonogenic retropharyngeal goiter is a rare case of persistent stridor in the neonatal period. TSH elevation, combined with raised FT3:FT4 ratio and disproportionately low serum thyroglobulin levels in the context of goitre and TSH elevation, should trigger molecular evaluation for thyroglobulin mutations. Suppressive therapy with thyroxine is not always effective in reducing the size of goitre associated with this condition and surgical intervention may be required.

P2-480

TBG deficiency and Central Congenital Hypothyroidism (CCH): Our experience in neonatal screening with TSH and T4

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Objective:

- Analyze CCH detection program results from 3 Autonomous Communities: TSH and total T4 (TT4) in dried blood spot (DBS) at initial screening (48 hours of life) and at retesting.

- Describe the characteristics of neonates with screening compatible with CCH.
- Consider whether TBG deficiency (TBGD) is an added difficulty in said study.

Materials and Methods: Retrospective study (May 2016-May 2020) of all neonates ≥ 33 weeks and/or ≥ 1500 grams referred to the Child Endocrinology services of 3 Communities due to low T4 (<6 $\mu\text{g/dL}$), out of a total of 105,858 CH screenings.

The positives for low T4 in the retesting compatible with CCH (low T4 and low/normal TSH) were analyzed. After determination in serum, the diagnoses were:

1. CCH: low free T4 (FT4) and low/normal TSH
2. TBG deficiency (TBGD): normal FT4 and TSH
3. Hyperthyrotropinemia: normal FT4 and elevated TSH
4. Euthyroid sick syndrome.

Clinical and laboratory variables were compared between CCH and TBGD. The evolution of the cases considered CCH was assessed.

Results: Forty-four neonates were referred due to low TT4, 15 corresponding to primary CH and 29 cases were compatible with CCH. The final diagnosis of the positives with initial suspicion of CCH was: 15 TBGD, 8 CCH, 5 hyperthyrotropinemia and 1 euthyroid sick syndrome.

CCH prevalence in this period was 1/13,333 screenings. Statistically significant differences were found in FT4 values when comparing CCH and TBGD (table).

All CCH started treatment with levothyroxine with a median age of 9.5 days (7-155). 1 multiple hormonal deficiency and 7 isolated CCHs have been diagnosed (according to evolution data).

6 out of 8 patients with CCH also had TBGD.

Conclusions:

- The determination of TT4 in neonatal screening has diagnosed 8 patients with CCH.
- TBG defect is very common in the population; TBGD diagnosis does not exclude a CCH, since they can coexist.
- Genetic studies would help to confirm CCH diagnosis.

*U Mann-Whitney	CCH (mean ± DE) n=8	TBGD (mean ± DE) n=15	
TSH screening (mIU/L)	1.8 ± 0.2	1.9 ± 0.9	ns
TT4 screening (mcg/dL)	2.2 ± 0.2	4.4 ± 0.9	0.000*
TSH retesting (mIU/L)	2.0 ± 0.0	1.9 ± 0.2	ns
TT4 retesting (mcg/dL)	2.3 ± 1.4	3.7 ± 1.3	0.034*
TSH serum (mIU/L)	2.8 ± 1.8	3.8 ± 0.9	ns
FT4 (ng/dL)	0.7 ± 0.1	1.5 ± 0.4	0.000*

P2-481

A case of hypothyroidism post bone marrow transplantation

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Introduction: – Changes in thyroid function and thyroid function tests occur in patients with β -thalassemia major (TM). The frequency of hypothyroidism in TM patients ranges from 4% to 29 % in different reports. Bone marrow transplantation (BMT) is based on destruction of the patient's bone marrow with rescue of haematopoietic stem cells from a donor. Chronic graft-vs-host disease (GVH) is the major complication post-BMT and mimics some autoimmune diseases, such as autoimmune hypothyroidism.

We report a case of 7 years old boy with diagnosis of Major beta thalassemia in age of 3 months The parents are consanguine and had one sister with heterozygote beta thalassemia. After two years of bone marrow transplantation the child presents a slow growth and symptoms of hypothyroidism confirmed by biological assays TSH 100 micro iu FT4 0.3 pmol/l anti thyroperoxidase antibody 307 ui/l and anti thyroglobuline antibody 1208 ui/l.

These diseases occur mainly in association with chronic GVH. The pathophysiology of chronic GVH and other autoimmune-like diseases post-BMT remains poorly understood. Different mechanisms have been postulated. Most of the autoimmune events (either chronic GVH or more specific diseases) seem to be related to a poor or inadequate immunologic recovery post-BMT with an imbalance between autoregulatory and autoreactive lymphocytes. Microchimerism and molecular mimicry have been recently evoked. A minority of cases (autoimmune thyroid disorders) is attributed to the direct transfer of autoreactive cells from donor to patient (adoptive immunity). Despite physiopathologic uncertainty, these autoimmune-like disorders post-BMT are an interesting model for primary autoimmune diseases.

P2-482

Iodine status and autoimmune thyroiditis in children; a case-control study in Sri Lanka

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Introduction: While there are many benefits of the National-Iodization program, excess iodine intake has been implicated as a triggering factor for autoimmune-thyroiditis (ATI). There is a scarcity of documented literature on this association in relation to the Sri Lankan setting.

Objectives: To evaluate the effects of iodine intake on the prevalence of autoimmune thyroiditis in children attending the Lady Ridgeway Hospital for Children.

Method: A case-control study was done with a case-to-control ratio of 1:1 among a total of 100 children between 5-14 years. Cases were mainly defined with biochemical investigations of free-thyroxine (FT4), thyrotropin (TSH), anti-thyroid peroxidase antibodies (Anti-TPO), and anti-thyroglobulin antibodies (Anti-Tg), in addition to clinical and radiological features. Children with diagnosed endocrine or autoimmune disorders and with a history of iodine-containing or anti-thyroid medications were excluded. Urinary iodine concentration (UIC) was measured as an indicator of iodine nutrition status as defined by the World Health Organisation. The non-parametric Mann-Whitney-U test and Spearman-correlation-coefficient were used in the analysis with a significance level of 5%.

Results: The median (IQR) ages of the cases and controls were respectively 11.5 (8.9-12.4) and 9 (6.7-12.2) years. The male-to-

female ratio of both groups was approximately 1:4. The median (IQR) levels of FT₄, TSH, Anti-TPO, and Anti-Tg among the cases were; 10.5 (7.1-12.0) pmol/L, 10.4 (3.4-49.8) mIU/L, 536.4 (169.6-1772.6) IU/L, and 189.2 (38.6-490.6) IU/L. The respective values among the controls were: 13.0 (12.1-14.4), 1.8 (1.3-2.2), 1.0 (0.6-1.5) and 1.5 (1.2-1.9). The median (IQR) of UIC of the cases and control were 125.3 (68.8-190.1) µg/L and 110.0 (77.3-178.3) µg/L respectively. There was no significant difference in UIC levels between cases and controls ($p=0.448$). UIC did not correlate with anti-TPO ($R=0.033$, $P=0.82$) and anti-Tg titres ($R=-0.169$, $P=0.244$).

Conclusions: Iodine nutrition status in children in both groups was optimal, based on urinary iodine concentration. Furthermore, there was no significant association between iodine intake and autoimmune thyroiditis.

P2-483

A 9-year-old girl with Van Wyk and Grumbach syndrome: precocious puberty as a rare consequence of hypothyroidism

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Background: The syndrome consisting of primary hypothyroidism, precocious puberty, and massive ovarian cysts was termed Van Wyk and Grumbach syndrome (VWGS) in 1960.

Chronic lymphocytic thyroiditis is the more common cause of hypothyroidism in children. In patients with severe longstanding hypothyroidism, the sella turcica may be enlarged due to thyrotrope hyperplasia. Puberty tends to be delayed in hypothyroid children in proportion to the retardation in the bone age, although in longstanding severe hypothyroidism, sexual precocity has been described. An elevated serum prolactin, the latter possibly due to raised TRH which is known to stimulate prolactin as well as TSH, has been described in some cases, but gonadotropin levels are not elevated. It has been hypothesized that this syndrome of pseudo-puberty in hypothyroid patients is due to cross- interaction of the extremely elevated serum TSH with the FSH receptor.

Case Presentation: A 9-year-old Mongolian girl was examined in region with severe iodine deficiency in the South of Siberia (in Republic of Tuva). She presented with sexual precocity (menstruation, and breast development but relatively little sexual hair), galactorrhea, overweight, headaches and fatigue. On evaluation, she was found to have short stature, delayed bone age and pituitary enlargement. Multicystic ovaries revealed on ultrasonography. Laboratory data revealed severe hypothyroidism with autoimmune thyroiditis.

Physical data. Height - 118 cm (below - 2SDS), weigh 41 kg, BMI = 31. The skin is dry, scratching. Cardiac sounds are rhythmic, 72 beats per minute. Arterial pressure is 90/50 mm Hg. Sex formula: $Ma_3A_1P_1Me_9$. The thyroid gland was diffusely enlarged 2. In hormonal analysis: TSH - 88.1 mU/L; free T₄ - 1.7 pmol/L; antibodies against thyroperoxidase - 715 U/L, prolactin - 1020 mU/L; LH 0.6 mU/L; FSH 0.5 mU/L; estradiol 14.6 pg/ml. X-ray of the wrist showed a delayed bone age (7 yrs). VWGS was diagnosed and

thyroid replacement was started with resolution of the symptoms. Therapy: L-thyroxine 100 mcg. The examination after 3 months: TSH was 1.8 mU/L; free T₄ - 16.7 pmol/L.

Conclusions: In a highly selected minority of children with untreated primary hypothyroidism, there is development of precocious puberty and progressively enlarging multicystic ovaries. The entire clinicopathologic picture reverts to normal status with the restoration of a euthyroid state by means of simple levothyroxine replacement therapy.

P2-484

Iodine Deficiency Cretinism in Tuva Republic

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Introduction: Iodine deficiency is the most common cause of mental retardation that can be prevented. The most serious consequence of iodine deficiency is cretinism.

The Republic of Tuva is one of 89 administrative territories of the Russian Federation. Tuva lies in the south of Siberia and bordering Mongolia. In 1997 we first discovered the pocket of severe iodine deficiency in the Republic of Tuva and found cases of endemic cretinism.

The Aim: To study the features of iodine deficiency cretinism in the Republic of Tuva.

Materials and Methods: We surveyed 287 children between the ages of 1.5 and 15 in the western districts of Tuva. A neurological examination was carried out; audiometry, ultrasound examination of hearing; psychometric assessment of mental development through verbal and non-verbal tests.

Results: According to our research, the prevalence of iodine deficiency cretinism in Tuva was 3.5%. Various forms of endemic cretinism have been revealed: mixedematous, neurological and mixed. Mixed cretinism prevailed (77.6%) and characterized signs of severe hypothyroidism, mental and growth retardation, emotional-will disorders. Patients with neurological cretinism were deafness in 75%, with serious mental deficit (idiocy or imbecility) combined with squint and characteristic spastic lesions of the limbs.

Conclusions: Severe iodine deficiency in Tuva Republic has a negative impact on the health and mental development of the population and requires constant adequate iodine prevention and monitoring of iodine deficiency.

Prevalence and associated factors of Congenital Hypothyroidism in Bogotá, Colombia. 2014–2020

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Introduction: As communicable diseases become less prevalent as a cause of death in children under the age of five, non-communicable diseases such as birth defects are major causes of infant mortality and disability in many countries. Congenital Hypothyroidism (CH) is a thyroid hormone deficiency present at birth. It occurs approximately in 1:2000 to 1:4000 newborns (NB), causing neurological deficits and long-term metabolic complications. Effective and timely screening is essential to treat those affected and prevent pathologies that impair their quality of life. This study seeks to analyze data provided by the screening program in the city of Bogotá – Colombia, taking into account the cases notified to the Sistema de Vigilancia en Salud Pública (SIV-IGILA) and to identify possible associated conditions that have an impact on the prevalence of this disease.

Methods: This is an observational, retrospective study, based on the data provided by the SIVIGILA database, which reports all the newborns with congenital anomalies during the 2014–2020 period in the city of Bogotá, Colombia. The ICD-10 nomenclature was used to classify the cases. The biological variables analyzed were birth, weight, sex, maternal age, associated malformations, and the presence of multiple pregnancies. The socioeconomic variables analyzed were maternal housing. Data were registered and analyzed using Microsoft Excel 2021.

Results: During the years of this study, the prevalence of NB reported as suspected with CH was 1:1220 NB, showing a stable trend on the linear tendency analysis; when adjusted for cases with confirmed high values of TSH in umbilical cord measurement, the prevalence is 1:3041 NB. Regarding the demographic data of the patients analyzed, it was found 54% were men and 46% women. Of the total CH cases with a reported weight, 20% weighted less than 2500 grams. 97.8% of the cases were isolated, without any other metabolic or anatomical birth defect. The mean maternal age was 26.9 (SD 6.7) years. 17.7% of the cases had mothers with housing in a rural area.

Discussion: The prevalence of confirmed CH cases with high TSH umbilical cord values is similar to that reported in other studies, although the prevalence of suspected cases is higher than expected. Studying the behavior of this event makes it possible to guide health actions to reduce said disease burden. Furthermore, future guidelines should seek to reduce underreporting, creating an opportunity for improvements in newborn screening.

Aetiology and different clinical condition of hypothyroidism in children and adolescents

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Introduction: Hypothyroidism is a common problem encountered by paediatric endocrinologists. In children, the prevalence of hypothyroidism is about 0.15% with female to male ratio on target to 2.8. Normal thyroid synthesis and its action on target tissues are necessary for normal metabolism through life, linear growth after birth and for normal development of the brain until 3 years of age. Endemic and nodular goiter, thyroiditis, congenital and acquired hypothyroidism are group of the most common thyroid disorders.

Objective: To evaluate clinical features, etiology and evolution of patients with hypothyroidism

Methods: Longitudinal retrospective study of patients diagnosed with hypothyroidism between 2004 and 2019. Study was conducted in the west of Algiers. Age at diagnosis, clinical characteristics and initial dose of treatment were recorded. Patients were classified according to etiology.

In congenital hypothyroidism, neurocognitive assessment was based on intelligence quotient (IQ).

Results: 74 cases were identified: 42 F/32 M, the patient's average age at diagnosis was 9 (range 0.1-144) months in congenital hypothyroidism, and 7 (range 1-15) years in acquired hypothyroidism. Consanguinity was present in 8 (11%) of cases, with a family history of thyroid disease in 28 (38%). In congenital hypothyroidism (25 cases), appearing symptoms were jaundice (11 cases), constipation (4 cases), delayed development (5 cases: late diagnosis) and others (4 cases). In acquired hypothyroidism (49 cases), the majority of patients were asymptomatic (diabetes and Down syndrome screening: 44 cases), 2 cases had short stature, 2 cases had delayed puberty. In the laboratory evaluation, we highlight: high TSH in all patients, low free T4 in 96 %, 3 patients had a subclinical hypothyroidism; elevated title of antiperoxidase were found in 40 patients. There were 25 patients with congenital hypothyroidism: 2 cases of Down syndrome, 11 cases of gland in situ. 40 patients who had Hashimoto's thyroiditis presented type1 DM, and 9 patients had Down syndrome. Majority of patients received L-thyroxin (96%) and mean age to start it in congenital hypothyroidism was 9 (range 0.1-114) months. Among re-evaluated patients (13 cases), 9 cases had permanent hypothyroidism at 3 years.

Conclusion: Many etiologies can be at the origin of hypothyroidism. It's important to distinguish the congenital from the acquired. The permanent congenital hypothyroidism is the commonest treatable cause of learning difficulties. The diagnosis remains late in our country, the only alternative is the screening facilities. Management and prognosis depend on etiology.

P2-487

Influenza A induced Thyrotoxic Storm Post Haematopoietic Stem Cell Transplantation

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Background: Thyroid storm is a rare occurrence of severe thyrotoxicosis, most commonly associated with Grave's disease and is reported to have a high morbidity and mortality. It is particularly rare in children. Whilst there is a scoring system to diagnose thyroid storm in adults, there is not an equivalent for children.

Here, we describe the case of a patient who developed thyroid storm secondary to influenza A infection.

Case Report: A 13-year-old girl had a matched unrelated donor transplant for CTPS1 deficiency immunodeficiency. Six months post-transplant, she developed heat intolerance and palpitations. On examination, she had a fine tremor but no goitre or exophthalmos. Her temperature was above 38 degrees C for two days, she was tachycardic with HR >140, flushed and had diarrhoea. There was no CNS dysfunction. She was found to have TSH < 0.01 mU/L and free T4 of > 100 pmol/L with fT3 of 17.0 pmol/L. She was negative for TSH receptor and TPO antibodies. Thyroid ultrasound demonstrated increased vascularity and heterogenous echogenicity.

Neutrophil count of $0.54 \times 10^9/L$ secondary to bone marrow transplant. She was found to be Influenza A virus positive at the time that she was symptomatic with thyroid storm.

As agranulocytosis is a possibility with carbimazole, it would be difficult to add this risk to her pre-existing post-transplant neutropenia. We therefore managed her with Lugol's iodine and intravenous hydrocortisone. Her thyroid function began to normalise within three days and T4 level was reduced to 29pmol/L one week after starting treatment. She then developed hypothyroidism despite withdrawal of Lugol's iodine and 2 months after the initial thyrotoxic phase was started on Levothyroxine. She currently takes 125 micrograms daily levothyroxine.

Discussion: This 13 year old patient developed thyrotoxicosis secondary to influenza infection. The clinical picture was of an acute thyroiditis eventually evolving into hypothyroidism. One previous case reports a young adult patient developing thyrotoxicosis secondary to H1N1 infection. However, there are no previous reported cases of thyrotoxicosis in children secondary to influenza A infection. There are no reports of stem cell transplant resulting in hyperthyroid storm.

This case highlights that it is important to maintain an open mind on differential diagnoses in patients with raised temperatures; if infection does not seem to explain all of the findings, consider other causes such as thyroid disorders. Influenza A may be a rare cause of acute thyroid dysfunction in children.

P2-488

The state of iodine deficiency in Krasnoyarsk territory according to results of neonatal TSH screening in 2019

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Background: Iodine deficiency is associated with goiter and impaired brain function. Neonatal thyroid-stimulating hormone (TSH) screening for congenital hypothyroidism used as an indicator of the degree of iodine deficiency. In the absence of iodine deficiency, the frequency of neonatal TSH above 5 mU/L whole blood is less than 3%. A frequency of 3%-19.9% indicates mild IDD. Frequencies of 20%-39.9% indicate moderate and above 40% severe IDD.

The Aim: to estimate the iodine deficiency in Krasnoyarsk territory according to the results of neonatal TSH screening in 2019.

Methods: An analysis of neonatal TSH screening was performed in 14,560 newborns participating in the national thyroid newborn screening program in 2019. The TSH concentration was measured in dry blood spots collected by heel stick on filter paper, 96 hours after birth, using DELFIA method.

Results: According to the data of the congenital hypothyroidism screening the rate of TSH < 5 mU/L was 9.4% in Krasnoyarsk territory (11.8% was in 2015; 23.9% in 2000) and corresponded to mild iodine deficiency. In different regions of Krasnoyarsk territory the rate of neonatal TSH < 5 mU/L varied from 1.4% in central Novoselovskiy district to 36.5% in northern Evenkiyskiy region. The state of iodine deficiency in Arctic Taimyrskiy region was better in 2019: the frequency of TSH < 5 mU/L was 16.5% (23.7% in 2015; 29.9% in 2000), but corresponded to moderate iodine deficiency. In Krasnoyarsk city the rate of TSH < 5 mU/L was 7.7% in 2019 (9.2% in 2015, 23.5% in 2000). These results indicate mild iodine deficiency.

Conclusion: Analysis of the neonatal TSH screening show mild iodine deficiency in central part of Krasnoyarsk territory. In Arctic Taimyrskiy and northern Evenkiyskiy regions saved moderate iodine deficiency. This demand continuous adequate iodine prophylaxis to prevent cognitive outcomes.

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Thyrotropic cell hyperplasia secondary to prolonged uncontrolled primary hypothyroidism

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Introduction: Prolonged evolution of an untreated hypothyroidism can lead to thyrotropic cell hyperplasia, which could be indistinguishable from a pituitary macroadenoma on resonance. Differential diagnosis is very important since it allows to avoid aggressive therapeutic behaviors.

Case Report: We show a 3-year-old girl who, in the context of a study due to psychomotor retardation, borderline head circumference and coarse features, presented in magnetic resonance an enlarged adenohypophysis (10.8mm) and bent, which compressed neurohypophysis, and TSH of 2021.9 mU / L.

She had insomnia, but no fatigue, visual disturbances, or headache. Parents had not noticed growth disturbance. She received laxatives for constipation. Her mother had two abortions and his uncle had type 1 diabetes. She showed microcephaly from 20 weeks of pregnancy with karyotype and aneuploidies in amniotic fluid normal, and magnetic resonance imaging and brain ultrasound at birth normal. No heel test was performed. Anthropometry at birth was normal. On examination she had a short stature (-2.75 SD), wide forehead and nose, and hypertelorism. Thyroid scintigraphy was performed, which is normal, and thyroid ultrasound showed pseudonodules and heterogeneous echogenicity. She showed Thyroxine 0.23 ng / dl, thyroglobulin 0.5 ng / ml, Ac Anti Thyroglobulin 1668.50 U / mL and Ac Anti TPO (microsomal) 2028.00 U / mL. Rest of pituitary hormonal axes, celiac disease and arrays were normal.

She started treatment with levothyroxine 50 mcg / day, with normalization of TSH and T4 in 2 months. Parents referred that she slept well, she did not need laxatives, and psychomotor development had greatly improved since she started levothyroxine treatment. As for the stature, she showed -1.82 SD and growth velocity with $p > 99$ (6.03 SD) at one year of treatment.

Conclusion: In conclusion, this case recalls the importance of a baseline study of all hormonal axes in any tumor of sellar origin that excludes non-surgical causes.

Thyroid dysharmonogenesis: a case report of two siblings with a heterozygous variant in the TPO gene

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Background: Congenital hypothyroidism (CH) is an inborn disease with an incidence rate of 1 case per 3,600 newborns of which 15-20% cases are associated with thyroid dysharmonogenesis. The *TPO* gene encodes thyroid peroxidase. Disease associated with this gene is usually transmitted in an autosomal recessive mode. Hypothyroidism-associated TPO variants are usually biallelic, limited evidence for cases in patients with heterozygous variants exists.

Methods: Thyroid imaging was performed using ultrasound (US) and scintigraphy (Tc99m). Serum thyroglobulin (TG) was detected by ELECSYS immunoassay method, TSH and free T4 were measured by ARCHITECT test system. Genetic data was obtained with targeted gene panel including 23 genes associated with CH using Illumina MiSeq System in patient 1 and the regions of interest were analyzed with Sanger sequencing.

Case Report: Patient 1 (proband): 13 yrs. old girl with CH. Neonatal TSH at 200 mU/L. US scan and scintigraphy showed *in situ* thyroid gland with extremely high blood flow and increased radiotracer uptake up to 3.3% (0.8-1.7). TG increased to 445 ng/ml. All of these studies were conducted after discontinuation of l-thyroxine therapy for two weeks at the age of 13. Patient 2: 10 yrs. old sister with normal thyroid. Patient 3: 8 yrs. old brother with CH and high level of neonatal TSH up to 180 mU/L. Clinical analysis results are similar to that of the proband in 8 yrs. age - increased ultrasound blood flow, radiotracer uptake to 3.9% and TG up to 273.4 ng/ml. Patient 4: 3 yrs. old brother with normal thyroid. The heterozygous known pathogenic variant in the *TPO* gene c.1188 1193delCGCCAGins10p. (Ala397Profs*76) was found in proband and confirmed by the mother, 10 yrs. old healthy sister and 8 yrs. old brother with CH. The heterozygous *SLC5A5* gene variant c.1192T>A p. Cys398Ser with an unknown clinical significance was detected in proband, mother, healthy 10 yrs. old sister and 3 yrs. old healthy brother. The father did not have any of those variants. Increased radiotracer uptake in proband's thyroid excluded the role of the variant in the *SLC5A5* (*NIS*) gene in the etiology of CH in this family.

Conclusions: The variant in the *TPO* gene might play the main role in the etiology of patient's 1 and patient's 3 CH. We are going to analyze proband's TPO gene with Sanger sequencing that may identify a new intron variant and verify the etiology of CH in this family.

Pediatric Graves' disease in southern Tunisia

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Background: Hyperthyroidism is uncommon in children. Graves' disease is the most common cause in pediatric population. The diagnosis is based on the presence of anti-TSH receptor antibodies. Pediatric Graves' disease has some peculiarities mainly in term of treatment and evolution, since its prognostic is different than adults.

Aim: The aim of this study is to describe the epidemiological, clinical and biological features of pediatric Graves' disease. We also evaluated the effectiveness of treatment and determining the risk factors of remission and relapse.

Methods: A retrospective chart review of all Pediatric Graves' cases referred to our department during 23 years (from January 1st 1997 to December 31st 2019).

Results: A total of 25 children met diagnostic criteria. Annual incidence rate was 1,08 case per year. The average age was 9,02 +/- 3,96 years. At diagnosis, weight was decreased with median weight -0,52 +/- 1,03 standard deviation, height was increased with median height 0,36 +/- 1,36 standard deviation. 18 children had goiter, 16 had exophthalmos, 14 had tachycardia and 4 children were hypertensive. Free T4 levels were elevated in 96% cases. TSH was suppressed in all cases. TRAK results were available in 8 cases and were positive in all of them. Initial treatment was with antithyroid medication and it was started in 23 cases. We used Benzylthio-uracile (BZU) in 14 cases and Thiamazole (Thi) in 9 cases. Initial mean BZU dose was 256,43 +/- 46 mg/1,73m²/j and mean Thi dose was 0,6 +/- 0,34 mg/Kg/j. Block and replace method was used in 4 cases. Radical treatment was proposed for one girl, it consisted of surgery (total thyroidectomy). After a mean duration of follow-up of 37,81 +/- 38,79 months, long term remission was obtained in 3 cases, short term remission in 2 cases. 2 children have relapsed and 12 were lost to follow up. During treatment, 8 children presented side effects from treatment.

Conclusion: Graves' disease treatment is cheap and safe but requires prolonged follow up.

- A**
 Abacı, Ayhan P2-4, P1-64, P1-115, P2-353
 Abali, Saygin P1-18
 Abawi, O. P2-180, P2-216
 Abawi, Ozair [FC9.1](#), P2-2, P1-103, P2-191
 Abbate, Marco P1-160, P2-477
 Abbou, Samuel P1-185
 Abdel Twab, Hossam P2-251
 Abdellah, Dami P2-392
 Abdellaoui, Wahiba P2-168, P2-275
 Abdelmeguid, Yasmine [P2-127](#), [P2-202](#)
 Abdelmeguid, Yasmine P2-384
 Abdiaei, Erfan P2-167
 Abdiaei, Hossein P2-167
 Abdoun, Dawood S. P2-119
 Abdulhadi-Atwan, Maha FC5.5
 Abebe, Bezaye [P2-153](#)
 Abernethy, Laurence P2-58
 Abinun, Mario FC10.5
 Abraham, Mary B. P2-230
 Abraham, Prakash P1-8
 Abu Libdeh, Abdulsalam P1-184
 Acar, Sezer P1-2
 Achermann, John P1-142, P2-238
 Achermann, John C. P2-19, P1-50, P2-406
 Achilleos, Orthodoxos P2-442
 Achir, Samia P2-366
 Achkar, Joy P2-468
 Achutegui, Irupe P2-124
 Acuña, Pilar [P2-81](#)
 Adam, Safwaan P1-8
 Adavastro, Marta P2-313
 Adaway, Jo FC1.1, P2-375
 Adel, Ashraf P2-296
 Aderotimi, Tobi P2-58
 Aerts, Isabelle P1-185
 Afonso Lopes, Lurdes P2-79
 Aftab, Sommayya [P1-17](#), P2-39, P2-45, P2-63, P2-64, [P1-70](#), [P1-133](#), P2-142
 Afzal, Nadeem P1-47
 Aghajanova, Elena M. [P1-161](#)
 Aghajanova, Yelena P2-49
 Aghayev, AghaRza P2-14
 Agosti, Massimo P2-172, P2-295
 Aguilar Abisad, Daniela P2-55
 Aguilar Riera, Cristina [P2-72](#), [P2-402](#)
 Agwu, Chizo P2-287
 Ahmad, Amar FC8.3
 Ahmed, Faisal FC1.2, P1-6, P1-43, P1-114
 Ahmed, Gaouzi P2-392
 Ahmed, Hannah P1-139, P1-140, P1-178, P2-255, P2-256, P2-264, P2-265, P2-266, P2-267, P2-268
 Ahmed, Mohamed E. P2-271, P2-331
 Ahmed, S. Faisal FC1.3, FC1.5, FC7.1, P1-3, P1-8, P1-46, P1-48, P1-72, P1-89, P1-110, P1-143, P1-146, P2-13, P2-375, P2-397
 Ahmed, Shayma [P2-416](#)
 Ahmed, Shaymaa [P2-241](#)
 Ahn, Moon Bae [P1-52](#), [P2-12](#), P2-131, P2-243, P2-378, P2-389, P2-415
 Aida, Mohandoussaid P2-44, P2-274, P2-245
 Aiello, Francesca [P2-70](#)
 Aissat, L. P2-469
 Aitkenhead, Helen P1-142
 Ajzensztejn, Michal P1-29
 Ak, Güneş P1-109
 Akakin, Dilek P2-371
 Akcaboy, Meltem P2-159
 Akcan, Neşe FC4.5
 Akiki, Simon P2-468
 Akkari, Miguel P2-87
 Akker, E.L.T. van den P2-216
 Aksglæde, Lise P2-349
 Aksu, Cagri [P2-78](#)
 Akulevich, Natallia P2-318, [P2-338](#)
 Al Abdwani, Raghad P2-11
 Al Enezi, Ayed P2-61
 Al Harthy, Rand [P2-140](#)
 Al Hashmi, Laila P1-25
 Al Kindi, Fatma [P2-140](#)
 Al Mamari, Ali P2-140
 Al Mukaddam, Mona FC6.4, HA1, P1-51
 Al Shaikh, Adnan P2-91, [P2-271](#), [P2-331](#)
 Al Shammari, Sameer [P2-61](#)
 Alaaraj, Nada [P1-139](#), [P1-140](#), [P2-12](#), [P2-104](#), [P1-178](#), [P2-105](#), [P2-131](#), [P2-241](#), [P2-243](#), [P2-264](#), [P2-265](#), [P2-266](#), [P2-267](#), [P2-268](#), [P2-269](#), [P2-255](#), [P2-256](#), [P2-291](#), [P2-306](#), [P2-307](#), [P2-325](#), [P2-328](#), [P2-329](#), [P2-415](#), [P2-416](#)
 Alalhabadia, Amit FC10.5
 Alan Selcuk, Nalan P2-62
 Al-Ansari, Alanoud P2-279
 Alapetite, Claire P1-185
 Alassaf, Abeer [P2-51](#)
 Alavanda, Ceren P1-18
 Alaya, Wafa P2-340, P2-345, P2-345
 Al-Badi, Hamid [P2-106](#)
 Albanese, Assunta P2-348, P2-356
 Albayrak, Serpil [P2-144](#), P2-422
 Albertsson Wikland, Kerstin P1-138, P1-162, P1-167, [P1-168](#), P2-354
 Albinni, Sulaima P1-54
 Albrethsen, Jakob P1-44
 Alcón, José Juan P2-316
 Alder, Lorna P2-197
 Aldubayee, Mohamed P2-91
 Alexander Siegfried Busch HA2
 Alexander, Ashley P1-170
 Alexander, Saji [P2-151](#)
 Alexandraki, Krystallenia FC7.1
 Alfandary Harani, Hadas P2-386
 Al-Farsi, Aws [P2-11](#)
 Alfutaisi, Abdallah P2-140
 Alghamdi, Abdul Aziz [P2-271](#), P2-331
 Alhemaidy, Noora P2-415
 Ali, Hamdy P2-241, P2-291
 Ali, Khadija P2-145, P2-152
 Ali, Maryam Foad P2-145, P2-164
 Ali, Salma R. FC7.1, P1-3, P1-8, [P1-110](#), P1-114, [P2-13](#)
 Alibrandi, Angela P1-73, P1-97, P2-189
 Alicante, Paola P2-293
 Alikasifoglu, Ayfer FC10.6, P1-62, P2-65, P2-117
 Alikasifoglu, Mehmet P2-65
 Alimussina, Malika [P1-46](#), P1-146, P2-397
 Aljubebeh, Jamal [P1-36](#)
 Al-Jumaili, Ali Hasan P2-100
 Al-Jumaili, Ali [P2-276](#)
 AlJuraibah, Fahad [P2-91](#)
 Allegri, Anna Elsa Maria P1-172
 Allegri, Anna P2-321
 Allende Sanzana, Fidel P2-23
 Allende, Fidel P2-1
 Allgrove, Jeremy FC6.2, P1-13, P1-60, P2-19, P2-98
 Allison S. Komirenko P1-161
 Almashanu, Shlomo FC10.2
 Al-Maskari, Balsam P2-106
 Almeida, Julia Português P1-155
 Almstrup, Kristian FC9.5
 Al-Musalhi, Buthaina P2-11
 Al-Naimi, Fatima P2-243, P2-291, P2-307

- Alonso, Pablo P2-480
Alos, Nathalie FC6.1
Aloulou, Hajer P2-46, P2-491
Al-Rahbi, Najwa P2-11
Al-Sabbari, Maryam P2-106
Alsaffar, Hussain P2-11, [P2-100](#), [P2-102](#),
[P2-106](#), [P2-108](#), [P2-119](#), P2-140,
[P2-145](#), [P2-152](#)
Alsafi, Athba P2-279
AlSagheir, Afaf P1-196, P2-91, P2-154
AlShareef, Itizan P1-196
Al-Shidhani, Azza P2-140
Altavilla, Domenica P2-357
Al-Thihl, Khalid P2-11
Altincik, Ayca [P2-121](#), [P2-272](#)
Altincik, Selda Ayca P2-14
Altunok, Yasemin Atik P2-141, P2-166
Altun, Ekin Zeynep [P2-174](#), [P2-175](#)
Altuoglu, Umut P2-277
Alves, Nygell S P2-184
Alves-Lopes, Rheure P2-397
Alvi, Sabah FC1.3, P2-367
Alvir, Jose P2-300
Alyaarubi, Saif P2-140
Alyafei, Fawzia P2-12, P2-131, [P2-241](#),
[P2-291](#), [P2-296](#), [P2-307](#),
[P2-325](#), P2-378, P2-416
Amann, Gabriele P2-429
Amano, Naoko P2-10
Amaratunga, Shenali Anne P1-57
Amaratunga, Shenali Anne [P1-56](#)
Amaro, Andrea P1-108
Amdemariam, Mikael P2-153
Amin, Arliena [P2-92](#), P2-412
Amin, Rakesh P1-114
Amin, Rakesh P1-13, P1-27, P1-70,
P1-170, P2-30
Amina, Bouhlassa [P2-419](#)
Amjad, S Basith P2-397
Ammerpohl, Ole P1-150
Amouroux, Cyril FC6.3
Amselem, Serge P2-253
Amsellem-Jager, Jessica P2-187, [P2-193](#),
[P2-200](#)
Anand, L. Alexis P2-26
Andersen, Marianne Skovsager [MTE2](#)
Andrade, Nathalia [FC3.4](#), P2-381
Andrés Esteban, Eva Maria [FC7.4](#),
P2-188
Andrews, Afiya [P1-179](#), P2-287
Andrews, Edward T. P2-19
Andrews, Edward [P2-112](#)
Angela Elvira Serranò P1-39
Angelelli, Alessia [P1-159](#)
Angelini, Sabrina P1-180
Anik, Ahmet P1-2
Anita C.S. Hokken-Koelega P1-129
Anjum, Muhammad Nadeem P2-63,
P2-64
Anjum, Muhammad Nadeem P2-64
Annelies van't Westeinde [P1-7](#)
Antao, Tiago P2-179
Antel, Jochen P2-370
Antell, Hannah P1-170, P2-30
Antignani, Rachele P1-148
Antolín, María P1-200
Antoniazzi, Franco [FC3.3](#), P1-197
Antonini, Sonir R [FC1.6](#)
Antosz, Aleksandra P2-196
Antwan, Agnes P2-126
Appelman-Dijkstra, Natasha
[FC1.5](#), [FC7.1](#)
Appelman-Dijkstra, Natasha P1-89
Apperley, Louise [P1-40](#), [P1-113](#), [P2-198](#),
[P2-214](#)
Arabaci Tamer, Sevil P2-371
Arasli Yilmaz, Aslihan [P2-473](#)
Arcari, Andrea Josefina P1-108
Arcari, Andrea P1-144
Arcari, Andrea P2-365
Arciniegas, Larry [P1-119](#), [P2-186](#)
Arciniegas, Larry P2-72
Ardicli, Didem P1-62
Arfa, Sondas P2-345
Argente, Jesús P2-248, P2-252
Argente, Jesús [FC2.1](#), [FC2.2](#), [FC2.3](#),
[FC7.4](#), [FC8.3](#), P1-118, P1-175, P2-188,
P2-281
Argente, Pilar [P2-224](#)
Ari, Hasan [P2-85](#), P2-383
Arianas, George P1-92
Arifoğlu Barış, İlter P2-333
Ariza Jimenez, Ana Belen [P2-489](#)
Ariza Jimenez, Jose Antonio P2-489
Armitage, Suzanne P2-58
Arnaud, Lilian [FC9.2](#), [FC9.4](#), P1-131,
P1-134
Arnhold, Ivo [FC3.4](#)
Aronson, A. Stefan P1-168, P2-354
Arosio, Maura [FC3.1](#), P1-122, P2-358
Arroyo Díez, Francisco Javier P2-362
Arroyo, Pablo P2-235
Arshad Cheema, Huma P1-17, P2-45,
P2-63, P2-64
Arshad, Huma P2-39
Arslan Ates, Esra P2-432
Arslan, Emrullah [P2-166](#), [P2-434](#)
Arslan, Kübra P2-385
Artola, Elena P2-461
Artola, Elena P2-480
Arundel, Paul P1-125, P1-130, P2-284
Ascenti, Giorgio P2-189
Ascunce, Nieves P2-461, P2-480
Aşıkovalı, Semih [FC5.6](#)
Aslam, Anıqa [P2-45](#)
Asmae, Touzani [P2-392](#)
Assarrar, Imane P2-57, P2-162, P2-322,
P2-329, [P2-343](#), [P2-388](#), P2-391,
P2-430, [P2-439](#), P2-443
Assirelli, Valentina [P1-85](#)
Ata, Aysun [P1-109](#), P2-141, P2-134,
P2-423
Ata, Melek Tunc P2-121
Ata, Pınar P1-18
Atabek, Mehmet Emre P2-114, P2-156,
P2-212, P2-476
Atapattu, Navoda P2-418, P2-482
Atay, Zeynep P1-2
Athanacio, Jon P2-126
Atik Altınok, Yasemin P2-134
Atik, Tahir [FC4.5](#), P2-434
Atkinson, Stuart N. P2-369
Atterbury, Abigail P1-133, P1-170, P2-30
Attia, Najya P2-145, P2-152
Auchus, Richard J. P1-8
Audi, Laura [FC8.3](#), P1-150
Auer, Matthias K. [FC1.1](#)
Augustijn, Dieuwertje [FC9.1](#)
Auth, Marcus P2-198
Avbelj Stefanija, Magdalena [YII.1](#)
Avdjieva-Tzavella, Daniela P2-312
Aversa, Luis P1-144
Aversa, Tommaso P1-73, P1-97, [P1-99](#),
P2-189, P2-196, P2-295, P2-357,
P2-462
Avril, Tristan [P1-181](#)
Awidah, Saniah P2-271, P2-331
Ayadi, Younes P2-340, P2-342, [P2-345](#)
Aycan, Zehra P2-48, P2-88, P2-89, P2-69,
P2-242, P2-314
Aydın, Duygu P2-42
Aykut, Ayca P2-434
Ayling, Ruth P1-23
Ayub, Aqeela [P2-142](#), [P2-164](#)
Azar, Ahlam [P2-50](#)
Azcona-Sanjulian, María Cristina [P2-204](#),
[P2-210](#)
Azevedo, Eduardo P2-68
Azoulay, Erez P2-201
Azza Al-Shidhani P2-11
Azzolini, Sara P2-172, P2-295
B
Bab, Sahar P2-80
Bacchelli, Chiara P2-406
Bacchetta, Justine [FC6.3](#), P2-98
Bachega, Tania A.S.S. P1-8
Bachega, Tânia Aparecida Sartori
Sanchez [FC1.2](#), P1-6
Bachega, Tânia Aparecida Sartori Sanchez
Bachega, Tania ASS P2-399
Bachmann, Sara [FC4.3](#)
Bacila, Irina [FC1.2](#), [FC1.3](#), P1-6
Bacopoulou, Flora [P2-344](#)
Badiu, Corin [FC7.1](#)
Badrous, Evan P2-251
Baena, Neus P2-288
Baetens, Dorien [FC5.5](#)
Baffico, Ave Maria [FC3.3](#)
Bagha, Merat [FC9.4](#), P2-246

- Bahl, Shailini P1-142
 Baioumi, Alaa [P2-59](#)
 Bakhamis, Sarah [P1-196](#), [P2-154](#)
 Balki, Hanife Gül [P2-423](#)
 Ball, Steve FC1.4
 Ballerini, M. Gabriela P1-144
 Ballerini, María Gabriela [P1-108](#), P2-261, P2-365
 Balsamo, Antonio P1-43, P1-85
 Baltu, Demet P2-29
 Banecka, Bozena P2-273
 Banerjee, Indraneel FC1.4, P1-24, P1-25, P1-61, P2-125
 Baneviciute, Kornelija P1-154
 Banfield, Laura P2-215
 Bang, Peter P2-283
 Baquedano, Paulina P2-408
 Baratela, Wagner A.R. P2-87
 Barberi, Carolina P2-208
 Bardet, Claire P1-58
 Barera, Graziano P1-160, P2-477
 Bar-Maisels, Meytal P1-59, [P2-80](#)
 Barnes, Nik P2-58
 Barnett, Tracie A. FC4.1
 Baron, Jeffrey P2-308
 Baroncelli, Marta YB1.5
 Baronio, Federico FC1.2
 Baronio, Federico FC1.5, FC7.1, P1-3, P1-6, P1-8, P1-43, P1-48, P1-58, P1-85, P1-143
 Barratt, Tim FC10.5
 Barrios, Vicente P2-248, P2-252, P2-281
 Bartelt, Heike P1-21
 Barutçuoğlu, Burcu P1-109
 Bas, Firdevs P1-41, P1-49, P1-53, P1-127, P1-128, P1-182, P2-277, P2-278
 Basaran, Seher P1-41, P1-127, P1-182
 Baschant, Ulrike P2-73
 Bascuas Arribas, Marta FC7.4
 Bassols, Judit P1-152, P2-181, P2-232, P2-236, P2-237, P2-240
 Basson, M. Albert FC8.2
 Bastepe, Murat P2-78
 Basu, Supriyo P2-157, P2-390
 Batista, Rafael L. P2-398
 Battelino, Tadej FC9.3, P1-143, Y11.1
 Baudrand Biggs, Rene P2-23
 Baudrand, Rene P2-1
 Baujat, Geneviève FC6.4
 Baujat, Geneviève HA1, P1-51
 Baur, Louise P2-227
 Bayburdyan, Gayane P2-49
 Bayramoglu, Elvan P1-2, P2-14, P2-242
 Baz, Ouidad [P2-351](#), [P2-366](#)
 Bazdarska, Y. P2-317
 Bazdarska, Yuliya [P2-20](#), P2-15, P2-258, P2-259
 Baz-Redón, Noelia P1-200
 Beales, Philip FC8.5
 Beardsall, Kathy P1-77
 Beaumesnil, Marion P2-200
 Beccaria, Kevin P1-185
 Beccuti, Guglielmo FC1.5
 Becker, Marianne [P2-103](#), P2-260
 Beckers, Dominique P1-45
 Beckert, Michael P1-161, P2-332
 Beckett, Rowan P1-77
 Bedecarrás, Patricia P1-144
 Bedeschi, Maria Francesca P1-122
 Beglinger, Svetlana FC4.3
 Begum, Farzana P2-110
 Begum, Rojina P1-23
 Behera, Kishore [P2-417](#)
 Behera, Smruti P2-417
 Behre, Hermann M. FC8.6
 Beisti, Anunciación P2-316
 Belkhatir, Khadidja [P2-157](#)
 Beltman, Maaike P1-134
 Beltrán, Daniela P2-485
 Beltrand, Jacques [FC4.2](#), P1-185, P2-128
 Belutti, Laura P1-50
 Belza, Amaia P2-480
 Ben Ameur, Salma P2-491
 Ben Omran, Tawfeg P2-105
 Ben Salem, Houda P2-340, P2-342
 Ben-Ami, Michal FC2.3
 Bend, Eric P2-179
 Benedetta De Martini, Lisa FC8.2
 Benedetti, Andrea FC4.1
 Benhalla, Nafissa P2-43
 Benhamou, Pierre-Yves P2-128
 Benouda, Siham P2-329, P2-343
 Bensalah, Meryem P2-47
 Ben-Skowronek, Iwona P2-273
 Benson, Matthew R. [P2-369](#)
 Benyakhlef, Salma [P2-168](#), P2-275, P2-376
 Berberoglu, Merih P2-69, P2-89
 Bereket, Abdullah P2-432
 Bereket, Abdullah P1-2, P1-18, P1-19, P1-49, P1-78, P1-102, P1-108, P1-144, P2-14, P2-25, P2-176, P2-196, P2-227, P2-261, P2-361, P2-371
 Bergendahl, Sophie [P2-354](#)
 Berkenou, Jugurtha FC3.1
 Bernardor, Julie [FC6.3](#)
 Berrade, Sara P2-210, P2-461, P2-480
 Bertherat, Jérôme P1-143
 Bertholt, Laura P2-480
 Bertholt, María Laura P2-461
 Bertola, Debora Romeo P2-287
 Bertola, Debora P2-381
 Besci, Ozge P1-64, [P2-4](#), [P2-353](#)
 Bettocchi, Ilaria P1-194
 Betz, Stephen P2-126, P2-235
 Betzmann, Deborah FC9.6
 Bezlepkina, Olga P2-146, P2-192, P2-364, P2-463, P2-490
 Bhansali, Anil FC8.3
 Bhardwaj, Girish P1-20
 Bhat, Nikita Gireesh [P2-113](#)
 Bhat, Nikita Gireesh [P1-23](#), [P2-113](#)
 Bhattacharyya, Nitai P2-298
 Biagetti, Betina FC8.3
 Biason-Lauber, Anna P2-396
 Bidlingmaier, Martin FC1.1, P1-173
 Biermasz, Nienke R. FC7.1
 Biermasz, Nienke P1-89
 Bieth, Eric P2-352
 Bigras, Jean-Luc FC4.1
 Bilir, Pelin P2-174, P2-175
 Bilir, Pelin P2-175
 Billette de Villemeur, Raphaëlle P1-123
 Bin-Abbas, Bassam P2-227
 Binder, Gerhard [FC9.6](#)
 Binou, Maria P1-103, P2-199, P2-205
 Biondi, Andrea FC3.6, P1-137, P1-145, P2-313
 Birkebæk, Niels Holtum FC1.2, P1-6
 Birkebaek, Niels [P1-14](#)
 Bisbinas, Vasiliki P2-147, P2-158
 Bison, Brigitte FC8.4, P1-83, P1-90, P2-350
 Bitsko, Rebecca P1-4
 Bizzarri, Carla [YB2.4](#)
 Blackburn, James FC8.3
 Blair, Joanne P1-10, P2-22, P2-35, P2-58, P2-350
 Blankenstein, Oliver P1-143, P2-411, P2-17, P2-31
 Błaszczuk, Ewa [P2-282](#)
 Blauwblomme, Thomas P1-185
 Blomberg Jensen, Martin [S11.2](#)
 Blum, W. P2-247
 Blumenfeld, Orit P2-123
 Blumenstock, Gunnar FC9.6
 Böber, Ece P1-64, P1-115, P2-4, P2-353
 Bober, Michael B. P1-125, P1-130
 Bocca, Gianni P1-1
 Bocheva, Yana P2-258, P2-259
 Bochkova, Larisa [P2-130](#)
 Boekhoff, Svenja [FC8.4](#), P1-82, P1-83, P1-90, P2-350
 Boekhoff, Svenja P2-350
 Boeters, Sanne P2-191
 Boettcher, Claudia [P2-116](#)
 Boldt-Houle, Deborah M. P2-369
 Bole-Feysot, Christine FC10.4
 Bolle, Stéphanie P1-185
 Bolmasova, Anna P2-327
 Bolotova, Nina P2-155
 Bölükbaş Özdemir, Şule P2-136
 Bonaita, Valentina P2-172
 Bonataki, Myrto [P2-38](#)
 Bonfanti, Riccardo P2-124
 Bonfig, Walter FC1.2, P1-3, P1-6, P1-8
 Bonino, Elisa P2-400
 Bonmatí, Alexandra P2-237
 Bonomi, Marco P1-143, P1-160, P2-358
 Bonroy, Carolien FC5.5

- Boogers, Lidewij S [FC5.1](#), [P1-48](#)
 Boot, Annemieke [P2-449](#)
 Borchers, Joonatan [P1-158](#)
 Borghammar, Camilla [P1-88](#)
 Boros, Emese [P1-45](#), [P1-190](#), [P2-260](#)
 Borysewicz- Sańczyk, Hanna [P2-56](#),
[P2-475](#)
 Bosch i Ara, Laura [P2-372](#)
 Bose, Chiranjit [P2-298](#)
 Bossowski, Artur [P1-199](#), [P2-56](#), [P2-455](#),
[P2-475](#)
 Bossowski, Filip [P1-199](#)
 Bostanci, İlknur [P2-368](#)
 Bottari, Antonio [P2-189](#)
 Boucenna, Hamza [P2-43](#)
 Bouferoua, Fadila [P2-43](#), [P2-486](#)
 Bouhours-Nouet, Natacha [FC10.3](#),
[P2-187](#), [P2-193](#), [P2-200](#)
 Bouichrat, Nisrine [P2-137](#), [P2-162](#),
[P2-322](#), [P2-382](#), [P2-391](#)
 Boukari, R. [P2-101](#), [P2-469](#)
 Boulanger, Cecile [P2-99](#)
 Bound, Chris [P2-110](#)
 Bourdeaut, Franck [P1-185](#)
 Bourgeois, Marie [P1-185](#)
 Bouterfas, Nabila [P2-43](#)
 Bouvattier, Claire [P1-143](#), [P1-181](#),
[P2-27](#), [P2-304](#)
 Boux de Casson, Florence [P2-193](#), [P2-200](#)
 Bouzamondo, Nathalie [FC10.3](#)
 Bouzidi, Nihed [P2-46](#)
 Boyadzhiev, Veselin [P2-15](#), [P2-258](#),
[P2-259](#)
 Boynukalin, Melahat Melek [P2-333](#)
 Boztug, Heidrun [P2-429](#)
 Boztug, Kaan [P2-429](#)
 Bozzola, Mauro [P2-286](#), [P2-295](#)
 Brabant, Séverine [P1-185](#)
 Brac de la Perrière, Aude [P1-143](#)
 Brachet, Cécile [P1-45](#), [P1-190](#), [P2-435](#)
 Brady, Jennifer [P2-24](#)
 Brain, Caroline [P1-13](#), [P1-60](#), [P1-101](#),
[P1-142](#), [P2-263](#), [P2-289](#)
 Brandalise, Silvia R. [FC1.6](#)
 Brandi, Maria Luisa [FC7.1](#), [MTE5](#)
 Brandsma, A.E. [P2-180](#)
 Brandt, Stephanie [P2-195](#)
 Braune, Katarina [P2-17](#)
 Bravlavsky, Débora [P1-108](#)
 Brener, Avivit [P2-201](#)
 Brenzoni, Luciana [P1-108](#)
 Brett, Connor [FC6.5](#)
 Brian K. Roberts [P2-234](#)
 Brichard, Benedicte [P2-99](#)
 Bridges, Nicola [P2-151](#)
 Brighthouse, James Robert [P1-15](#)
 Brioude, Frederic [P2-253](#)
 Brix, Susanne [P1-33](#)
 Brnjarchevska-Blazevska, Teodora [P2-138](#)
 Brooke, Sarah [P2-320](#)
 Brooksbank, Katriona [P2-397](#)
 Brown, Matthew A. [FC6.4](#), [HA1](#), [P1-51](#)
 Brucker, Sara [P1-143](#)
 Brüggewirth, Hennie T. [P1-48](#)
 Brüggewirth, Hennie [FC5.5](#)
 Brungs, Rosemary [P1-96](#)
 Brusgaard, Klaus [FC4.6](#)
 Bruzzi, Patrizia [FC10.1](#), [P1-164](#), [P2-310](#)
 Bryce, Jillian [FC1.2](#), [FC1.5](#), [FC7.1](#), [P1-3](#),
[P1-6](#), [P1-8](#), [P1-43](#), [P1-48](#), [P1-72](#),
[P1-89](#), [P1-110](#), [P1-114](#), [P2-13](#)
 Brzezinskaia, Lyubov [P2-440](#), [P2-431](#)
 Buchanan, Charles R. [P2-19](#)
 Buchanan, Charles [P1-142](#)
 Buck, Jackie [FC6.2](#), [P1-13](#)
 Bueno, Ana Carolina [FC1.6](#)
 Bugdayci, Onur [P1-19](#)
 Bugrul, Fuat [P1-2](#)
 Bühlmeier, Judith [P2-370](#)
 Bulfamante, Antonio [FC8.3](#)
 Bulfamante, Gaetano [FC8.3](#)
 Bulut, Eman [P2-476](#)
 Buonocore, Federica [P2-238](#)
 Buonocore, Federica [P2-19](#), [P2-238](#)
 Burckhardt, Marie-Anne [FC4.3](#)
 Burghard, M. [P2-216](#)
 Burkitt-Wright, Emma [P1-124](#)
 Burman, Pia [P1-89](#)
 Burren, Christine [P1-130](#)
 Busch, Alexander S. [FC9.5](#)
 Buschmann, Leona Katharin [P1-82](#)
 Busiah, Kanetee [FC7.3](#), [P1-185](#)
 Busiah, Kanetee [P1-185](#)
 Butler, Gary E. [FC5.2](#)
 Butler, Gary [P1-32](#), [P1-162](#), [P2-263](#)
 Butt, Tareed Ahmed [P2-142](#), [P2-164](#)
 Büyükinan, Muammer [FC4.5](#)
 Buyukylmaz, Gonul [FC10.6](#)
 C
 Cabral, Larissa [P2-67](#)
 Cachia, Mario J. [FC8.2](#)
 Cafarella, Giulia [P2-357](#)
 Caglar, Gizem [P2-383](#)
 Cagnard, Nicolas [P1-193](#)
 Cahn, Ranit [P1-184](#)
 Calafiore, Mariarosaria [P1-73](#), [P1-153](#)
 Calcaterra, Valeria [P2-295](#)
 Calevo, Maria Grazia [P2-321](#)
 Caliebe, Almuth [P1-150](#)
 Calli, Cem [P2-374](#)
 Calvo, Ariadne [P2-218](#)
 Camarinho, Ricardo [P2-248](#)
 Camats, Núria [P1-43](#), [P1-197](#), [P1-200](#),
[P2-402](#)
 Campagnoli, Myrna P. [P2-219](#)
 Campillo-Calatayud, Ana [P2-248](#), [P2-252](#)
 Campino Johnson, Carmen [P2-23](#)
 Campino, Carmen [P2-1](#)
 Campos, Ariadna [P2-129](#)
 Campos-Martorell, Ariadna [P1-200](#)
 Cancela, Vanesa [P2-316](#), [P2-403](#), [P2-438](#)
 Candela, Egidio [P1-85](#)
 Candler, Toby [P1-195](#)
 Canestrino, Gennaro [P2-402](#)
 Cangiano, Biagio [P1-160](#)
 Canoruc Emet, Dicle [FC10.6](#)
 Canteiro Rodrigues, Cláudia [P2-75](#)
 Capalbo, Donatella [P1-173](#), [P2-293](#)
 Cappa, Marco [P1-143](#)
 Carceller, Fernando [P2-348](#), [P2-356](#)
 Cardinale, Giuliana Marcella [P2-295](#)
 Cardinalli, Izilda A. [FC1.6](#)
 Cardon, Greet [P2-122](#)
 Cariboni, Anna [FC8.1](#), [FC8.2](#)
 Carine de Beaufort [P2-103](#)
 Carlsson, Martin [P1-135](#), [P1-138](#)
 Carneiro, Zumira [P2-67](#), [P2-68](#)
 Carnell, Sonya [FC10.5](#)
 Carrara, Silvia [P2-346](#)
 Carré, Aurore [FC10.4](#), [P1-193](#)
 Carreras-Badosa, Gemma [P1-152](#),
[P2-181](#), [P2-232](#), [P2-236](#), [P2-237](#),
[P2-240](#)
 Carroll, Paul V. [P1-8](#)
 Carruthers, Paul [WG7.3](#)
 Caruso, Manuela [P2-295](#)
 Carvajal, Cristian [P2-1](#), [P2-23](#)
 Carvalho, Ana Isabel [P2-79](#)
 Casale, Sara [P1-85](#)
 Casalini, Emilio [P2-321](#)
 Casano, Simona [P2-213](#)
 Casella, Samuel J. [P1-161](#)
 Cassidy, Kelly [P2-233](#)
 Cassio, Alessandra [P1-85](#), [P1-194](#), [P2-70](#),
[P2-208](#)
 Castanet, Mireille [FC6.3](#)
 Castano, Luis [P1-81](#), [P1-89](#), [P2-74](#)
 Casteels, Kristina [FC4.2](#), [P1-45](#), [P1-72](#),
[P2-260](#)
 Castelli-Gair Hombria, James [P2-427](#)
 Castets, Sarah [P1-84](#)
 Castinetti, Frederic [FC7.1](#)
 Casto, Celeste [P1-97](#)
 Castro, Sebastián [P2-261](#)
 Casula, Letizia [P1-198](#), [P2-213](#), [P2-456](#)
 Catalán, Ana [P2-210](#)
 Catellani, Cecilia [P1-180](#), [P2-405](#)
 Cattini, Umberto [P2-310](#)
 Cattoni, Alessandro [FC3.6](#), [P1-137](#),
[P1-145](#), [P2-209](#), [P2-313](#)
 Cavaco, Branca M. [P2-79](#)
 Cavalieri, Marilene [P2-67](#)
 Cavalli, Luana [P2-219](#)
 Cavarzere, Paolo [FC3.3](#), [P1-197](#), [P2-295](#)
 Cayir, Atilla [P2-14](#), [P2-25](#)
 Ceccarini, Giovanni [P2-209](#)
 Ceccato, Filippo [FC7.1](#), [P1-8](#)
 Ceccherini, Isabella [P1-159](#)
 Çelik, Ahmet [P2-423](#)

- Centonze, Chiara [P2-250](#)
 Ceran, Aysegul [P2-69](#), [P2-89](#)
 Cermak, Jakub [P2-297](#)
 Čermáková, Ivana [P2-309](#)
 Černá, Jana [P2-309](#)
 Cesaretti, Graziano [P2-462](#)
 Cetinkaya, Semra [P1-43](#), [P2-28](#), [P2-40](#),
[P2-48](#), [P2-85](#), [P2-88](#), [P2-94](#), [P2-159](#),
[P2-242](#), [P2-302](#), [P2-314](#), [P2-315](#),
[P2-333](#), [P2-355](#), [P2-368](#), [P2-383](#),
[P2-473](#)
 Ceylaner, Serdar [P1-79](#), [P2-278](#)
 Chabchoub, Imen [P2-46](#), [P2-491](#)
 Chabowski, Adrian [P2-455](#)
 Chae, Hyun-Wook [P1-136](#)
 Chagin, Andrei [S6.2](#)
 Chahinez, Habi [P2-419](#)
 Chai, Jinghua [P2-235](#)
 Chan, Li F. [P2-19](#)
 Chandler, Christopher [FC8.3](#)
 Chandrasekaran, Suchitra [FC2.6](#)
 Chandwani, Manju [P2-118](#), [P2-367](#)
 Chang, Guoying [P2-414](#)
 Chanson, Philippe [P1-143](#)
 Charles, Séverine [P1-58](#)
 Charmandari, Evangelia [P1-103](#), [P1-105](#),
[P1-106](#), [P1-112](#), [P1-117](#), [P2-2](#), [P2-161](#),
[P2-173](#), [P2-183](#), [P2-185](#), [P2-205](#)
 Charpentier, Guillaume [FC4.2](#), [P1-22](#),
[P2-128](#)
 Chatterjee, Sumana [P1-173](#), [P2-287](#)
 Chatzakis, Christos [P2-34](#)
 Chatzipanagiotou, Stylianos [P1-35](#)
 Chaudhary, Shumaila [P2-64](#)
 Chaussain, Catherine [P1-58](#)
 Chawla, Meghna [P1-20](#)
 Chaya, Taro [FC8.2](#)
 Cheetham, Tim [FC1.3](#), [FC10.5](#), [P2-19](#),
[P2-450](#)
 Chelghoum, Imane Lydia [P2-351](#), [P2-481](#)
 Chen, Hongshan [P2-77](#), [P2-319](#)
 Chen, Jenny [P2-126](#)
 Chen, Linqi [P1-141](#)
 Chen, Qiuli [FC3.2](#), [P2-53](#), [P2-77](#), [P2-83](#),
[P2-225](#), [P2-319](#), [P2-393](#), [P2-394](#)
 Chen, Ruimin [P2-393](#)
 Chen, Ting [P1-141](#)
 Chen, Walter [P2-227](#)
 Chen, Xiuli [P1-141](#)
 Chen, Yao [P2-414](#)
 Chen, Yong [P2-300](#)
 Chen, Zhixin [P2-53](#), [P2-319](#)
 Cheng, Hooi Peng [P2-26](#), [P2-92](#)
 Cheng, Xinran [P2-393](#)
 Cheon, Chong Kun [P2-336](#)
 Cherubini, Valentino [P2-295](#)
 Chesover, Alexander [P1-191](#)
 Chessler, Steven [P1-161](#)
 Cheung, M.S. [P1-15](#), [P2-9](#)
 Cheung, Moira [FC6.5](#), [P1-121](#), [P2-98](#)
 Chiaraluce, Sofia [FC3.6](#)
 Chiavaroli, Valentina [Y11.2](#)
 Chifu, Irina [FC1.5](#)
 Chifu, Irina-Oana [FC7.1](#)
 Chikani, Ugo [P2-424](#)
 Childs, Alexandra [P1-75](#)
 Chini, Larissa [P2-67](#)
 Chiniara, Lyne [P2-435](#)
 Chiotis, Christos [P1-92](#)
 Chivu, Olimpia [P2-260](#)
 Cho, Kyoung Soon [P1-52](#)
 Cho, Terry [P1-125](#), [P1-130](#)
 Cho, Won Kyoung [P1-52](#)
 Choi, Jin Ho [P1-136](#)
 Choong, Catherine S. [P2-230](#)
 Christesen, Henrik [FC4.6](#)
 Christoforidis, Athanasios [P2-32](#)
 Christopoulos, Panagiotis [P2-34](#)
 Chrousos, George [P2-344](#)
 Chueca, Maria [P2-204](#), [P2-210](#), [P2-461](#),
[P2-480](#)
 Chugunov, Igor [P2-364](#)
 Chumas, Paul [P2-367](#)
 Chun, Sangwoo [P2-472](#)
 Chung, Sochung [P1-136](#)
 Chung, Wendy [FC2.1](#), [P2-222](#)
 Ciancia, Silvia [FC10.1](#), [P1-129](#), [P2-21](#),
[P2-310](#)
 Cianfarani, Stefano [YB1.4](#)
 Ciara McDonnell [P2-332](#)
 Ciccone, Sara [P2-295](#)
 Cicek, Dilek [P1-49](#)
 Cift, Hakan Turan [P2-62](#)
 Cimbek, Emine Ayça [P1-94](#)
 Cinar, Hasibe Gokce [P2-383](#)
 Cirillo, Francesca [P2-405](#)
 Cirillo, Grazia [P1-173](#)
 Cittaro, Davide [P2-286](#)
 Ciurtin, Coziana [FC5.2](#), [P1-32](#)
 Čížek, Jindřich [P2-309](#)
 Çizmecioğlu Jones, Filiz Mine [P1-79](#),
[P2-42](#), [P2-165](#), [P2-474](#), [P2-478](#)
 Claahsen, Hedi [FC1.2](#), [P1-6](#)
 Claahsen-van der Grinten, Hedi L. [P1-1](#),
[P1-43](#), [P1-110](#), [P1-143](#)
 Clark, Adrian J. [P2-19](#)
 Clarke, Ellie [P2-198](#)
 Clayton, Peter [FC1.4](#), [P2-19](#), [P2-239](#)
 Cleal, Jane [FC7.2](#)
 Clelland, Colin [P2-416](#)
 Clément, Florencia [P2-261](#)
 Clément, Karine [FC2.2](#)
 Clemente, María [P1-119](#), [P1-200](#), [P2-72](#),
[P2-129](#), [P2-186](#), [P2-402](#)
 Cocca, Alessandra [FC6.5](#)
 Coeli-Lacchini, Fernanda B. [FC1.6](#)
 Cokkinos, Dennia [P2-344](#)
 Colao, Annamaria [P1-143](#)
 Cole, Michael [FC10.5](#), [P2-450](#)
 Comba, Atakan [P2-84](#)
 Comincini, Sergio [P2-286](#)
 Congenital hypothyroidism with
 gland-in-situ study group [FC10.3](#)
 Conlon, Niamh [FC4.6](#)
 Conlon, Tracey Anne [P2-24](#)
 Conway, Gerard S. [P1-50](#), [P2-406](#)
 Cooke, Laura [FC7.2](#)
 Cools, Martin [P1-150](#)
 Cools, Martine [FC1.5](#), [FC5.5](#), [FC7.1](#),
[P1-8](#), [P1-43](#), [P1-44](#), [P1-45](#), [P1-48](#),
[P1-114](#), [P1-143](#), [P1-166](#), [YB2.1](#)
 Cooper, Cyrus [FC7.2](#)
 Corica, Domenico [P1-73](#), [P1-97](#), [P1-99](#),
[P2-189](#), [P2-196](#), [P2-462](#)
 Cormier-Daire, Valerie [P1-125](#), [P1-130](#)
 Corredor Andrés, Beatriz [P2-111](#), [P2-263](#),
[P2-281](#)
 Corripio, Raquel [P2-197](#), [P2-288](#)
 Cosgrove, Karen [P1-25](#)
 Coşkun, Nurcan [P2-84](#)
 Costa, Durval [P2-41](#)
 Costa, Eduardo C. [P1-8](#)
 Costa, Eduardo Correa [FC1.2](#), [P1-6](#)
 Costa, Elaine MF [P2-399](#)
 Cottrell, Emily [P1-173](#), [P1-179](#), [P2-287](#)
 Couck, Pedro [P2-122](#)
 Coutant, Régis [FC10.3](#)
 Coutant, Régis [P1-132](#), [P2-187](#), [P2-193](#),
[P2-200](#)
 Coviello, Domenico [FC3.3](#)
 Craen, Margarita [P1-45](#)
 Craig, Sian [P2-30](#)
 Crawford, Rebecca [P2-215](#)
 Crespo, Berta [P2-406](#)
 Crinò, Antonino [P2-172](#)
 Crisóstomo, Mafalda [P2-41](#), [P2-75](#)
 Cristian, Seiltgens [P2-81](#)
 Crocco, Marco [P1-172](#)
 Crowne, Elizabeth [FC1.3](#), [P1-111](#),
[P2-19](#)
 Crozier, Sarah [FC7.2](#)
 Cucinotta, Ugo [P2-211](#)
 Cuenca-Carcelén, Sandra [P1-175](#)
 Cullen, Kathryn [P1-4](#)
 Curatola, Selenia L. [P1-97](#)
 Curatola, Selenia [P1-39](#), [P2-189](#)
 Curtis, Elizabeth [FC7.2](#)
 Cutfield, Wayne [P1-138](#)
 Czarniecka, Agnieszka [P2-475](#)

D

- D'Arco, Felice [FC6.5](#)
 da Cruz, Aparecido Divino [P2-184](#)
 da Silva Jr, Rui M.P. [FC1.6](#)
 Daftardar, Hadeer [P2-271](#), [P2-331](#)
 Dağdeviren Çakır, Aydılek [P1-38](#)
 Dahir, Kathryn [P1-12](#)
 Dahlgren, Jovanna [P1-169](#)
 Dahmane, Nabila [P2-43](#)
 Dallago, Renata [P2-420](#)

- Dall'Antonia, Alberta P1-122
Damar, Cagri P1-189
Dambkowski, Carl P2-303
Damen, Layla P1-165
D'Amico, Federica [P2-211](#)
D'Angelo, Stefania FC7.2
Daniel, Eleni P1-8
Daniele, Natalie P1-58
Daniëlle C. van der Kaay P1-129
Danne, Thomas FC7.1
Dantas, Marina P2-55
Dantas, Naiara FC3.4, P2-381
D'apremont Ormeño, Ivonne P2-23
D'apremont, Ivonne P2-1
Darcan, Şükran P2-134, P2-141, P2-423
Darcan, Şükran FC4.5, FC5.6, P1-67, P1-109, P2-166, P2-374, P2-434
Darendeliler, Feyza P1-8, P1-41, P1-49, P1-53, P1-127, P1-128, P1-182, P2-277, P2-278
Das, Urmi FC1.3
Dashkevich, Helena P2-190
Dastamani, Antonia FC4.6, FC8.5, P1-65, P1-72, P1-170
Dattani, Mehul FC1.3, FC8.3, P1-13, P1-84, P1-101, P1-114, P1-133, P1-142, P2-30, P2-263, P2-406
Dattani, Mehul T. FC8.2, P1-50, P1-89, P1-170, P2-19
Dauriz, Marco P2-405
Davelyn E. Hood [P2-234](#)
Davey, Nicola [P2-160](#)
David, Francesco [P2-456](#)
Davidovits, Miriam P2-386
Davies, Justin H. FC1.3, FC7.2, FC10.5, P1-43, P1-47, P1-143, P2-13, P2-19, P2-471
Davis, Elizabeth A. FC4.3, P2-230
Dawson, Jeremy FC1.2, P1-6
Day, Jonathan P2-284
Daye, Munise P2-212
de Almeida, Débora Ribeiro P2-305
de Aquino, Erika Carvalho P1-155
deArribaMuñoz, Antonio P2-240, [P2-316](#)
De Baere, Elfride FC5.5, P1-45
De Bergua, Josep Maria P1-125, P1-130
deBruin, Christiaan P2-308
de Castro, Margaret FC1.6
De Cunto, Carmen L. FC6.4, HA1, P1-51
de Fluiter, Kirsten FC2.5, P1-33
De Franco, Elisa P1-66
de Groot, C.J. P2-216
de Groot, Cornelis P2-191
De Gruijter, Nina M FC5.2
deKort, Sandra W.K. P1-1
De La Cerda Ojeda, Francisco P2-98
De Leon, Diva [P2-235](#)
De Leon-Crutchlow, Diva [S5.1](#)
De Mey, Lynn P2-459
de Morais, Walison José P1-155
De Rijke, Yolanda FC5.5, FC9.1
de Roux, Nicolas P1-188
De Schepper, Jean [P1-166](#), P2-260, P2-459
de Silva, Shamya P2-482
De Silva, UAMD P2-418
de Ville de Goyet, Maëlle P2-99
de Vries, Friso P1-89
De Vries, Liat FC10.2, P1-8, P2-386, Y11.1
De Waele, Kathleen P1-45, P1-114
deZegher, Francis P1-152, P2-181, P2-232, P2-236, P2-237, P2-240
Deakin, Mark FC4.4
Dech, Gastón P2-261
Dede, Eirini P2-451
Deeb, Asma P2-102
Degtyarev, Michael P2-490
Deiana, Giuseppina P2-208
Dekkers, Olaf M. P1-89
DeKoven, Mitch P2-300
Del Sindaco, Giulia [FC3.1](#)
Del Valle Ferreras, Marcos P2-111
Del Valle Torres, Ignacio P1-50, P2-406
del Valle, Ignacio P2-238
Delion, Mathieu P2-187
Delles, Christian P2-397
Delopoulos, Anastasios P1-112, P2-173, P2-183
Delvecchio, Maurizio P2-172, P2-295
Demetriou, Charalambos P2-238
Demibilek, Huseyin FC4.6
Demir, Günay P2-134, P2-141, P2-166
Demir, Korcan P1-2, P1-64, P1-115, P2-4, P2-353
Demirel, Nihal P2-88
DemolEliaz, Sharon P2-386
den Heijer, Martin FC5.1
Denes, Francisco T P2-399
Denzer, Christian P1-120
Depoorter, Sylvia P2-260
Derbel, Salma [P2-329](#), P2-439
Derikx, Joep P.M. P2-452
Derikx, Joep P1-91
Derinkuyu, BetulEmine P2-28, P2-383
Derkaoui, Nada P2-168, P2-322, P2-388
Devries, Liat FC1.2, P1-6
Deyanova, Y. [P2-317](#)
Dharmaraj, Poonam FC6.6, [P2-58](#)
Dhillon, Waljit [PL1](#)
Di Donato, Giulio P1-85
Di Guisto, Vicki FC7.1
Di Ioia, Rose FC6.1
Di Iorgi, Natascia P1-159, P1-172, P2-321
Di Marco, Santo FC3.6, P1-137, P1-145, P2-313
Di Mase, Raffaella P2-293
Di Natale, Valeria [P1-194](#)
Di Pinto, Rosita P2-293
Di Prima, Elena P2-357
Di Rocco, Frederico P1-185
diSanti Rodrigues, Andresa P2-420
Di Stefano, Marina P2-477
Di Tonno, Raffaella P2-124
Diamant, Rotem P1-171
Diamantino, Catarina P2-33
Dias, Lara Araújo P1-155
Diaz Escagedo, Patricia [FC6.1](#)
Diaz, Cristina P2-203
Díaz-Roldán, Ferran P2-181
Didi, Mohamed P1-76, P2-233, P2-377
Didier-Mathon, Hortense P1-193
Diebold, Sabrina P1-126
Dies Suárez, Pilar P2-120
Diesendruck, Benjamin [P2-87](#)
Diez-Lopez, Ignacio P1-149, [P2-218](#), [P2-229](#), [P2-403](#), [P2-426](#), [P2-438](#), P2-461, [P2-470](#), P2-480
Digweed, Dena P2-17
Dikaikou, Eirini P2-38, P2-360, [P2-401](#), P2-451
Dikou, Maria P2-206, P2-223
Dimitri, Paul FC10.5, [P2-246](#)
Dimopoulos, Ioannis P1-92
Dinç, Hasan P1-94
Dinçer, Tuba P2-76
Ding, Yu P1-156, P2-414
Diou, Christos P1-112, P2-173, P2-183
Dipasquale, Laura P2-295
Direk, Gul P1-49
Diver, Louise A. P1-46, P1-146
Divino, Victoria P2-300
Dobscha, Katherine [P2-303](#)
Docente, Chiara P2-124
Doffinger, Rainer FC7.5
Dogan, Durmus P1-2
Doğan, Gül P2-84
Doğan, Kenan P2-42
Doger, Esra P2-14
Dollfus, Hélène FC2.2
Dombrowsky, Gregor P1-150
Domenice, Sorahia P2-398, P2-399, P2-420
Dominguez-Menendez, Gonzalo [P2-1](#), [P2-23](#)
Donaldson, Malcolm P2-450
Doneray, Hakan P2-95
Dong, Guanping P2-379, P2-393
Dong, Zhiya P2-393
Donini, Valentina FC10.1
Donzeau, Aurelie P2-187, P2-193, P2-200
Doodson, Louise P1-65
Döring, Michaela FC9.6
Dörr, Helmuth G. P1-138, P1-143
Dossi, Teresa P2-408
Dost, Axel P2-116
Dotremont, Hilde P2-260
Dovc, Klemen [WG3.2](#)
Doykov, Ivan P2-404

- Doz, François P1-185
 Drake, Amanda FC10.5
 Draoui, Najat [P2-57](#)
 Drapeau, Vicky FC4.1
 Drellichman, Guillermo P1-144
 Drew, Samantha E.V. P1-27, P1-70
 Driul, Daniela P2-295
 Drongitis, Pavlos P1-100
 Druce, Maralyn FC7.1
 du Pré, Pascale P2-8
 Du, Minlian P2-77
 Duarte, Ana Filipa P2-467
 Duarte, Mariana P2-3, P2-339
 Dubern, Béatrice P1-123
 Dubinski, Ilja FC1.1
 Dubois, Josée FC6.1
 Dufour, Christelle P1-185
 Duncan, Emma P1-15
 Dunger, David P1-33, P2-450
 Dunne, Mark J. P1-24, P1-25, P1-61, P2-125
 Dunner, Jennifer P1-11
 Dupont, Elisabeth P2-122
 Dura, Teodoro P2-480
 Duranteau, Lise P2-304
 Durmaz, Asude P2-434
 Dusatkova, Petra P1-56, P1-57
 Dutta, Pinaki FC8.3
 Duzova, Ali P2-29
 Dvořáková, Marcela P2-309
 Dyer, Roger P1-195
 Dyrka, Kamil [P2-311](#)
 Dziecioł, Janusz P2-475
 Dzivite Krisane, Iveta P2-228
- E**
 Easter, Shelley P2-221
 Eberle, Birgit P2-308
 Eckert, Alexander P1-21
 Eddiry, Sanaa P2-352
 Ederra, Maria P2-480
 Edouard, Thomas [P1-124](#)
 Edri, Shalom P2-82
 Ekinci, Saniye P2-341
 El Houssinie, Moustafa P2-59
 El Kersh, Mahmoud Mohi El-Din P2-127
 El Khairi, Ranna P1-114
 El Lababidi, Eva P2-309
 El Mehraoui, Ouafae P2-162
 El Yamani, Nada [P2-275](#)
 Elango, Rajavel P1-195
 Elashry, Reham P2-202
 Elawwa, Ahmed [P2-104](#), P2-131, [P2-290](#), [P2-328](#), P2-335, P2-395
 Elbova, Lenka P1-56
 Elfride De Baere P1-44
 Elfvig, Maria [P1-88](#)
 El-Hawary, Amany [P2-251](#)
 Elias, Felipe P2-420
 Elkina, Stanimira [P2-312](#)
- Ellaiti, Mona P1-8, P1-48
 Ellard, Sian P1-66
 Ellerth, Ebba P1-104, P2-270
 Elliott, Mark P2-367
 Elmaoğulları, Selin P2-28, [P2-40](#), P2-94, P2-302, [P2-333](#)
 Elorza, Amaia P2-203
 El-Rahi, Hiba P2-50
 Elsayed, Shaymaa P2-127, P2-202, [P2-335](#), [P2-395](#)
 Elsedfy, Heba FC1.2, P1-6, P2-59
 Elsiddig, Sohair P1-139, P1-140, P1-178, [P2-255](#), [P2-256](#), [P2-264](#), [P2-265](#), [P2-266](#), [P2-267](#), [P2-268](#), [P2-290](#), [P2-325](#)
 Elson, Ruth P1-111
 Elsworth, Rebecca P1-111
 Eltan, Mehmet [P1-18](#), P1-19, P1-49, P1-102, [P2-432](#)
 Emeksiz, Hamdi Cihan P1-2
 Emeriau, Fabienne P2-193, P2-200
 Emma, Franceso P2-98
 Empting, Susann P1-72
 Enchev, Yavor P2-20
 Engelsman, Anton F. P2-452
 Engstler, Gernot P2-429
 Enikeeva, Sofia [P2-441](#)
 Er, Eren [FC5.6](#), [P2-141](#), P2-166
 Erbaş, Ibrahim Mert [P1-64](#), [P1-115](#), P2-4, P2-353
 Ercan, Oya P2-292
 Erdeve, ŞenaySavaş P2-40, P2-473
 Erdmann, Friederike FC9.6
 Eremyan, Aikaz P2-490
 Erfurth, Eva-Marie P1-88
 Erica L.T. van den Akker FC1.5
 ErisenKaraca, Seda P1-2, P2-69, P2-89
 Erlandson-Parry, Karen P2-198, P2-233
 Ernst, Caroline P1-166
 Ernstsson, Camilla [P1-104](#), P2-270
 Ertan, Yeşim P2-374
 Esen, Nisa P1-78, P2-361
 Esen, Senem P2-355
 Eskander, Antoine P1-191
 Espada, Mercedes P2-461, P2-480
 Esposito, Daniela FC7.1
 Esther, González P2-224
 Eun Kim, Sung P1-52
 Evangelopoulou, Catherine P2-206, P2-223
 Evanson, Jane FC8.3
 Evasi, Veronica P1-145
 Eveslage, Maria FC8.4, P1-90, P2-350
 Evin, Ferda [FC4.5](#), [P1-67](#), P2-141
 Eyal, Ori FC10.2
 Eyüboğlu, İlker P1-94
- F**
 Fabbri-Scallet, Helena P1-43
 Fabregas, Ana P1-119, P2-186
- Fadila, Bouferoua [P2-44](#), [P2-245](#), [P2-274](#)
 Faiçal Barros, Laura Abi P1-155
 Faienza, Maria Felicia P2-295
 Faisal, Rehab [P2-119](#)
 Fakiolas, Stefanos P2-38
 Falhammar, Henrik FC1.5, FC7.1, P1-8
 Fang, Shona P1-12
 Farag, Marwa P2-12, P2-290
 Fardella Bello, Carlos E. P2-23
 Fardella, Carlos P2-1
 Faria Junior, José Antonio Diniz [P2-398](#)
 Farokh-Nezhad, Ramesh P1-37
 Farooqi, Sadaf FC2.1, [FC2.3](#), P1-31, P2-222
 Farrar, Mallory [P1-3](#)
 Fatma Feyza Darendeliler P1-43
 Fatti, Letizia Maria P2-346
 Fattori, Ermanna P1-197
 Fava, Daniela P1-159, P1-172, P2-321
 Favalli, Valeria P2-124
 Fawzy, Dina P2-127, P2-384
 Fawzy, Nagla P2-61
 Federici, Silvia P2-358
 Feldkamp, Joachim P2-464
 Feldt-Rasmussen, Ulla P1-135
 Feng, Biyun [P2-323](#), P2-414
 Fenske, Wiebke K. P1-143
 Ferhani, Y. P2-101
 Fernandes, Ana Catarina P2-467
 Fernández Álvarez, Paula P2-72
 Fernandez, Belen P2-229
 Fernández, Concepción P2-480
 Fernández, María Celia P2-261
 Fernández, María Concepción P2-461
 Fernández, Paula P2-402
 Fernandez-Aranda, Fernando P2-227
 Fernández-Cancio, Mónica P1-200
 Fernandez-Luque, Luis P2-246
 Ferrari, Simona P1-194
 Ferraro, Cristina P1-144
 Ferraz-de-Souza, Bruno P2-19
 Ferrer, Marta P2-316
 Ferri, Daniel P1-112, P2-173, P2-183
 Ferri, Marion P1-95
 Festa, Adalgisa P1-148, P1-173, P2-70
 Fettah, Ali P2-159
 Fidan, Nurdan Fidan P2-359
 Field, Daniel FC8.2
 Filis, Konstantinos P1-112, P2-173, P2-183
 Fintini, Danilo YB1.4
 Firde, Belachew P2-153
 Fisaletti, Melissa FC6.1
 Fisch Shvalb, Naama [P2-386](#)
 Fischer, Margit Bistrup [FC5.3](#), FC9.5
 Fischeleva, Elena P2-284
 Fitas, Ana Laura P2-33
 Flammier, Sacha FC6.3
 Flanagan, Sarah P1-25, P1-68, P1-75, [P2-244](#)

- Flechtner, Isabelle P2-253
 Flett, Martyn P2-397
 Flitsch, Jörg FC8.4
 Flück, Christa E. P1-43, P1-103, P2-2, YB2.1
 Föcker, Manuel P1-187, P2-370
 Forino, Concetta P2-295
 Formosa, Nancy FC8.2
 Forsythe, Elizabeth FC8.5
 Fortes, Jakeline S P2-184
 Fossati, Chiara P2-209
 Foster, Peter P1-25
 Fotiadou, Anatoli P2-442
 Fowler, Melissa P2-126
 Fox, Michelle C. FC8.6
 Franc, Sylvia FC4.2, P1-22, P2-128
 Franchitto, Nicolas P2-352
 Francuz, Tomasz P2-282
 Franssen, Delphine YB2.2
 Frederiksen, Hanne HA2
 Freel, Marie P1-146
 Freire, Analía Verónica P1-108
 Freire, Analía P1-144, P2-365
 Fresneau, Brice P1-185
 Friedrich, Carsten FC8.4
 Friedrich, Matthias G FC4.1
 Frohock, Anne-Marie P2-157
 Frontino, Giulio P2-124
 Fu, Junfen P1-34, P1-156, P2-177, P2-178, P2-379, P2-393
 Fudvoye, Julie P2-260
 Fugazzola, Laura FC7.1
 Fuhr, Uwe P2-411
 Fujiwara, Ikuma P2-10
 Funari, Mariana FC3.4
 Furukawa, Takahisa FC8.2
 Fylaktou, Eirini P2-32, P2-37
- G**
 Gabet, Yankel P1-59, P2-80
 Gächter, Pascal P2-453
 Gagunashvili, Andrey P2-406
 Gait, Lucy P1-40, P2-198, P2-233
 Galán Gómez, Enrique P2-362
 Galazzi, Elena P2-346
 Galcheva, S. P2-317
 Galcheva, Sonya P2-15, P2-20, P2-258, P2-259
 Galhardo, Júlia P2-3, P2-75, P2-339
 Galhardo, Julia P2-41
 Galli-Tsinopoulou, Assimina P1-100
 Gallo, Manuela P2-213
 Gallucci, Marcella P2-208
 Gama, Ester P2-148
 Gan, Cheng Guang P2-26
 Gan, Hoong Wei FC7.1, P1-13, P1-72, P1-89, P1-114, P1-170, P2-372
 Gangi, Silvana P1-122
 Garcia Bruce, Hernan P2-23
 Garcia Casales, Zuriñe P2-218
 Garcia Castaño, Alejandro P2-74
 García García, Emilio José P2-115
 García, Cristian P2-408
 Garcia, Emma P2-288
 Garcia, Hernan P2-1, P2-163
 Garcia, Marta P2-407
 García-Miñaur, Sixto P1-124
 García-Rastrilla, Rut P1-118
 Garfield, Alastair P1-116, P2-179
 Gargari, Piyas P2-298
 Garibaldi, Luigi P2-409
 Garibay-Nieto, Nayely P2-227
 Garner, Terence P2-239
 Garrec, Nathalie FC4.2
 Garten, Antje FC2.4, P2-73
 Gartner, Silvia P2-129
 Gasowska, Marta P2-455
 Gasperini, Serena FC3.6
 Gaston-Massuet, Carles FC8.3, P2-287
 Gat-Yablonski, Galia P1-59, P2-80, YI1.1
 Gaudino, Rossella FC3.3, P1-197
 Gavra, Maria M. P2-360
 Gawlik, Aneta P2-176, P2-196, P2-207, P2-282
 Gawlik, Jakob P2-282
 Gaztambide, Sonia P1-81, P1-89
 Gazzin, Andrea P2-400
 Gea, Alfredo P2-210
 Geffner, Mitchell E. P1-138
 Genitsaridi, Sofia-Maria P1-117
 Genitsaridi, Sophia P2-185
 Genthner, N. P2-107, P2-247
 Genzel, Daniela FC8.4
 Georgiou, Christos P1-69
 German Angulo, Paloma P2-111
 German, Alina FC10.2
 Gernay, Caroline P1-190
 Geronikolou, Styliani P2-344
 Gerou, Spyridon P1-100
 Gevers, Evelien FC1.3, FC6.2, P1-13, P1-23, P1-60, P1-84, P1-133, P2-16, P2-113, P2-262, P2-289, P2-299
 Ghauri, Rooha Ijaz P1-70
 Ghigo, Ezio P1-143
 Giabicani, Eloïse P1-123
 Giacchetti, Federico P1-122
 Giani, Elisa P1-185
 Giannopoulos, Andreas P2-147, P2-158
 Giannopoulou, Eleni Z. P1-120
 Giavoli, Claudia P1-122, P2-358
 Gieburowska, Joanna P2-282
 Gielen, Jan P1-166
 Gies, Inge P1-166, P2-459
 Gil Margolis, Merav P2-347
 Gil Poch, Estela P2-362
 Gil, Merav FC10.2
 Gilani, Misha P1-157
 Gilbert, Clare P1-65
 Gilboa, Inbar P2-201
 Gilligan, Niamh P1-24
 Gillis, David P2-82
 Gilyazetdinov, Kamil Nailevich P2-336
 Gimenez, Paul P2-128
 Gimenez-Legarre, Natalia P2-122
 Giordano, Roberta FC1.5, FC7.1, P1-8
 Giri, Dinesh FC7.5, P2-221
 Gjokopulli, Agim P2-36
 Globa, Eugenia P1-43, P1-48, P1-66, P2-139, P2-169
 Gluck, Anna K FC6.2
 Gnanalingham, Kanna FC8.3
 Godfrey, Keith FC7.2
 Godot, Cécile FC4.2
 Goff, Nicole P1-84, P1-101
 Gogel, Jasmin P1-126
 Gohlke, Bettina P2-116
 Goiano, Ellen de Oliveira P2-87
 Gokmen, Gokhan P2-121
 Gökşen, Damla FC4.5, FC5.6, P1-67, P1-109, P2-166, P2-134, P2-141, P2-374, P2-423, P2-434
 Goldstone, Anthony FC2.1
 Gomes, Susana P2-33
 Gomez Conde, Sara P2-74
 Gómez Gila, Ana Lucía P2-115
 Gomez, Roy P1-135, P1-138
 Gómez-Vilarrubla, Ariadna P1-152, P2-181, P2-232, P2-236, P2-237, P2-240
 Gonc, E. Nazli P1-62, P2-117
 Gonc, Nazli FC10.6, P2-29, P2-65, P2-341
 Gonçalves, João P2-33
 Gong, Chunxiu P2-393
 Gong, Yan P2-379
 Gonzalez Aragon, Camila P2-55
 Gonzalez, Maria Regina P2-203
 Gonzalez Briceno, Laura G. P1-185
 Gonzalez-Gil, Esther M. P2-122
 Gonzalez-Temprano, Nerea P2-403, P2-438
 Gorriigan, Rebecca FC6.2
 GOSgene Discovery P1-50
 GOSgene UCL FC8.2
 Gotta, Verena FC4.3
 Gou, Peng P2-393
 Goycoolea, Nicolas FC8.3
 Gozzi, Tiziana P1-30
 Grabow, Desiree FC9.6
 Graell, Montserrat P2-248
 Graham, Nikki FC7.2
 Graham, Selina P2-257
 Grandone, Anna P1-148, P1-173, P2-70, P2-295
 Graneiro, Ana P2-55
 Grant, Maree P2-230
 Grasmann, Corinna P1-187, P2-370
 Grau, Gema P2-203, P2-407, P2-461, P2-480
 Gravholt, Claus H. P1-143, WG8.2
 Greenfield, Andy P1-49

- Greggio, Nella Augusta P2-172
 Gregory, John W. P2-19
 Gregory, Louise C. [FC8.2](#)
 Griffiths, Rebecca P1-191
 Grigalionienė, Kristina P1-154
 Grigore, Teodora P1-199
 Grijp, Celien [FC5.5](#)
 Grill, Jacques P1-185
 Grimberg, Adda P1-138
 Grinspon, Romina P. P1-144
 Grisuk, Ivan P2-54, P2-132
 Groessl, Michael P2-2
 Grootjen, Lionne [P1-165](#)
 Grope, Ilze P2-228
 Grosse, Scott P1-4
 Grozinsky-Glasberg, Simona [FC1.5](#), [FC7.1](#)
 Grugni, Graziano P1-114, P2-172
 Gruszczynska, Katarzyna P2-196
 Gryngarten, Mirta P1-144, P2-365
 Gu, Wei P2-379
 Guadilla, M. Luisa P2-407
 Guan, Yanfen [FC8.6](#)
 Guaragna Filho, Guilherme P1-8
 Gubaeva, Diliara [FC4.6](#), [FC7.6](#), [P1-74](#), [P2-231](#)
 Güemes, Maria [FC7.4](#), P1-175
 Guerra-Cantera, Santiago P2-248, P2-252
 Guerra-Júnior, Gil P1-43
 Guerrini-Rousseau, Léa P1-185
 Guglielmi, Davide P1-159, [P1-172](#)
 Guglieri, M. P2-9
 Guisez, Tanguy P1-166
 Gulcek, Omer Nazım P1-62
 Güleray Lafcı, Naz P2-85, P2-94, P2-28, P2-302
 Gulhan, Bora P2-29, P2-341
 Gumeniuk, Olga P2-130, [P2-155](#)
 Gunasekara, Budhi P2-418
 Gunasekara, Chathura P1-195
 Gunatilake, Sonali P2-444
 Gunn, Harriet [P2-404](#)
 Guo, Song [FC3.2](#), P2-53, [P2-83](#), [P2-225](#), P2-319, [P2-394](#)
 Guo, Ziheng P2-379
 Gupta, Anu P2-300
 Gupta, Prakamya [FC8.3](#)
 Gur, Emel P2-292
 Guran, Tulay P1-2, P1-18, P1-19, P1-43, P1-48, [P1-49](#), P1-78, P1-102, P2-14, P2-25, P2-48, P2-196, P2-361, P2-371, P2-432
 Gurpinar Tosun, Busra P1-2, P1-18, P1-19, P1-48, P1-49, [P1-78](#), [P2-14](#)
 Gutiérrez, Junier M. [FC1.6](#)
 Gutiérrez, Marcela E. P1-144
 Guvan, Ayla [FC1.2](#), P1-6, P1-8
 Guzzetti, Chiara P1-198, [P2-213](#), P2-295, P2-456
- H**
 Habacht, Daniela [P2-429](#)
 Habif, Sara P1-109
 Haddow, Laura P2-397
 Hadi, Wasnaa [P2-100](#), [P2-108](#), P2-145, P2-152
 Hadziselimovic, Faruk [P2-436](#)
 Haerynck, Filomeen [FC5.5](#)
 Haeusler, Gabriele P1-54, P2-387
 Hagen, Casper P [FC5.3](#), [FC9.5](#), [HA2](#)
 Hahner, Stefanie [FC1.5](#)
 Haider, Ammar [P2-64](#)
 Haim, Alon [FC10.2](#)
 Hajikhanova, Aygün P1-64
 Halberstadt, J. P2-180
 Halbsguth, Ulrike P2-2
 Halford, Jason C.G. P2-227
 Haliloglu, Belma [P2-62](#)
 Hall, Caroline P1-24, P1-25, P2-125
 Hallgrimsdottir, Sigrun [P1-55](#), [P2-71](#)
 Halloun, Rana [FC10.2](#)
 Halvadžhiyan, Irina P2-20, P2-312
 Hamed, Noor [P2-12](#), [P2-104](#), [P2-105](#), [P2-131](#), [P2-241](#), P2-243, [P2-291](#), [P2-306](#), P2-307, P2-378, [P2-389](#), [P2-415](#)
 Hamilton Shield, Julian P [FC7.5](#), P1-111, P2-221
 Hamza, Boucenna P2-44, P2-245, P2-274
 Hamza, Rasha [FC7.3](#)
 Hamza, Sherin P1-98
 Han, Joan [FC2.2](#)
 Handforth, Jennifer P1-15, P2-150
 Handkiewicz- Junak, Daria P2-475
 Hanein, Sylvain [FC10.4](#)
 Hannan, Fadil [S2.2](#), [FC6.2](#)
 Hannema, Sabine E [FC5.1](#), P1-1, P1-48
 Hannema, Sabine [FC1.2](#), [FC5.5](#), P1-6, P1-43, P1-150
 Haqq, Andrea [FC2.2](#)
 Harasymiw, Lauren [P1-4](#)
 Hariri, Caleb P2-5
 Harley, Gemma P1-11
 Harley, Rachael [P1-98](#)
 Harmatz, Paul P1-125, P1-130
 Harnois-Leblanc, Soren [FC4.1](#)
 Haroon, Farah P2-64
 Harper, Simon P1-61
 Harris, Julie P2-182
 Hartmann, Michaela F. P1-107, P2-176, P2-196
 Hartoft-Nielsen, Marie-Louise P2-332
 Harvey, Charlotte [FC6.5](#)
 Hasegawa, Tomonobu P2-10
 Hashem, Rabab [P2-151](#)
 Hashim, Raihana [P2-444](#), [P2-482](#), [P2-52](#)
 Hassel, David P1-126
 Hassim, Mohamad Suffian P2-26
 Hatipoglu, Nihal P1-49
- Hattersley, Andrew P2-109
 Hauffa, Berthold P1-187
 Haufler, Florentina P1-54, [P2-387](#)
 Hawcutt, Daniel P1-10, P2-35
 Hawkes, Colin Patrick P2-24
 Hawkins, Federico G. P2-188
 Hawley, James [FC1.1](#)
 Haws, Robert [FC2.2](#)
 Hawton, Katherine [FC7.5](#), [P2-221](#)
 He, Jing P2-300
 He, Qing P2-78
 He, Wei P1-3
 Hebebrand, Johannes P1-187, P2-370
 Hefter, Ari P2-82
 Heger, Sabine P1-120
 Heinrichs, Claudine P1-190, P1-45
 Heldt, Katrin P1-30
 Helen McGloin P1-13
 Hellinga, Ilse [FC5.1](#)
 Helvacioğlu, Didem P1-18, P1-19, P1-102, P2-432
 Henderson, Mélanie [FC4.1](#)
 Hennocq, Quentin P1-181
 Henriksen, Louise S. [FC5.4](#)
 Hernandez, Jone Miren P2-403, P2-438
 Hero, Matti P1-163, P1-186
 Herregods, Nele P1-166
 Herrlinger, Silke P1-21
 Herrmann, Gloria P1-120
 Hersmus, Remko P1-48
 Hess, Melanie [FC4.3](#)
 Heubner, Angela P2-98
 Hewat, Thomas [P1-68](#), P1-75
 Hiess, Manuela P1-44
 Higgins, Lucy P2-239
 Hilczer, Maciej P1-174
 Hildebrand, Julia P2-215
 Hilger, Julia [P2-31](#)
 Hilliquin, Stéphane P1-58
 Hinderhofer, Katrin P2-308
 Hindmarsh, Peter P1-101, P1-142, P2-16, P2-19, P2-263
 Hinney, Anke P1-187, P2-370
 Hinton, Elanor [P1-111](#)
 Hiort, Olaf P1-43, P1-48, P1-150
 Hiram-Bab, Sahar P1-59
 Hirani, Dhruti [P2-110](#)
 Hirose, Thiago P2-67, P2-68
 Hiroshima, Shota P2-457, P2-460
 Hirtz, Raphael [P1-187](#), [P2-370](#)
 Hızarcıoğlu Gulsen, Hayriye P2-341
 Hmida, Nada P2-340
 Hochberg, Ze'ev P2-176, P2-196
 Hoebeke, Piet P1-44
 Hoeks, Sanne [FC9.1](#)
 Hoernschemeyer, Daniel P2-332
 Hoffmann, Sandra P1-126
 Hofman, Paul P1-161
 Högl, Wolfgang P1-12, P2-86, P2-98, P2-332

Højby Rasmussen, Michael FC9.3
Hokken-Koelega, Anita FC2.5, P1-33,
P1-165, P2-294
Holl, Reinhard W. P1-21
Holloway, John FC7.2
Holmgren, Anton P1-162, P1-168,
P2-354
Holterhus, Paul-Martin P1-9, P1-48,
P1-147, P1-150, P1-187, P2-370
Homaei, Ali P2-433
Homoki, Janos P1-107
Hong, Janet Yeow Hua P2-26, P2-92,
P2-412
Hopkins, Jasmin P1-75
Horikawa, Reiko FC9.3, P2-280
Hornig, Nadine P1-9, P1-150
Horrocks, Iain P1-11
Hörtenhuber, Thomas P2-86
Horvath, Tamas L. P1-87
Hoskins, Steve P1-170, P2-30
Hou, Ling P2-379
Houchard, Aude FC6.4, HA1, P1-51
Houghton, Jayne FC4.6, P1-66, P1-68,
P1-75, P2-244
Hove, Hanne B. P2-332
Hovnik, Tinka YI1.1
Howard, Sasha S10.2, FC8.1
Howard-James, Naomi P2-262
Howell, Denise FC10.5
How-Yaw, Stephanie P2-118
Hsiao, Edward C. HA1, FC6.4, P1-51
Hua, Yifan P1-107, P2-176
Huang, Alyssa FC2.6
Huebner, Angela P1-143, P2-19
Hughes, Claire P1-101, P2-19
Huisinga, Wilhelm P2-411
Hulse, Tony P1-29, P2-19
Human Developmental Biology
Resource P1-50
Huneker, Erik FC4.2
Hunter, Steven J. P1-8
Huntsman-Labed, Alice P2-284
Huopio, Hanna P1-186
Hürmüzlü Közler, Selen P1-79, P2-42,
P1-143, P2-165, P2-478
Husebye, Eystein FC1.5
Hussain, Khalid YB1.2
Hussain, Suhaimi P2-143
Huttunen, Heta P1-186
Huynh Thi Vu, Quynh P2-135
Hwa, Vivian P1-173
Hwang, Il Tae P1-63, P1-136, P2-171
Hymos, Anna P2-149
Hällqvist, Jenny P2-404

I
Iabbassen, Malek P2-47
Ibañez, Lourdes P1-138, P1-152, P2-181,
P2-232, P2-236, P2-237, P2-240
Ibba, Anastasia P1-198, P2-213, P2-456

Ibrahim, Amany P2-337
Ibrahim, Sandra P2-395
Ichetovkin, Ilia P2-179
Iezzi, Maria Laura P2-295
Igbokwe, Rebecca P1-143
Ignacio, Bergadá P2-365
Ijaz, Sadaf P2-164
Ilia, Georgia P2-34
Illouz, Frédéric FC10.3
Improda, Nicola P2-293
Imran, Ahmed P2-63
Imre, Rurik P2-122
Inacio, Marlene P2-399
Inskip, Hazel FC7.2
Intemann, Timm P2-224
Inzaghi, Elena YB1.4
Ioakeimidis, Ioannis P1-112, P2-173,
P2-183
Ioannidis, Anastasios P1-35, P1-92
Iordanidou, Aikaterini P2-16
Iotova, Violeta FC1.2, P1-6, P1-8, P2-15,
P2-20, P2-122, P2-258, P2-259,
P2-312, P2-317
Irving, Melita FC6.5, P1-121, P1-125,
P1-130, P2-284, P2-332
Isaac, Alvaro P2-67
Isbilen, Elif P1-177, P2-269
Ishida, Miho P1-50, P2-238
Isidori, Andrea M. FC7.1
Işık, Esra FC4.5
Işıklar, Hafize P2-134, P2-166
Itani, Maya P2-243, P2-291, P2-296,
P2-307, P2-325
Iughetti, Lorenzo FC10.1, P1-164,
P1-180, P2-172, P2-295, P2-310
Ivannikova, Tatiana P2-463
Ivo, Catarina Rodrigues P2-33

J
Jääskeläinen, Jarmo P1-158
Jabbar, Shamila P2-125
Jabot-Hanin, Fabienne FC10.4
Jairam, Carol P2-110
Jakimovska, Anastasija P2-138
Jalilova, Arzu P2-134, P2-374
Jalilova, Lala P1-62, P2-117
Jamal, Anouar P2-376
James, Chela P2-406
James, Phil P1-195
James, Syril P1-185
Jamjoom, Majd P2-271, P2-331
Jančevska, Aleksandra YI1.1
Jännäri, Meeri P1-199
Janner, Marco P1-43, P2-453
Jarvis, Sheba P2-110
Jarzab, Barbara P2-475
Jauze, Louisa P1-58
Jayakody, Chamath P2-413, P2-428
Jeha, George P2-66
Jensen, Rikke B. FC9.5

Jerome, Joseph P1-68
Jesič, Maja YI1.1
Jheeta, Amrit P2-257
Jhingran, Priti P2-300
Ji, Yanchun P2-177, P2-178
Jiménez, Catalina P2-97, P2-163
Joeng, Hee-Koung FC8.6
Johannsen, Trine Holm HA2
Johannsson, Gudmundur FC7.1, P1-135
Johnson, A. P2-9
Johnson, Mae P2-8
Johnson, Matthew P1-66, P1-75, P2-109
Johnston, Colin P1-8
Johnstone, Edward P2-239
Jonas, Nicolaas P2-479
Jones, Emma P2-110
Jones, Greg P1-146
Jones, Jeremy P1-79, P2-165, P2-42,
P2-474, P2-478
Jones, Julie FC1.4
Jones, Tim FC4.3
Jorch, Norbert P2-464
Jorge, Alexander A.L. P2-280
Jorge, Alexander FC3.4, P2-381
Jorge, Rafael Baches P2-87
Jørgen Schou, Anders FC4.6
Jørgensen, Mette P1-101
Jørgensen, Niels FC5.4
Joseph, Shuko P1-11
Jour, Celine P2-291, P2-296, P2-325
Jourdren, Marie P2-187
Judith, Bühlmeier P1-187
Juliana, Christine P2-235
Jung, Min Ho P1-52
Jung, So Yoon P1-192
Junqueira, Thais FC1.6
Juriaans, Alicia P2-294
Jürimäe, Jaak P1-16
Jury, Elizabeth FC5.2, P1-32
Just, Steffen P1-126
Juul, Anders FC5.3, FC5.4, FC9.5, HA2,
P1-44, P1-143, P2-349

K
Kaba, İlknur P2-359, P2-373
Kabolova, Kseniya P2-410, P2-425
Kafetzi, Maria P2-38, P2-206, P2-223
Kafi, Imane P2-351
Kafi, Salima P2-351
Kager, Leo P2-429
Kahlert, Christian P1-30
Kalaitzopoulou, Electra P1-69
Kalay Şentürk, Nida Gülderen P1-38
Kaleva, Nartzis P2-312
Kalinchenko, Natalia P1-43, P2-364
Kallefullah Mohammad, Jasmina FC4.6
Kalvachová, Božena P2-309
Kammoun, Hassen P2-46
Kammoun, Thouraya P2-46, P2-491
Kamp, G.A. P2-216

- Kamp, Hetty J van der FC1.2, P1-1, P1-6
 Kamrath, C. P2-247
 Kamrath, Clemens P1-21, P2-107, P2-326
 Kanaka-Gantenbein, Christina P2-32, P2-37
 Kandemir, Nurgun FC10.6, P1-62, P2-65, P2-117
 Kang, Seokjin P2-454
 Kannu, Peter P1-125, P1-130
 Kanumakala, Shankar P1-29
 Kaplan, Emel H. Aytac P2-254
 Kaplan, Frederick S. HA1, FC6.4, P1-51
 Kapoor, Ritika FC8.3
 Kaprio, Jaakko P2-224
 Karabatsou, Sophia P2-185
 Karabouta, Zacharoula P2-147, P2-158
 Karacan Küçükali, Gülin P2-28, P2-85, P2-94, P2-242, P2-302, P2-314, P2-315, P2-368
 Karagoz, Nurinisa P2-278
 Karagoz, Tefvik P2-341
 Karagüzel, Gülay P1-94, P2-76
 Karakılıç Özturan, Esin P1-53, P1-128, P1-182, P2-277, P2-278
 Karaman, Birsan P1-41, P1-127
 Karaman, Volkan P1-182
 Karamfilova, Teodora P2-15
 Karampatsou, Sofia-Iliada P1-117
 Karaoglan, Murat P2-144, P1-177, P1-189, P2-254, P2-269, P2-422
 Karatsiolis, Platonas P2-107, P2-326
 Karavidopoulou, Youla P1-112, P2-173, P2-183
 Karavitaki, Niki FC7.1
 Karayazlı, Ayşe Merve P2-423
 Kardelen Al, Aslı Derya P2-278
 Karen Erlandson-Parry P1-40
 Karenina Osorto, Cynthia P2-227
 Kareva, Maria P2-18, P2-330
 Kariyawasam, Dulanjalee FC4.1, FC10.4, P1-185
 Kärkinen, Juho P1-163
 Karlsson, Leif P1-7
 Karrou, Marouan P2-137, P2-322, P2-329, P2-391, P2-430, P2-439, P2-443
 Kartal Baykan, Emine P2-25
 Karyiawasam, Dulanjalee P1-193
 Kasatkina, Elvira P2-410, P2-425, P2-440, P2-431
 Kaskhkalda, Dina P1-183
 Kaski, Juan Pablo P1-169
 Kassari, Penio P1-112, P1-117, P2-173, P2-183, P2-185, P2-205
 Kastelan, Darko FC8.3
 Kasyanova, Yulia P2-192
 Katsa, Maria Efthymia P1-35
 Katsanis, Nicholas P1-105
 Katugampola, Harshini FC8.5, P1-101, P1-133, P1-170, P1-84, P2-8, P2-9, P1-89, P2-30
 Kaufman, Keith D. FC8.6
 Kaushal, Ashleen P2-215
 Kaushik, Shivaani P2-151
 Kawai, Masanobu S2.1
 Kaya, Serpil P1-94
 Kaygusuz, Sare Betul P1-18, P1-19, P1-49, P2-14, P2-361, P2-371
 Kaypmaz, Saadettin P2-76
 Kearney, Tara P1-8
 Kee, Sarah FC2.6
 Keen, Richard FC6.4, HA1, P1-51
 Keevil, Brian FC1.1, FC1.3, P2-375
 Kehr, Stephanie FC2.4
 Kelberman, Dan P1-50, P2-406
 Kelepouris, Nicky P1-169, P2-280
 Kelly, Andrea MTE4
 Kendir Demirkol, Yasemin P1-2, P2-14
 Kenny, Julia P1-15
 Kerkhof, Gerthe P1-129, P1-165, P2-294
 Kernohan, Andrew P1-146
 Kero, Jukka P1-199
 Kerr, Sue FC4.4
 Keselman, Ana P1-108, P2-381
 Keskin, Mehmet P2-144, P1-177, P2-254, P2-269, P2-422
 Keskin, Meliksah P2-85, P2-94, P2-242, P2-315, P2-333, P2-355
 Kessler, Noah P1-195
 Khadidja OuldKablia, Samia P2-47
 Khalil, Ahmed P1-139, P1-140, P1-178, P2-255, P2-256, P2-264, P2-265, P2-266, P2-267, P2-268
 Khan, Khalid P2-437
 Khater, Doaa P2-421
 Khelafi, N. P2-101
 Kiefer, Florian W. P1-143
 Kiess, Wieland FC2.4, P2-73
 Kiewert, Cordula P1-187, P2-370
 Kilci, Fatih P2-42, P1-79, P2-165, P2-474, P2-478
 Kılıc Erkek, Ozgen P2-121
 Kilic, Mustafa P2-28, P2-333
 Kilpin, Kate P2-221
 Kim, Eun Young P1-63, P2-171
 Kim, Goo Lyeon P2-472
 Kim, Jae Hyun P1-136
 Kim, Seul Ki P1-52
 Kim, Shin Hee P1-52
 Kim, Yoo-Mi P1-136
 Kirchhoff, Martha EE1.2
 Kiriwaththuduwa, K.S.U. P2-52
 Kirk, Jeremy FC10.5
 Kirkgoz, Tarık P2-196
 Kirmizibekmez, Heves P1-2
 Kirstein, Anna FC2.4, P2-73
 Kiseleva, Elena P2-410, P2-425, P2-431, P2-440
 Kishnani, Priya P1-12
 Kivela, Jemina P2-122
 Kizilcan Cetin, Sirmen P2-69, P2-89
 Klatka, Maria P2-149
 Kleber, Michaela P1-147
 Kleinendorst, L. P2-180, P2-216
 Klink, Daniel FC5.1, P2-260
 Kloft, Charlotte P2-411
 Klose, Daniela P1-21
 Klötting-Blüher, Nora P2-73
 Kmiha, Sana P2-46, P2-491
 Kobayashi, Hironori P2-10
 Koç, Gonca P2-423
 Kocak Eker, Hatice P1-49
 Koch, Gilbert FC4.3, P2-453
 Kodytková, Aneta P2-309
 Koehler, Katrin P2-19
 Kohlsdorf, Katja P2-195
 Kokoreva, Kristina P2-364, P2-431, P2-440
 Kolbach, Marianne P2-408
 Koledova, Ekaterina FC9.2, FC9.4, P1-131, P1-134, P2-246, P2-250, P2-257
 Kolesinska, Zofia P1-43
 Kollcaku, Laurant P2-36
 Kolodkina, Anna P2-441
 Kolouskova, Stanislava P1-57, P2-309
 Komlosy, Nicci FC1.4
 Kondev, Toni P2-20
 Koniari, Eleni P1-106
 Konrad, Daniel P2-396, P2-453
 Konushova, Marina P2-490
 Kooli, Mariem P2-342, P2-345
 Korbonits, Marta FC8.3
 Kosovtsova, Ganna P1-183
 Kostareva, Anna P1-42
 Koster, Emma P2-191
 Kosteria, Ioanna P2-360, P2-451
 Kostopoulou, Eirini FC2.3, P1-35, P1-69, P1-92
 Kotanidou, Eleni P P1-100
 Koulman, Albert P1-33
 Kouri, Chrysanthi P1-43
 Kourilaba, Georgia P1-117
 Koutaki, Diamanto P1-112, P2-161, P2-173, P2-183
 Koutrouveli, Eleni P2-451
 Kovač, Jernej YI1.1
 Kovalenko, Tatyana P2-217, P2-249
 Kredel, Taylor P2-126
 Krepischi, Ana FC3.4
 Krieger, Avihu P1-171
 Kriström, Berit P1-167
 Krivova, Yuliya P1-74
 Krone, Nils FC1.2, FC1.3, P1-3, P1-6, P1-110, P2-19
 Krone, Ruth FC1.3
 Krstevska-Konstantinova, Marina P2-138
 Krude, Heiko P2-17
 Kshatriya, Maya P2-215
 Kucharska, Anna Malgorzata P2-462
 Kucukatay, Vural P2-121

Kudryashova, Elena P1-42
 Kulikowski, Leslie D. P2-398
 Kulle, Alexandra [P1-9](#), P1-147, P1-150,
 P1-187, P2-370
 Kumar, Ram P1-113
 Kumaran, Anitha P2-112
 Kume, Tuncay P2-4
 Kurban, Sevil P2-114, P2-156
 Kurnaz, Erdal [P2-25](#), [P2-88](#), P2-314
 Kusalová, Kateřina P2-309
 Kusnetzow, Ana Karin P2-126
 Kwinta, Przemko P1-71
 Kwong, Ruth [P1-80](#)
 Kyprianou, Nikolina [FC8.3](#)
 Kyriakou, Andreas FC1.3, P1-157

L

Laakso, Saila P1-158
 Labarta, José Ignacio P2-316
 Lachal, Sylvain P1-22, P2-128
 Lachlan, Katherine P1-43
 Ladha, Tasneem P1-179
 Ladj, M.S. P2-469
 Lafci, Naz Guleray P2-159, P2-314
 Lagos, Carlos F. P1-50
 Lahlou, Najiba P2-193
 Lahn, Valentina P1-21
 Laing, Peter P1-40
 Lajic, Svetlana P1-5, P1-7, P2-7, P1-143
 Lakmini, Chamila P2-418
 L'Allemand, Dagmar P1-30, P1-43,
 P2-453, P2-363, P2-396
 Lambert, Anne Sophie [P1-95](#), P1-181
 Lamprecht, Tabea P1-9, [P1-147](#)
 Lamprinou, Zoe P2-442
 Landes, Caren FC6.6
 Landis, Sarah P1-121
 Lang, Peter FC9.6
 Lang-Muritano, Mariarosaria P1-43,
 P2-396
 Langone, Marta P2-124
 Langton Hower, Simon C FC7.5, P2-221
 Lanzaro, Francesca P1-148
 Lanzinger, Stefanie P2-116
 Laptev, Dmitry P2-146
 Larimore, Kevin [P2-66](#)
 Laron, Zvi [P2-123](#)
 Larreina de la Fuente, Leire P2-438
 Lasolle, Helene P1-89
 Lassoued, Najoua [P2-340](#), [P2-342](#), P2-345
 Latrech, Hanane P2-57, P2-137, P2-162,
 P2-168, P2-275, P2-322, P2-329,
 P2-343, P2-376, P2-382, P2-388,
 P2-391, P2-430, P2-439, P2-443
 Latronico, Ana Claudia [WG5.1](#)
 Latyshev, Oleg P2-364, P2-410, P2-425,
[P2-431](#), [P2-440](#)
 Lauber, Anna P2-427
 Lauener, Roger P1-30
 Laurer, Elisabeth P2-86

Lauriola, Silvana P1-197
 Laver, Thomas P1-68, P1-75
 Laverdière, Caroline FC6.1
 Lavi, Eran P1-184
 Lawrence, Gabriella P2-123
 Lawrence, Neil [FC1.2](#), FC1.3, P1-3, [P1-6](#)
 Lawson, John P1-96
 Lazar, Liora P1-171
 Lazarevic, Dejan P2-286
 Lazzerotti, Alessandra P2-209
 Le Duc, Diana P2-73
 Le Masne, Quentin FC9.2, P1-131
 Le Quan Sang, Kim-Hanh HA1
 Le Quesne Stabej, Polona FC8.2, P1-50,
 P2-406
 Le Tallec, Claire FC4.2, P2-128
 Lebenthal, Yael P2-201
 Lebl, Jan P1-56, P1-57, P1-124, P2-309
 Leborgne, Christian P1-58
 Lee, Boma P2-397
 Lee, Hae Sang [P1-136](#)
 Lee, Jeongho P1-192
 Lee, Na Yeong P1-52
 Lee, Warren [P2-334](#)
 Lee, Wonae P2-447
 Lee, Young Ah P1-136
 Lees, Melissa P2-289
 Leese, Graham P. P1-8
 Legendre, Marie P2-253
 Léger, Juliane P1-143, P1-181
 Leheup, Bruno P1-132
 Leiva, Antonio P1-130
 Leka-Emiri, Sofia [P2-206](#), [P2-223](#)
 Lekka, Eirini P1-112, P2-173, P2-183
 Lemay, Annelies P1-45
 Lemelle, Lauriane P1-185
 Lemon, Jennifer FC6.6
 Lemos, Ana P2-148
 León, Jose Luis P2-204
 Leon, Maria Clemente FC1.2, P1-6
 Lerario, Antonio FC3.4
 Lettieri, Antonella FC8.1, FC8.2
 Levaillant, Lucie [FC10.3](#), P2-187, P2-193,
 P2-200
 Levent, Hilal Nisva P2-371
 Levi della Vida, Francesca P2-208
 Levi, Floris FC10.2
 Lewiński, Andrzej P1-174
 Lewis, Rohan FC7.2
 Lhoucin, Balouch P2-392
 L'Hours, Marie-Clémence P2-193, P2-200
 Li Pomi, Alessandra P1-97, P1-153,
 P2-462
 Li, Juan P2-414
 Li, Pin P2-379
 Li, Qun P2-414
 Li, Xin [FC3.5](#), P2-414
 Li, Yanhong FC3.2, P2-53, P2-77, P2-319
 Liapi, Maria [P2-464](#)
 Liatis, Stavros P2-122

Liberman, Alon [WG3.3](#)
 Libiouille, Cécile P1-190
 Libuda, Lars P1-187, P2-370
 Lichiardopol, Corina Raducanu FC1.2,
 P1-6
 Lichtarowicz-Krynska, Ewa P1-142
 Liddington, Mark P2-367
 Lienhardt-Roussie, Anne FC6.3
 Lim, Rachel Qian Hui [P1-23](#), [P2-113](#)
 Lim, Sharon [P2-289](#)
 Lima, Eloise M.R. P2-219
 Lin, John FC1.4
 Lin, Lin P2-19
 Lin, Yen-Fan [P2-257](#)
 Linca, Elisa P2-466
 Lindsay, Robert P1-146
 Lines, Kate E FC6.2
 Linglart, Agnès FC3.1, FC6.3, FC7.1,
 P1-12, P1-58, P1-95, P1-138, P2-27,
 P2-98, P2-304
 Lionne N. Grootjen P1-129
 Lip, Gregory P1-10, P2-35
 Lisboa, Natalia Gomes P2-398
 Lisboa, Nathalia FC3.4
 Lithander, Fiona P1-111
 Liu, Yingyan [P2-83](#)
 Livera, Gabriel P1-50
 Ljubicic, Marie L. [HA2](#), FC9.5
 Loch Batista, Rafael [P2-420](#)
 Loche, Sandro [CON2.1](#), P1-198, P2-213,
 P2-250, P2-295, P2-456
 Lodefalk, Maria P1-86
 Loftus, Jane [P2-300](#)
 Logan, Karen P2-110
 Logghe, Karl P2-260
 Lohiya, Nikhil [P1-76](#), [P2-233](#), [P2-377](#)
 Löhner, Katharina P2-449
 Lokulo-Sodipe, Oluwakemi P2-157
 Longaretti, Roberta [P2-124](#)
 Lonja, Paolina P2-211
 Looijenga, Leendert H.J. P1-48
 Lopes, Lurdes P2-3, P2-33, P2-41, P2-75,
 P2-339, P2-467
 Lopez Dacal, Jimena C. [P1-144](#)
 López Menau, María Cristina P2-111
 López Sánchez, Belén P2-111
 López Siguero, Juan Pedro P2-227
 Lopez Vargas, Elena P2-489
 Lopez, Adar P2-201
 López-Bermejo, Abel P1-152, P2-181,
 P2-232, P2-236, P2-237, P2-240
 Lorente, Isabel P2-229
 Lorenz, Judith [P2-73](#)
 Lorenzini Ceradelli, Francesca P1-159
 Lottspeich, Christian FC1.1
 Loukili, Mohamed Aymane P2-376
 Loukopoulou, Sofia P2-205
 Lourenco, Charles P2-67, P2-68
 Lousada, Lia [P2-399](#)
 Lu, Wenli P2-393

Lubrano, Luigi P1-197
 Lucaccioni, Laura FC10.1, P2-310
 Lucas-Herald, Angela K. P1-43, P1-46,
 P1-48, P1-146, P2-397
 Lucheze, Bruna FC3.4
 Ludgate, Marian P1-195
 Lugarà, Cecilia P1-99, P2-211
 Luger, Anton FC7.1
 Lui, Julian S6.1, P2-308
 Luna Bastante, Loreto P2-111
 Lundberg, Elena P1-104, P1-167, P2-270
 Luo, Feihong P2-393
 Luo, Xiaoping P2-379, P2-393
 Luongo, Caterina P1-148, P2-70
 Luton, Dominique P1-193
 Lutterman, Sarah P2-446
 Luu Hong Ngoc, Phuong P2-135
 Lymperopoulos, Giorgos P1-112, P2-173,
 P2-183
 Lynda, Sekfali P2-245, P2-274
 Lysy, Philippe P2-99, P2-260

M

Ma, Huamei FC3.2, P2-53, P2-77, P2-225,
 P2-319, P2-393, P2-394
 Maadheed, Maryam A.L. P2-416
 Maaloul, Ines P2-46
 Macías, María P2-204, P2-210
 Maddaluno, Ivan P1-148
 Madeo, Simona F. P1-164, P2-172,
 P2-310
 Madera, Maria P2-470
 Madhu, Rajesh FC6.6
 Madsen, Andre P2-349
 Madureira, Guiomar P2-399
 Madureira, Inês P2-33
 Maeso, Sandra P1-149, P2-426
 Mäestu, Evelin P1-16
 Maffei, Massimo FC3.3
 Maffei, Pietro FC7.1
 Maffei, Claudio P2-227
 Magana, Maria P1-35
 Maggioni, Irina P1-108
 Maghnie, Mohamad P1-138
 Maghnie, Mohamad P1-159, P1-172,
 P2-295, P2-321, S8.1
 Magid, Yael FC10.2
 Maglaveras, Nicos P1-112, P2-173,
 P2-183
 Magnová, Olga P2-309
 Maharaj, Avinaash P1-80, P1-173,
 P1-179, P2-19, P2-287
 Mahesh, Buddika P2-482
 Mahfouz Abdel Rahman, Alshaimaa
 P2-337
 Mahmood, Adil P2-110
 Mahmoud, Ahmed P1-44
 Main, Katharina M. FC5.4
 Maiorano, Nadia Gabriella P1-159
 Maitz, Silvia P1-137, P2-209, P2-313

Makazan, Nadezhda P2-18
 Makhoul, Kevin P2-50
 Makhoul, Peter P2-50
 Mäkitie, Outi P1-158
 Makkonen, Kristiina P1-199
 Makridakis, Manousos P1-106
 Makrilakis, Konstantinos P2-122
 Malaquias, Alexandra FC3.4, P2-87,
 P2-381
 Male, Christoph P1-54
 Malerba, Federica P2-321
 Maltoni, Giulio P1-72, P2-70, P2-208
 Malysheva, Natalya P2-192
 Mamatkulov, Elbek Abdumonnanovich
 P2-336
 Marni, Chiara P2-295
 Mammadova, Jammala P2-14
 Man, Elim P1-142
 Manai, Federico P2-286
 Mancioffi, Valentina P2-295
 Mandraffino, Giuseppe P1-39
 Maniatis, Aristides K. P1-161
 Manios, Yannis P2-122
 Manolakos, Emannouil P2-401
 Manou, Maria P1-112, P2-173, P2-183,
 P2-199, P2-205
 Mantovani, Giovanna FC3.1
 Manzur, A. P2-9, P2-30
 Mao, Meng P1-161
 Marasini, Lucia P1-159
 Marazuela, Monica FC7.1
 Marcato, Fernanda P2-68
 Marcelis, Lionel P2-459
 Marchueta Elizagarate, Izaskun P2-115
 Margit Bistrup Fischer HA2
 Marieke, den Brinker P1-166
 Marino, Rose FC6.4, HA1, P1-51
 Markison, Stacy P2-126
 Markosyan, Renata P1-8, P2-49
 Markou, Athina P1-105
 Maroto, Anna P1-152
 Marti, Amelia P2-204, P2-210
 Martin, Ayelen P2-261
 Martinerie, Laetitia FC6.3, P1-181
 Martinez de la Piscina Martin, Idoia
 P1-43, P1-81
 Martinez Ramos, Raquel P2-420
 Martinez, Alejandro P2-1, P2-408
 Martinez-Aguayo, Alejandro P2-23
 Martinez-Calcerrada, José-María P2-237
 Martinez-Villanueva, Julián P2-188
 Martin-Gutierrez, Lucia FC5.2
 Martín-Rivada, Álvaro FC7.4, P1-118,
P2-248, P2-252, P2-281
 Martos-Moreno, Gabriel Á. FC2.2, FC2.3,
P1-12, P1-118, P1-175, P2-188, P2-252
 Maryam Fuad Ali P2-152
 Maryam Razzaghy-Azar P2-167
 Marzatico, Alice P1-194
 Masera, Nicoletta P2-209

Mason, Leah P2-390
 Mas-Parés, Berta P1-152, P2-181, P2-232,
 P2-236, P2-237, P2-240
 Massa, Guy P2-260
 Massa, Valentina FC8.3
 Mastorakos, George P2-34
 Mat Amin, Noor Arliena P2-26
 Matarazzo, Patrizia P1-93, P2-295, P2-400
 Mathapati, Dannaya P2-118
 Mathieu, Marie-Ève FC4.1
 Matthews, Debbie WG8.3
 Matthews, John FC10.5
 Mavrogianni, Christina P2-122
 Mazen, Inas P1-8, P1-43
 Mazur, Artur P2-207
 Mazzeo, Louise P1-121
 McCallum, Lindsay P2-397
 McCormack, Shana FC2.3
 McCormick, Peter J. P1-179
 McDevitt, Helen P1-125, P1-130
 McDonnell, Ciara P2-262
 McElreavey, Ken P1-48
 McGlacken-Byrne, Sinéad M FC4.6,
P1-27, P1-170, P2-8, P2-406
 McGowan, Neil P1-146
 McGowan, Ruth P1-46, P1-146
 McIntosh, Diana P1-157
 McLean, Cal P2-221
 McMillan, Martin P1-46, P1-146, P2-13
 McNealis, Vanessa FC4.1
 McNeilly, Jane D. P1-46, P1-146
 Mead, Victor P1-170
 Medina Bravo, Patricia Guadalupe
 P2-120
 Medina Urrutia, Aida P2-120
 Meek, Hannah P1-70
 Megarbane, Andre P2-50
 Meireles, Ana Belezza P1-125
 Meissner, Thomas P2-116
 Mejia de Beldjenna, Liliana P2-74, P2-93
 Melhorn, Susan FC2.6
 Melikyan, Maria FC4.6, FC7.6, P1-74,
 P2-231, P2-327
 Mellado, Cecilia P2-408
 Menabò, Soara P1-194
 Menahem, Chen P2-80
 Menassa, Rita P1-143, P2-47
 Mendelsohn, Espen Eliyahu P1-184
 Méndez Pérez, Pilar P2-362
 Mendizabal, Geraldine FC8.6
 Mendonca, Berenice B P2-398, P2-399,
 P2-420
 Mengel, Eva P1-16
 Mengistu, Zalalem P2-110
 Mesfin, Mahlet P2-244
 Mesonero, Saray P2-426
 Mesonerp, Sara P2-470
 Messaoudi, Najoua P2-137, P2-162,
P2-322, P2-329, P2-343, P2-382,
P2-391, P2-430, P2-439, P2-443

- Messina, Maria Francesca P1-99
 Messina, Valeria P1-7, [P1-5](#)
 Messini, Beatrice P2-295
 Metherell, Lou P1-80
 Metherell, Louise A. P1-173, P1-179, P2-19, P2-287
 Meyer, Gesine P1-143
 Michal Yackobovitz-Gavan P2-347
 Michalacos, Stefanos P2-38, P2-206, P2-223, P2-401, P2-442, P2-451
 Michalak, Justyna P2-56
 Michalakos, Stefanos P2-360
 Miettinen, Päivi P1-163, P1-186
 Migazzi, Matteo P2-405
 Mikhno, Hanna [P2-194](#), P2-220
 Miklosz, Agnieszka P2-455
 Milenkovic, Tatjana FC1.2, P1-6, Y11.1
 Miletta, Maria Consolata [P1-87](#)
 Miller, Bradley S. P2-300, P2-369
 Miller, Jennifer [P1-31](#)
 Mills, Kevin P2-404
 Mimouni, Safia P2-351, P2-366, P2-481
 Minamitani, Kanshi P2-10
 Minasi, Lysa B P2-184
 Mingozzi, Federico P1-58
 Miraglia Del Giudice, Emanuele P1-148, P1-173, P2-70
 Miranda, Mirela C. P1-8
 Miron, Marie-Claude FC6.1
 Mitchell, Rod FC8.3
 Mitrofanova, Lubov FC7.6
 Mittleman, Robert FC2.2
 Mladenov, V. P2-317
 Mladenov, Vilhelm P2-15
 Moal, Valérie P2-193, P2-200
 Mockeviciene, Giedre P1-154
 Modeva, Iskra P2-109
 Moeller, Ida P1-116, [P2-179](#)
 Moenig, Isabel P1-43
 Mogas, Eduard P2-129, P2-186
 Moghetti, Paolo P2-405
 Mohamed, Boualam P2-392
 Mohan, Meena P2-150
 Mohandoussaid, Aida P2-43
 Mohnike, Klaus P1-72, P2-284
 Moia, Claudia P2-286
 Molin, Åsa P1-104, P2-270
 Molina Angulo, Blanca FC7.4
 Molina, Carlos A.F. FC1.6
 Molina, Marcela P2-163
 Molinari, Silvia FC3.6, P1-137, [P1-145](#), [P2-209](#)
 Molinas, Catherine P2-352
 Moline, Sara YB2.2
 Möllers, Martin P2-464
 Molnar, Denes P2-224
 Mondal, Sunetra [P2-298](#)
 Mondello, Isabella P1-73, P1-153
 Monteiro, Rúbia V P2-184
 Montero-Lopez, Rodrigo [P2-86](#)
 Montezano, Augusto C P2-397
 Mooij, Christiaan P1-1, P1-91, [P2-446](#), [P2-448](#), [P2-452](#)
 Moon, Rebecca FC7.2
 Mooney, Vicki P2-227
 Moore Valdes, Rosario P2-23
 Moore, Gudrun P2-238
 Moore, Rosario P2-1
 Moore, Sophie P1-195
 Morabito, Letteria Anna P2-189
 Morace, Carmela P1-39
 Moraes, Daniela R. P2-398
 Morán, Lorena P1-144
 Morbée, Lieve FC5.5
 Moreira, Ayrton C FC1.6
 Morel, Yves P2-47
 Morell-Azanza, Lydia P2-204
 Moreno, Luis P2-122, P2-224
 Moreno, Nadjeda P2-406
 Morgan, Kate P1-65
 Morin, Carole FC4.1
 Moro, Mirella P2-346
 Morris, Andrew P1-76
 Morrison, Niamh P2-450
 Mouraux, Thierry P1-45, P2-260
 Mourtzi, Niki [P1-105](#)
 Moutsanas, Vissarios P2-32
 Mozzillo, Enza P1-72
 Mughal, M. Zulf P1-15
 Mührer, Julia P1-43
 Mukherjee, Swati P1-121
 Mukhopadhyay, Satinath P2-298
 Müller, Hermann L. FC8.4, P1-82, [P1-83](#), P1-89, P1-90, P2-350, S3.2
 Munarin, Jessica P1-93, P2-462
 Munns, Craig P2-58
 Muntoni, F. P2-9
 Muradyan, Irina [P2-465](#)
 Muratoğlu Şahin, Nursel P2-85, P2-94, P2-314, P2-315, P2-355
 Murianni, Agnese P1-198, P2-213
 Murillo Vallés, Marta P2-72
 Murillo, Marta P1-28
 Murphy, Dermot P1-157
 Murphy, Nuala FC4.6, P1-84, P2-24
 Murray, Philip P2-487
 Murray, Robert FC10.5
 Murri, Virginia P1-197
 Mushtaq, Imran P1-101
 Mushtaq, T. P2-9
 Muslimova, Elena P1-125, P1-130
 Myśliwiec, Małgorzata P2-301
 N
 Nabila, Boukhedouma P2-245
 Nabila, Bouterfas P2-44, P2-245, P2-274
 Nabila, Dahmane P2-44, P2-245
 Nadarajah, Ajantha P2-215
 Nadeem Anjum, Muhammad P1-17, P2-45
 Nadeem, Muhammad P2-39
 Nadgir, Ulhas P1-161
 Naeem, Nimra P1-111
 Nafissa, Benhalla P2-44, P2-245, P2-274
 Nagaeva, Elena P2-463, P2-490
 Nagasaki, Keisuke P2-10, P2-457, [P2-460](#)
 Nakamura, Akie P2-10
 Nakamura-Utsunomiya, Akari P2-10
 Nalbantoglu, Ozlem P2-14
 Napoli, Flavia P1-159, P1-172, P2-321
 Naranjo, Cristina P2-461
 Narayan, Kruthika P1-111
 Nash, Elizabeth P2-113
 Nassim, Nouri P2-419
 Nasso, Chiara [P2-357](#)
 Natarajan, Anuja [P2-160](#)
 Naugolny, Larissa [P2-90](#)
 Navardauskaite, Ruta P1-72, [P1-154](#)
 Navarro Moreno, Constanza [P2-115](#)
 Navasardyan, Lusine P2-49, P2-465
 Neale, Ann P2-234
 Nebe, Michèle FC2.4, P2-73
 Nef, Serge P2-396
 Neirinck, Jana FC5.5
 Neocleous, Vassos P1-143
 Netchine, Irene P1-123, P2-253
 Neumann, David P2-309
 Neumann, Uta FC1.2, P1-6, P1-143, [P2-17](#), P2-31, [P2-411](#)
 Neve Myers, Pernille P1-33
 Neville, Kristen P1-96
 Nevo-Schenker, Michal WG3.3
 Nguyen Khoa Binh, Minh [P2-135](#)
 NGuyen Quoc, Adrien FC10.4
 Nguyen, Thom P2-66
 Nicol, Barbara [WG4.1](#)
 Nicolaidis, Nicolas [P1-106](#), P2-185
 Nicolas, Georges [P2-468](#)
 Nicolino, Marc P1-132
 Nicolosi, Maria Laura [P1-137](#)
 Nicolussi Principe, Lara P1-197
 Niedziela, Marek P1-43, P1-48, P2-311
 Nierop, Andreas F.M. P1-162, P2-354
 Nieschlag, Eberhard FC8.6
 Nieveen van Dijkum, Els J.M. P2-452
 Nikitina, Irina FC7.6, [P1-42](#)
 Niklasson, Aimon P1-162, P1-168, P2-354
 Niklinska, Wiesława P2-455
 Nikolaeva, Nadezhda P2-155
 Nilsson, Margareta P1-88
 Nilsson, Ola P1-55, P2-71, P2-98, [YB1.5](#)
 Nimri, Revital P2-170
 Nir, Judith FC10.2
 Nishi, Miriam P2-398, P2-420
 Nishigaki, Satsuki P2-10
 Nitschke, Patrick FC10.4, P1-193
 Nix, Paul P2-367
 Noczynska, Anna FC1.2, P1-6, P1-43, P1-176, YB2.1

Noronha, Renata P2-381
 Norton, Rick P2-179
 Nosetti, Luana P2-172
 Noumi, Mustapha P2-101, P2-469
 Nourbakhsh, Mitra P1-37, P2-167
 Nourbakhsh, Mona P1-37, P2-167
 Nouzha, Rami P2-392
 Novak, Eva Y11.1
 Novotná, Dana P2-309
 Nowotny, Hanna F. FC1.1, FC1.5, P1-143
 Numakura, Chikahiko P2-10
 Nunes, Julia P2-68
 Nuñez, Francisco Javier P2-403, P2-438
 Nutter, Paul P1-61
 Nuyt, Anne-Monique FC4.1
 Nyman, Andrew P2-150
 Nyuzuki, Hiromi P2-457, P2-460

O

Oakley, Juliette P2-221
 Obara-Moszyńska, Monika P2-311
 Oberhauser, Sarah P2-363
 Obermannova, Barbora P1-57, P2-309
 Ocaka, Louise FC8.2, P1-50, P2-406
 Ocello, Laura P2-313
 Ochoa, Fernanda P2-81
 Ochoa, Maria Fernanda P2-1
 Ochoa-Molina, Maria Fernanda P2-23
 O'Connell, Michele P2-13
 Odeleye, Esther P2-112
 Ogawa, Yohei P2-457, P2-460
 Ohayon, Olga FC2.1, FC2.3, P1-31, P2-222
 Ojeda-Rodríguez, Ana P2-204, P2-210
 Okminyan, Goar P2-410, P2-425, P2-431, P2-440
 Okońska, Maja P2-301
 Okorokov, Pavel P2-192
 Okur, Fatma Visal P2-29
 Okur, Iclal P2-28, P2-315, P2-383
 Oleari, Roberto FC8.1, FC8.2
 Olerich, Kelsey FC2.6
 Oliveira, Vinícius da Silva P1-155
 Oliver, Nick P2-110
 Olivier, Patricia FC6.1
 Olszewska, Marta P1-71
 Omar, Omneya Magdy P2-96
 Omar, Tarek P2-395
 Onay, Hüseyin FC4.5, FC5.6, P1-67
 Onder, Asan P1-2
 Oner, Nergis P2-159
 Ong, Ken P1-33, P2-16
 Onu, Justus P2-424
 Oosterhuis, J. Wolter P1-48
 O'Rahilly, Stephen P2-182
 Oral, Elif FC2.1, FC2.3
 Orbach, Daniel P1-185
 Orbak, Zerrin P1-2, P2-95
 Orman, Burçe P1-43, P2-159, P2-355
 Oron, Tal P1-171

Orozco Morales, Jose Antonio P2-120
 Ortega Castelló, Eduardo P1-124
 Ortolano, Rita P1-194
 O'Shea, Elaine P1-24, P1-25, P1-61
 Osimani, Sara P2-172
 Osokina, Irina P2-483, P2-484, P2-488
 Östman-Smith, Ingegerd P1-124
 O'Toole, Stuart P2-397
 Otte, Anna FC8.4, P1-83
 Otto, Marije FC4.3
 Oude Ophuis, B. P2-216
 Owen, Catherine P2-6
 Owens, Martina P1-60
 Özalkak, Şervan P2-94, P2-242, P2-314, P2-368
 Ozbaran, Burcu P2-434
 Özbay Hoşnut, Ferda P2-333
 Ozbek, Mehmet Nuri FC4.5, P2-14
 Ozcan Murat, Nurhan P1-2
 Özdemir, Necmettin P2-423
 Özen, Samim FC4.5, FC5.6, P1-67, P1-109, P2-134, P2-141, P2-166, P2-374, P2-423, P2-434
 Ozgiray, Erkin P2-374
 Ozhan, Bayram P2-121, P2-272
 Özişik, Hatice FC5.6
 Özkan, Behzat FC4.5
 Özkınay, Ferda FC4.5
 Ozon, Alev FC10.6, P2-29, P2-65, P2-341
 Ozon, Z. Alev P1-62, P2-117
 Ozono, Keiichi P1-12, P2-284
 Ozsu, Elif P2-69, P2-89
 Oztoprak, Ulkuhan P2-473
 Öztürk, Ayşe Pınar P1-53, P1-128, P2-277, P2-278
 Ozturk, Nurinnisa P2-95

P

Padeira, Gonçalo P2-79
 Padidela, Raja P2-98, P2-262, YB1.5
 Padilla, Nelly P1-5, P1-7
 Padmanabhan, Sandosh P2-397
 Paganoni, Alyssa J.J. FC8.2
 Paganoni, Alyssa FC8.1
 Pagnano, Angela FC3.1
 Paino, Roberta P2-172
 Paketçi, Ahu P1-115
 Palma, Laura FC3.3, P1-197
 Paltoglou, George P1-103, P2-34, P2-161, P2-185
 Palumbo, Stefania P1-173
 Pampanini, Valentina YB1.4
 Pandzic Jaksic, Vladka FC7.1
 Pani, Danda FC8.3
 Pankowska, Ewa HDI2.3
 Pankratova, Maria P2-330
 Panos, Alexandros P2-451
 Papadakis, Georgios G. P2-363
 Papadea, Polyxeni P1-69

Papadopoulou, Marina P1-112, P2-173, P2-183, P2-185, P2-205
 Papageorgiou, Ifigeneia P1-106
 Papon, Jean Francois P1-95
 Papoulidis, Ioannis P2-401
 Paraluppi, Valentina P2-213
 Paramasivam, Nagarajan P2-308
 Paraskevopoulos, Dimitrios FC8.3
 Paraskevopoulou, Niki P2-299
 Parent, Anne-Simone YB2.2
 Parıldar, Zuhail P1-109
 Parini, Rossella FC3.6
 Parissone, Francesca P1-145
 Park, Julie FC4.4, P1-10, P2-22, P2-35
 Park, So Yun P2-454
 Parpagnoli, Maria P1-164, P2-295
 Parteno, Cristina P2-348, P2-356
 Parveen, Asmat P2-142
 Parzynski, Craig P2-300
 Paschou, Stavroula A. FC7.1
 Pascu, Bogdan Mihai P2-466
 Pasquali, Daniela P2-70
 Pasquini, Tai L.S. P2-244
 Passalidis, Alexandros P2-442
 Pasternak, Jesse P1-191
 Patel, Kashyap P1-75, P1-68, P2-169
 Patel, Leena FC1.3, FC7.3
 Patel, Nishal P2-113
 Patil, Atul P1-20
 Patjamontri, Supitcha P1-46, P1-146, P2-375
 Patsch, Janina P1-54
 Patti, Giuseppe P1-172, P2-321
 Pauer, Sophie P2-429
 Pauwels, Christian P1-185
 Pearce, Simon FC10.5, P2-450
 Pease Gevers, Evelien F. FC8.3
 Peckham, Hannah FC5.2, P1-32
 Pees, Christiane P1-54
 Peet, Aleksandr FC7.3
 Pehlivan, Enes P2-62
 Peixinho, Julha P2-68
 Pellicer, Adelina P2-252
 Peltek Kendirci, Havva Nur P2-84, P2-136, P2-359, P2-368, P2-373
 Peña, Fernanda P2-408
 Peng, Junjie P1-32
 Peng, Junxiang P2-350
 Pennisi, Patricia P2-261
 Pepaj, Orsiol P1-197
 Pepe, Giorgia P1-73, P1-97, P1-99, P1-153
 Perchard, Reena P2-239
 Percussor Silva, João Vitor P2-305
 Pereira Lemos, Ana P2-3, P2-339
 Pereira, Alberto M. FC1.5, FC7.1, P1-89
 Pérez, Jacobo P2-197, P2-288
 Pérez-Jurado, Luis A. P1-118
 Perez-Ruiz, Diego P1-25
 Perle, Eva P2-228

Perou, Ruth P1-4
 Perrault, Melissa FC6.1
 Perrot, Valérie P2-283
 Perry, Colin P1-8, P1-146
 Persani, Luca FC1.5, FC7.1, P1-114, P1-198, P2-346, P2-358
 Peskavaya, Nadzeya [P2-318](#)
 Peskett, Emma P2-238
 Pession, Andrea P1-194, P2-208
 Petakov, Milan P1-84
 Peterkova, Valentina P2-18, P2-146, P2-192
 Peters, Catherine FC8.5, P1-13, P1-27, P1-70, P1-101, P1-114, P1-133, P1-142, P1-170
 Petersen, Jørgen H. HA2, FC5.4, FC9.5
 Petrou, Vasilios P2-206, P2-223
 Petrova, Chayka P2-312
 Petrova, Irina P2-217, P2-249
 Petryk, Anna P1-12
 Pfister, Marc FC4.3, P2-453
 Phillip, Moshe P1-59, P1-171, P2-80, P2-170, P2-347, P2-386, YI1.1, WG3.3
 Phillips III, John P1-125, P1-130
 Phylactou, Leonidas A. P1-143
 Piaditis, Georgios P1-105
 Picard, Jean-Yves P2-442
 Pico, Antonio P1-135
 Pieridou, Chariklia [P2-60](#)
 Pietrobelli, Angelo FC3.3
 Pietropoli, Alberto P1-169, P2-280
 Pignata, Claudio P1-173
 Pignolo, Robert J. FC6.4, P1-51
 Piketty, Marie-Liesse P1-185
 Pimenta, Jeanne M. P1-121
 Pimlott, Helen P1-25
 Pineda, Pablo [P2-485](#)
 Pineda-Torra, Ines P1-32
 Pinhas-Hamiel, Orit FC2.3, FC10.2
 Pinnamaneni, Raga Mallika P2-479
 Pinto, Francisca P1-9
 Pinto, Graziella P1-185, P2-253
 Pinto, Renata Machado [P1-155, P2-184, P2-305](#)
 Piotraschke, Lena P2-285
 Piras, Francesco FC9.4
 Pistorio, Angela P1-159
 Pitteloud, Nelly P2-363
 Pivko-Levi, Dikla FC10.2
 Pivodic, Aldina P1-167
 Pizza, Fabio P1-85
 Plachy, Lukas P1-57, [P1-72](#)
 Plášilová, Ivana P2-309
 Plazzi, Giuseppe P1-85
 Poggi Mayorga, Helena P2-23
 Poggi, Helena P2-1
 Polak, Michel [EE1.1](#), FC4.2, FC10.4, P1-138, [P1-169](#), P1-185, P1-193, P2-253, P2-283

Pole, Jason P1-191
 Polgreen, Lynda E. P2-284
 Polnik, Dariusz P2-455
 Poluzzi, Silvia P1-180
 Pomahacova, Renata P2-297, P2-309
 Ponmani, Caroline P1-29, P2-150
 Pop, Raluca [P2-285](#)
 Popova, Galina P2-312
 Porras, Begoña P2-461, P2-480
 Porro, Matteo P1-122
 Porter, John P2-17
 Portillo, Nancy P1-81
 Poyrazoglu, Sukran FC1.2, P1-6, P1-8, [P1-41](#), P1-43, P1-49, P1-53, P1-127, P1-128, P1-182, P2-277, P2-278
 Pozo-Román, Jesús P1-175
 Pozzi, Clara P2-124
 Pozzobon, Gabriella P2-348, P2-356
 Prada, Silvina P1-144
 Prasad, Rathu P1-80, P2-19
 Pratap, Rajat [P2-390](#)
 Prathivadi Bhayankaram, Nuthana [P2-487](#)
 Prats-Puig, Anna P1-152, P2-232, P2-236, P2-240
 Preda, Cristina FC8.3
 Predieri, Barbara FC10.1, P1-180, P2-310
 Prentice, Andrew P1-195
 Prentice, Philippa [P1-60, P1-13](#), P1-133
 Prezerakos, Panagiotis P1-92
 Price, Abigail P2-150
 Prichard, Jonathan FC10.5
 Priego Zurita, Ana Luisa [P1-89](#)
 Probst-Scheidegger, Ursina FC1.2, P1-6
 Profka, Eriselda P1-122
 Proshchina, Alexandra P1-74
 Prosvirina, Anna [P2-327](#)
 Pruhova, Stepanka P1-56, P1-57, P2-297
 Průhová, Štěpánka P2-309
 Prunier-Mirebeau, Delphine FC10.3
 Prylutska, Veranika P2-190
 Puerto-Carranza, Elsa P1-152, P2-181, P2-232, P2-236, P2-237, P2-240
 Puges, Laura P2-461, P2-480
 Puget, Stéphanie P1-185
 Puig Domingo, Manuel FC7.1
 Pullen, Debbie FC6.2
 Purge, Priit P1-16
 Purushothaman, Preetha [P1-65](#)
 Pyrzak, Beata P2-462

Q

Qadir, Mazhar P2-64
 Qamar, Younus P2-19
 Qi, Yulan P2-66
 Quattrocchi, Emilia [P2-98](#)
 Qudrat, Syeda Mamoonah P2-164
 Quedas, Elisangela FC3.4
 Qureshi, Abid Ali P2-63
 Qureshi, Tabinda Naz P2-11

R

Raafat, Shaymaa P2-127, P2-202, [P2-384, P2-421, P2-445](#)
 Rabenstein, Hannah P1-120
 Rachmiel, Marianna P2-90
 Radziszewska, Anna FC5.2, P1-32
 Raftopoulou, Christina P1-103, P2-185
 Rai, Ashutosh FC8.3
 Raimann, Adalbert [P1-54](#), P2-262, P2-387, YB1.5
 Raine, Joseph P1-13
 Raivio, Taneli P1-163, P1-186
 Rajabali, Sakina FC8.2
 Rajas, Fabienne P1-58
 Raket, Lars Lau HA2
 Rakicioglu, Hande [P2-107](#), P2-326
 Rakus-Kwiatosz, Anna [P2-273](#)
 Ramalho, Fernando S FC1.6
 Ramalho, Leandra N.Z. FC1.6
 Ramanan, Athimalaipet FC7.5
 Rami, Imane P2-388, P2-443
 Ramponi, Giulia P2-313
 Randell, Tabitha FC1.3
 Rangasami, Jayanti P1-13
 Rani, Tanzeela P2-164
 Rania, Khalfallah P2-46
 Ranke, Michael B. P1-138
 Rankova, Kamelia [P2-258, P2-259](#)
 Rankova, Kameliya P2-312
 Rappold, Gudrun A. [P1-126, P2-308](#)
 Rask, Eva P1-86
 Raskin, Julie P2-234, [P2-244](#)
 Ravegnini, Gloria P1-180
 Raverot, Gerald P1-89
 Rayol, Micheline FC3.4
 Raziq, Abdur P2-164
 Razzaghy-Azar, Maryam P1-37
 Rbiai, Najoua P2-376
 Reddy, Monika P2-110
 Reddy, Nithya P2-479
 Redpath, Yvette P1-29
 Rees, D Aled P1-8
 Regal, Luc P2-459
 Regan, Lesley P2-238
 Reincke, Martin [S1.1](#)
 Reinehr, Thomas P1-9, P1-120, [P1.8](#)
 Reisch, Nicole FC1.1, FC7.1, P1-8, P1-143, P2-411
 Remedios Mateo, Laura P2-111
 Remer, Thomas P1-107, P2-176
 Remillard, Claire P2-78
 Remmel, Liina P1-16
 Renholm, Petra P1-104, P2-270
 Rentsch, Katharina FC4.3
 Rérat, Solène P2-193, P2-200
 Resmini, Eugenia FC8.3
 Reszec, Joanna P2-455
 Rey, Rodolfo A. P1-144
 Reyes, Monica P2-78
 Reynaert, Nele P2-260

- Reynolds, Courtney P1-151
Reynolds, Rebecca [WG2.2](#)
Reynoso, Ricardo P2-227
Rezende, Raissa FC3.4, [P2-381](#)
Rezende, Teresa P2-148
Rhie, Young-Jun P1-136, P2-227
Ribalta, Teresa FC8.3
Rica, Itxaso P1-81, P1-89, P2-203, [P2-407](#), P2-480
Ricav, Itxaso P2-461
Riccio, Simona P1-148
Richter, Sandy P2-73
Rico-Bautista, Elizabeth P2-235
Riedl, Stefan P1-44, P2-429
Riegman, Kimberley L. FC8.2
Rieko Tadokoro-Cuccaro P1-43
Riera-Pérez, Elena P2-181
Rigamonti, Andrea P2-124
Rigaud, Charlotte P1-185
Righi, Beatrice [P1-8](#), P1-180, P2-405
Rios, Beatriz [P2-81](#)
Riphagen, Shelley P1-15
Rivas, Angelica P2-215
Rivera, Josefa P2-197, P2-288
Robert J. Pignolo HA1
Roberts, Catherine P2-19
Robinson, George FC5.2, [P1-32](#)
Robinson, Iain C.A.F. FC8.2
Rocha, C. P2-218
Rochtus, Anne P1-45, P2-260
Rockman-Greenberg, Cheryl P1-12
Rodanaki, Maria [P1-86](#)
Rodari, Giulia [P1-122](#), [P2-358](#)
Rodien, Patrice FC10.3
Rodrigue, Danielle P1-95
Rodrigues, Marcela P2-87
Rodríguez Gutiérrez, Daniel [P2-396](#), P2-427
Rodríguez, Amaia P2-407, P2-461, P2-480
Rodriguez, Amaya P2-203
Rodríguez, María Eugenia P1-108
Roduit, Caroline P1-30
Roeth, Ralph P1-126, P2-308
Rogoff, Daniela P1-125, P1-130, P2-303
Rohayem, Julia P1-143
Rohrer, Tilman R. P1-169
Rojas Gil, Andrea Paola P1-35, P1-69, P1-92
Romanenkova, Elizaveta [P2-146](#)
Romano, Alicia P1-169
Romaykina, Daria P2-410, P2-425
Roncaroli, Federico FC8.3
Ronghe, Milind P1-157
Ronzitti, Giuseppe P1-58
Rooman, Raoul P1-138
Ropelato, M. Gabriela P1-144
Ropelato, María Gabriela P1-108, P1-144, P2-261, P2-365
Ros Peña, Andrea P2-72
Rosenbauer, Joachim P1-21
Rosenthal, Stephen [PL5](#)
Rosimont, Manon [P1-185](#)
Ross, Richard P1-8, P2-17
Rosser, Elizabeth C FC5.2
Rossi, Giuliana P1-197
Rossi, Massimiliano P1-125
Rothenbuhler, Anya FC3.1
Rothermel, Juliane P1-147
Rotteveel, J. P2-216
Rouf, Siham P2-57, P2-137, P2-162, P2-168, P2-275, P2-322, P2-329, P2-343, P2-376, P2-382, P2-388, P2-391, P2-430, P2-439, P2-443
Roujeau, Thomas P1-185
Rouleau, Stéphanie P2-193, P2-200
Rovelli, Attilio FC3.6
Roze, Zane [P2-228](#)
Rozenkova, Klara P1-72
Rudkova, Ekaterina [P2-54](#), [P2-132](#)
Russell, John P2-367
Russo, Gianni P1-8, P1-143
Russo, Paola P2-224
Rutigliano, Irene P2-172
Ryalls, Michael FC6.2
Ryan, Fiona FC1.3
Ryan, Paul [P1-26](#)
Ryckx, Sofie [P2-459](#)
Rysz, Izabela [P2-149](#)
Ryzhkova, Daria FC7.6
- S**
Saal, Howard P1-125, P1-130
Sabrina, Khensal [P2-419](#)
Sacco, Michele P2-172
Sachar-Lavie, Iris WG3.3
Sachlas, Athanasios P1-35
Sadoine, Jérémy P1-58
Sadovska, Barbora P2-297
Saeed, Anjum P1-17, P2-39, P2-45, P2-63, P2-64
Saenger, Paul FC9.3, P1-161
Saffari, Fatemeh [P2-433](#)
Saha, Chinmay P2-298
Sahoo, Subrat P2-417
Sainte-Rose, Christian P1-185
Şakar, Merve P2-28, [P2-48](#), P2-85, [P2-94](#), P2-302, [P2-314](#)
Sakka, Sophia [P1-29](#), [P2-150](#)
Salazar, Alexander P2-485
Salem, Nanees P2-251
Salerno, Maria Carolina P1-173, P2-293, P2-295
Sallemi, Alessia P1-197
Salles, Jean Pierre FC6.3, P1-125, P1-130, P1-132, P2-352
Salles, Juliette [P2-352](#)
Salomon-Estebanez, Maria P1-24, P1-25, P1-61, P2-125
Salunke, Pravin FC8.3
Salvatoni, Alessandro [P2-172](#), [P2-295](#)
Salvatore, Silvia P2-172
Samaan, Constantine [P2-215](#)
Samara-Boustani, Dinane P1-185, P2-253
Samartino, Ana P2-68
Sameer, George P2-61
Sampron, Nicolas FC8.3
Samsonova, Lubov P2-364, P2-410, P2-425, P2-431, P2-440
San Martin, Amaia P1-149
San Martin, Amaya P2-218
Sánchez Ruiz, Daniel P2-115
Sánchez-Garvín, Dunia P2-197
Sánchez-Holgado, María P2-252
Sanctis, Luisa De FC1.2, P1-6, P1-93, P2-400
Sandy, Jessica [P1-96](#)
Sankar, Sailesh FC6.2
Santili, Claudio P2-87
Santini, Ferruccio P2-209
Santos-Simarro, Fernando P1-125, P1-130
Sap, Suzanne [GPED1.1](#)
Saraff, Vrinda P1-125, P1-130
Sarafis, Ioannis P1-112
Sarafoglou, Kyriakie P1-4
Sarah E. Flanagan FC4.6
Sarakaeva, Leyla P1-42
Sarasua, Ainhua P2-461, P2-480
Sarasua-Miranda, Ainhua P1-149, P2-218, P2-229, P2-426, P2-470
Sarıkaya Özdemir, Behiye [P2-302](#)
Sarkozy, Anna P2-30
Sarmiento, Karen P2-485
Sartori, Chiara P1-180, P2-405
Sartorio, Alessandro P2-172
Sastre, Ana [FC6.2](#)
Sastry, Aparna P1-146
Sastry, Jairam P1-157
Saunders, Michael P2-284
Sav, Aydın P2-62
Savage, David P2-182
Savage, Martin O. P1-173, P2-287
Savarirayan, Ravi [P1-125](#), [P1-130](#), P2-284, P2-332
Savaş Erdeve, Şenay P2-28, P2-48, P2-85, P2-88, P2-94, P2-159, P2-242, P2-302, P2-314, P2-315, P2-333, P2-355, P2-368, P2-383
Sävendahl, Lars [FC9.3](#)
Savic, Ivanka P2-7
Savova, Radka P2-109
Sawadogo, Kiswendsida P2-99
Sawano, Kentaro [P2-457](#), P2-460
Sawicka, Beata [P2-56](#)
Saygılı, Füsun FC5.6
Sayin, Emine P2-272
Scalais, Emmanuel P2-103
Salfi, Luca P2-293
Scarano, Emanuela P1-164

- Scaroni, Carla P1-143
Schalin-Jantti, Camilla FC7.1
Scharfmann, Raphaël P1-193
Schauermann, Marcel P1-107, P2-176
Scheel, Lone FC5.3
Scheffer-Rath, Mirjam P2-449
Schelstraete, Petra FC5.5
Schiano di Cola, Roberta P2-70
Schiavone, Maurizio P2-321
Schierloh, Ulrike P2-103
Schilbach, Katharina P1-173
Schirmer, Melanie P1-120
Schirmer, Melanie P2-195
Schmidt, Heinrich FC1.1
Schnabel, Dirk P2-98
Schoeneberg, Dillon FC8.5
Schoenmakers, Nadia P2-479
Schott, Dina A. P1-1
Schröder, Mariska A.M. P1-1
Schur, Ellen FC2.6
Schwarz, Peter P2-122
Schweikert, Hans-Udo P1-150
Schwitzgebel, Valérie P1-84
Scimia, Cecilia FC2.1, FC2.3, P1-31, P2-222
Scozzarella, Andrea P1-194
Scrideli, Carlos A. FC1.6
Scuruchi, Michele P1-39
Scuvera, Giulietta P1-122
Seefried, Lothar P1-12
Seifert, Monika P1-176
Seiltgens, Cristián P2-97
Sekfali, Lynda P2-43
Selvarajah, Bhavana P2-22
Selveindran, Nalini M. P2-26, P2-92, P2-412
Selver Eklioglu, Beray P2-114, P2-156, P2-212, P2-476
Selver, Muhammed Burak P2-114
Semler, Oliver P2-98, P2-262
Senanayaka, Ayodya P2-52
Seneca, Sara P2-103
Seneviratne, Sumudu P2-413, P2-428
Senniappan, Senthil FC4.4, P1-40, P1-76, P1-113, P2-198, P2-214, P2-233, P2-377
Senyazar, Gizem P2-69, P2-89
Serbis, Anastasios P1-100
Serin, Gürdeniz P2-423
Sert, Caroline P2-283
Sertedaki, Amalia P1-105, P1-106, P2-32, P2-37, P2-158, P2-161
Sestan-Pesa, Matija P1-87
Seven Menevse, Tuba P1-2, P1-18, P1-19, P1-49, P1-78, P2-14
Sevilla, Julián P2-281
Sewaybricker, Leticia FC2.6
Sfar, Mohamed Habib P2-340, P2-342, P2-345
Sfez, Annie FC4.2
Shabbir, Syed Abdul P2-246
Shah, Bhavik P1-116, P2-222
Shah, Pratik Hasmukh P1-23, P2-113
Shah, Pratik FC4.6, P1-133, P2-19
Shah, Suneri FC8.6
Shaheen, Tahir P1-17, P2-39, P2-45, P2-63, P2-64
Shahid, Gulbin P2-142
Shaikh, Guftar P1-72, P1-114, P1-124
Shaikh, M. Guftar P1-98, P1-146, P1-157
Shaikh, Mohamad G. P2-19
Shalewa, Ugege P2-424
Shalitin, Shlomit P2-170, P2-347
Shamsher, Maria P2-142
Shanabrough, Marya P1-87
Shankar, R. Ravi FC8.6
Shantsila, Helen P1-10, P2-35
Shapiro, Lucy P2-287
Sharaf, Muna P1-184
Sharifi, Roya P1-37
Sharifli, Samir P2-292
Sharifova, Sabina P2-292
Shaukat, Mehmood P2-64
Shaunak, Meera P1-47, P2-471
Shaw, Nick P2-60
Sheket, Sevim P2-258, P2-259
Shen, Chen P2-375
Sheppes, Tamar P2-201
Shibata, Nao P2-457, P2-460
Shields, Beverley P1-68
Shim, Young Suk P1-63, P2-171
Shmoish, Michael P2-176, P2-196
Shreder, Ekaterina P2-490
Shtait, Biana P1-59, P2-80
Shu, Aimee D. P1-161
Shulman, Lester P2-123
Shvalb, Nir P2-386
Shyshko, Julia P2-190
Sibinovska, Olgica P2-138
Siddle, Kathryn P2-58
Side, Lucy P1-47
Siedler, Kai P1-21
Siersbæk, Julie FC4.6
Siesjö, Peter P1-88
Siklar, Zeynep P2-69, P2-89
Šilar, Jiří P2-309
Silva, Isabella P2-68
Silver, Matt P1-195
Simões, Joana P2-41, P2-75
Simon, Albanne P1-185
Simon, Dominique P1-181
Şimşek, Fatma P2-385
Sindichakis, Marina P1-21
Sinéad M. McGlacken-Byrne P1-50
Sircili, Maria Helena P P2-399
Sirvent, Sara P2-188
Şişman, Ali Rıza P1-115
Skae, Mars P1-125, P1-130
Skakkebæk, Niels E. FC5.4
Skipitari, Marianna P1-69
Skoric, Tanja FC8.3
Škvor, Jaroslav P2-309
Slavcheva, Olga P2-109
Slimani, Lotfi P1-58
Smirnova, Marija P1-154
Smith, Natalie P2-30
Smith, Rachel B. P2-375
Smith, Sarah P1-98
Smuel Zilberberg, Keren P2-170
Smyczyńska, Joanna P1-174
Smyczyńska, Urszula P1-174
Smyrnaki, Penelope Smyrnaki P2-37
Snajderova, Marta P1-57, P2-297, P2-309
Snow, Claire P2-6
Snowden, Stuart P1-33
Soares, Marcela Batista P1-155
Sobu, Elif P1-2
Sofiane, Benmaouche P2-44
Sokhal, S. P2-101
Solanky, Nita P2-238
Solari Guajardo, Sandra P2-23
Solari, Sandra P2-1
Solberg, Paulo FC3.4
Soler, Laura P1-200
Soliman, Ashraf, P1-139, P1-140, P1-178, P2-12, P2-104, P2-105, P2-131, P2-241, P2-243, P2-255, P2-256, P2-264, P2-265, P2-266, P2-267, P2-268, P2-271, P2-279, P2-290, P2-291, P2-296, P2-306, P2-307, P2-325, P2-328, P2-331, P2-335, P2-378, P2-389, P2-395, P2-415, P2-416
Solmaz, Asli Ece P2-434
Solntsava, Anzhalika P2-54, P2-132, P2-133, P2-190, P2-194, P2-318, P2-338
Sommer, Grit P1-43, P1-103, P2-2
Song, Mengjia P1-141
Song, Wenjie P1-161
Songailiene, Jurgita P1-154
Sönmez, Hafize Emine P2-478
Sorakunnas, Eero P1-163
Soranna, Davide P2-346
Soria, Marcela P1-144
Soriano-Guillén, Leandro P2-252
Sotillos, Sol P2-427
Southward, Suzanne FC4.4
Sowithayasakul, Panjarat P1-82, P1-83, P1-90, P2-350
Span, Paul N. P1-1
Spano, Alice P2-209
Sparks, Kathryn FC8.5
Spiers, Alexander P2-375
Spilioti, Diamantina-Xanthi P2-118, P2-367
Spiliotis, Bessie FC2.3, P1-35, P1-69, P1-92
Spinoit, Anne-Françoise P1-44
Spinty, Stefan FC6.6

- Spoudeas, Helen P1-142, P2-372
 Sprecher, Simon P2-427
 Springer, Alexander P1-44
 Sproll, Patrick P2-396
 Squadrito, Francesco P2-357
 Squadrito, Violetta P2-357
 Stachanow, Viktoria P2-411
 Stachow, Rainer P2-116
 Staels, Willem P2-459, [YI1.5](#)
 Staley, Christine P2-126
 Stancampiano, Marianna R. P1-8, P1-48, P1-160
 Staník, Juraj [YI1.3](#)
 Stanković, Sandra YI1.1
 Starzyk, Jerzy B. P2-207
 Stawerska, Renata P1-138, P1-174
 Stears, Anna P2-182
 Stecchini, Mônica F. FC1.6
 Steele, Caroline FC10.5
 Stefanopoulos, Leandros P1-112, P2-173, P2-183
 Stefanova, Elisaveta P2-312
 Steffens, Britta P2-453
 Stegmann, Barbara J. FC8.6
 Steinbeck, Katharine P2-404
 Steven, Mairi P2-397
 Stevens, Adam P2-239
 Stevenson, Brian P2-396
 Stevenson, Mark FC6.2
 Stevenson, Paul G. P2-230
 Stewart, Murray FC2.1, FC2.2, FC2.3, P1-31, P2-222
 Stikkelbroeck, Nike M.M.L. P1-8
 Stipančič, Gordana YI1.1
 Stoicheva, R. P2-317
 Stojanovic, Marko P1-84
 Stokes, Helen FC1.4
 Storr, Helen L. P1-173, P1-179, P2-283, P2-287
 Stoupa, Athanasia FC10.4, P1-193, [P2-253](#)
 Stoyanova, M. P2-317
 Stożek, Karolina P2-475
 Straetemans, Saartje P1-1
 Street, Maria Elisabeth P1-164, [P1-180](#), [P2-405](#)
 Strich, David P2-82
 Strnadel, Jiří P2-309
 Strogilos, Rafael P1-106
 Struthers, R. Scott P2-126
 Stuart, Annemarie Verrijn P1-72, P1-150
 Study Group Hypogonadotropic Hypogonadism P1-188
 Sturchler, Emmanuel P2-126
 Su, Pen-Hua P2-257
 Su, Su-Huei P2-257
 Suh, Byung-Kyu P1-52
 Sukalo, Alexander P2-190
 Sukarova-Angelovska, Elena [P2-138](#)
 Sumnik, Zdenek P1-57, P1-72, P2-297, P2-309
 Sun, Hui P1-141
 Sundberg, Karin FC5.3
 Sundgren, Pia C. P1-88
 Suntharalingham, Jenifer P1-50, P2-19, [P2-238](#)
 Suntharesan, Jananie [P2-418](#)
 Surekli Karakus, Ozlem P2-371
 Sweep, Fred C.G.J. P1-1
 Swerdlhoff, Ronald S. FC8.6
 Sylvestre, Marie-Pierre FC4.1
 Symth, Alistair P2-367
 Szalecki, Mieczysław P2-455
 Sze Lyn Wong, Jeanne P2-26, P2-92
 Szinnai, Gabor FC4.3, [P2-453](#)
 T
 Tack, Lloyd P1-43, [P1-44](#), [P1-45](#)
 Tahri, Abir P2-162, [P2-443](#)
 Tajima, Toshihiro P2-10
 Takazawa, Kei P2-10
 Talbi, Abir [P1-188](#)
 Tamaddon, Askan P1-88
 Tamborlane, William [PL2](#)
 Tamme, Reeli [P1-16](#)
 Tan, Rachael FC8.3
 Tang, Yijun [P2-414](#)
 Tankova, Tsvetalina P2-122
 Tarantola, Giulia P2-477
 Tarcin, Gurkan P2-292
 Tardy-Guidollet, Véronique P1-143, P2-47
 Tarkoff, Joshua P2-55
 Tartaglia, Marco P1-124
 Tasdelen, Neslihan P2-62
 Tauber, Maithé P2-352
 Tavernier, Simon FC5.5
 Tayeb, Tara Hussein P1-56
 Taylor, Norman FC1.3
 Taylor-Miller, Tashunka P1-111
 Tazibt, Oulebsir P2-366
 Teinturier, Cecile P1-95
 Temple, I. Karen [S12.1](#)
 Tenenbaum, Ariel P1-171
 Tenenbaum-Rakover, Yardena FC10.2
 Tenhola, Sirpa P1-186
 Tenoutasse, Sylvie P1-190
 Terrak, R. P2-101, P2-469
 Teofoli, Francesca P1-197
 Teoh, Sze Teik P2-26, [P2-143](#)
 Tessaris, Daniele P1-93, [P2-400](#)
 Thabane, Lehana P2-215
 Thakker, Rajesh V FC6.2
 Thakrar, S. P2-9
 Thalassinou, Caroline P1-185, P2-253
 Thankamony, Ajay FC1.2, P1-6, P1-77
 Theocharis, Paraskevi P1-15
 Theodoropoulou, Eleni P1-112, P2-173, P2-183
 Thiabat, Hanan F. P1-159
 Thom, Katharina P1-54
 Thomas, Muriel [P2-260](#)
 Thomas, N. Simon P2-19
 Thomas, Nick FC8.3
 Thomas-Teinturier, Cecile [P2-27](#), P2-304
 Thompson, Dominic FC6.5
 Thornton, Paul S. [P1-151](#), P1-161
 Thursfield, Rebecca FC4.4
 Tihonovich, Julia P2-441
 Tilleman, Kelly P1-44
 Tillmann, Vallo P1-16
 Timmermans, Demi P1-165
 Timpel, Patrick P2-122
 Tischlinger, Katharina P2-86
 Titman, Andrew P2-22
 Titovich, Elena P2-146
 Tittel, Sascha R. P2-116
 Tiulpakov, Anatoly FC7.6
 Tobias, Edward S. P1-46, P1-146
 Todorović, Slađana YI1.1
 Tokarska, Agnieszka P2-282
 Toksoy, Guven P2-277
 Toledano, Hellen P2-347
 Toledano, Mireille B. P2-375
 Toledo, Arthur H.T. [P2-87](#)
 Tollerfield, Sally P1-133, P1-170, [P2-30](#)
 Tolstikova, Olena [P2-226](#), [P2-458](#)
 Tomasini, Rosangela P1-119, P2-186
 Tomé-Masa, Irene P1-175
 Tomlinson, Jeremy W. P1-8
 Toni, Ledjona [P1-57](#)
 Tonnhofer, Ursula P1-44
 Topaloglu, Rezan P2-29
 Toppari, Jorma FC5.4
 Toprak, Emine Kılınç P2-121
 Torales, Jorge FC8.3
 Toraman, Bayram P2-76
 Torel Ergur, Ayca P2-174, P2-175, [P2-385](#)
 Tornese, Gianluca FC7.3, P2-295
 Tornicasa, Vincenzo P2-250
 Toromanović, Alma YI1.1
 Toro-Ramos, Martin P2-227
 Torpiano, John G. FC8.2
 Torres Tamayo, Margarita P2-120
 Tosi, Flavia P2-405
 Tosun, Ilker P2-95
 Touraine, Philippe P1-135, P1-143, P1-185, [S12.2](#)
 Tourki, Yousra P1-22, P2-128
 Touyz, Rhian P2-397
 Traeger-Synodinos, Joanne P1-105
 Tragomalou, Athanasia [P1-112](#), [P2-173](#), [P2-183](#), [P2-199](#), [P2-205](#)
 Tragomalou, Nansy P2-199
 Tran, Thai Hoa FC6.1
 Trasande, Leonardo [WG2.1](#)
 Trettene, Adolfo Andrea P1-164, P2-295
 Trevelyan, Nicola P2-112
 Trezzi, Cecilia P2-124

Tropeano, Angelo [P1-39](#), [P1-97](#)
 Tropeano, Yesica [P1-65](#)
 Trouvin, Marie-Agathe [P2-304](#)
 Truong, Lisa [P1-151](#)
 Tse, Jenny [P2-300](#)
 Tseretopoulou, Xanthippi [P2-479](#)
 Tsigos, Constantinos [P1-105](#)
 Tsinopoulou, Vasiliki Rengina [P1-100](#)
 T'Sjoen, Guy [P1-8](#)
 Tsochev, K. [P2-317](#)
 Tsochev, Kaloyan [P2-258](#), [P2-259](#)
 Tucci, Silvio [FC1.6](#)
 Tuli, Gerdi [P1-93](#), [P2-400](#), [P2-462](#)
 Turan, Hande [P2-292](#)
 Turan, Serap [P1-2](#), [P1-18](#), [P1-19](#), [P1-49](#),
[P1-78](#), [P1-102](#), [P2-14](#), [P2-25](#), [P2-62](#),
[P2-196](#), [P2-361](#), [P2-371](#), [P2-432](#)
 Turan, Serkan [P1-115](#)
 Turchina, Svitlana [P1-183](#)
 Turgut, Gozde Tutku [P2-277](#)
 Türkyılmaz, Ayberk [P2-25](#)
 Turner, C. [P2-9](#)
 Turner, Kelly [P1-27](#)
 Turner, Lucy [FC6.6](#)
 Turolla, Lorenzo [FC3.3](#)
 Tutaya Egusquiza, Dellanira Pamela
[P2-402](#)
 Twigg, Steve [WG1.2](#)
 Tzortzopoulou, Adelais [P2-442](#)

U

Uçar, Ahmet [P1-38](#)
 Uçar, Mert [P1-109](#)
 UCL Genomics [P1-50](#)
 Uday, Suma [P2-60](#)
 Ullah, Irfan [P2-11](#)
 Ulman, Ibrahim [P2-434](#)
 Umano, Giuseppina Rosaria [P1-148](#)
 Unger, Nicole [P1-143](#)
 Ünsal, Nafiye [P2-40](#)
 Unsal, Yagmur [P2-29](#), [P2-65](#), [P2-341](#)
 Unsworth, Rebecca [P2-110](#)
 Upners, Emmie N. [HA2](#), [FC9.5](#)
 Urs Zumsteg [FC4.3](#)
 Urueña, Ana [P2-485](#)
 User, Idil Rana [P2-341](#)
 Utkus, Algirdas [P1-154](#)
 Uyguner, Oya [P2-277](#)
 Uyguner, Zehra Oya [P1-182](#)

V

Vadina, Tatiana [P2-490](#)
 Vakaki, Marina [P2-401](#)
 Vala, Beatriz [P2-148](#)
 Valentino, Kevin [FC6.2](#)
 Valenzise, Mariella [P1-39](#), [P2-211](#),
[P2-357](#), [P2-462](#)
 Valls, Aina [P1-28](#)
 Van Aken, Sara [P1-45](#), [P2-260](#)
 van Beek, André P. [P1-135](#)

van Beijsterveldt, Inge [FC2.5](#), [P1-33](#)
 van Beuzekom, Charlotte N. [P1-89](#)
 Van Bever, Yolande [FC5.5](#), [P1-48](#)
 Van Damme, An [P2-99](#)
 Van De Velde, Julie [FC5.5](#)
 van den Akker, Erica L.T. [FC1.2](#), [FC7.1](#),
[FC9.1](#), [P1-1](#), [P1-6](#), [P1-103](#), [P1-114](#),
[P2-2](#), [P2-21](#), [P2-180](#), [P2-191](#)
 van den Berg, Sjoerd A.A. [P2-21](#)
 van den Eynde, E. [P2-180](#)
 van der Grinten, Hedi L. Claahsen [P1-3](#)
 van der Straaten, Saskia [P1-45](#), [P2-260](#)
 van der Velden, Janiëlle A. [P1-1](#)
 van der Voorn, B. [P2-180](#), [P2-191](#), [P2-216](#)
 van Dommelen, Paula [FC9.2](#), [FC9.4](#),
[P1-131](#), [P1-134](#), [P2-250](#)
 van Duyvenvoorde, Hermine A. [P2-308](#)
 van Haelst, M.M. [P2-216](#)
 van Herwaarden, Antonius E. [P1-1](#)
 Van Hulst, Andraea [FC4.1](#)
 Van Laecke, Erik [P1-44](#)
 van Lieshout, Jelmer [P2-448](#)
 van Rooijen, Jesse J. [P2-452](#)
 van Rossum, E.F.C. [P2-180](#)
 van Rossum, Elisabeth [P1-114](#), [P2-191](#)
 van Santen, H.M. [P2-216](#)
 van Schaik, J. [P2-216](#)
 van Schouten-Meeteren, A.Y.N. [P2-216](#)
 van Telling, Vera [P1-1](#)
 van Trotsenburg, A.S. Paul [P2-452](#)
 van Trotsenburg, Paul [P1-91](#), [P2-446](#),
[P2-448](#), [P2-452](#)
 Van Vliet, Guy [P2-435](#)
 van Wittenberghe, Laetitia [P1-58](#)
 van Zoonen, Renate [P1-134](#)
 van't Westeinde, Annelies [P1-5](#)
 Vanbesien, Jesse [P2-459](#), [P2-260](#)
 Vannelli, Silvia [P1-164](#), [P2-295](#)
 van't Westeinde, Annelies [P2-7](#)
 Vargas, Laura [P2-288](#)
 Varimo, Tero [P1-186](#)
 Vartzelis, Georgios [P2-360](#)
 Vasilakis, Ioannis-Anargyros [P2-161](#)
 Vasilev, Teodor [P2-109](#)
 Vasques, Gabriela [FC3.4](#)
 Vass, Angela [P2-52](#)
 Vassiliadi, Dimitra [FC7.1](#)
 Vasyukova, Olga [P2-192](#)
 Vega, Elizabeth [P1-119](#)
 Vela, Amaia [P2-407](#), [P2-461](#), [P2-480](#)
 Vela, Amaya [P2-203](#)
 Velletri, Maria Rosa [P1-73](#), [P1-153](#)
 Vêncio, Ricardo Z.N. [FC1.6](#)
 Vendrig, Lianne [P1-91](#)
 Verberne, Hein [P2-446](#)
 Verburg, Frederik [P2-446](#)
 Verdin, Hannah [FC5.5](#), [P1-44](#), [P1-45](#)
 Verganelakis, Dimitrios A. [P2-360](#)
 Verissimo, David [P2-467](#)
 Verkauskiene, Rasa [P1-72](#), [P1-154](#)

Verloes, Alain [P1-124](#)
 Vermont, Clementien [FC5.5](#)
 Viaud, Magali [P2-253](#)
 Vieites, Ana [FC1.2](#), [P1-6](#)
 Viera, Soraia [P2-110](#)
 Vierucci, Francesco [P2-462](#)
 Vigone, Maria Cristina [P1-160](#), [P2-477](#)
 Vijayanand, Sathyakala [P2-230](#)
 Vila, Greisa [P1-135](#)
 Vilella, Leyre Aurora [P1-149](#)
 Vilella, Leyre [P2-218](#)
 Villa, Roberta [P1-122](#)
 Villalon, Flor [P2-438](#), [P2-403](#)
 Villani, Michela [P2-405](#)
 Villeneuve, Emma [P1-22](#)
 Vincenzi, Monica [P1-160](#), [P2-477](#)
 Vincenzi, Monica [P1-197](#)
 Virella, Daniel [P2-79](#)
 Virtanen, Helena E. [FC5.4](#)
 Visalli, Giulia [P2-357](#)
 Viuff, Dortha [P2-332](#)
 Vlachopapadopoulou, Elpis Athina
[P2-38](#), [P2-442](#), [P2-451](#)
 Vlachopapadopoulou, Elpis [P1-138](#),
[P2-206](#), [P2-223](#)
 Vlachopapadopoulou, Elpis-Athina
[P2-360](#), [P2-401](#)
 Vladimirova, Victoria [P2-18](#)
 Vlasblom, Eline [P1-134](#)
 Vodopiutz, Julia [P2-387](#)
 Voelkl, Jakob [S11.1](#)
 Voet, Bernard [P2-17](#)
 Vogel, Megan [P1-116](#)
 Vojtková, Jarmila [P1-143](#)
 Volkava, Nataliya [P2-133](#)
 Von der Decken, Isabel [P2-396](#), [P2-427](#)
 von Schnurbein, Julia [P1-120](#), [P2-195](#)
 Vorontsov, Alexandr [P2-18](#)
 Vourdoumpa, Aikaterini [P1-112](#), [P2-161](#),
[P2-173](#), [P2-183](#)
 Voutilainen, Raimo [P1-186](#)
 Vukovic, Rade [P1-8](#), [Y11.1](#)
 Vural, Serpil [P1-30](#)
 Vuralli, Dogus [FC10.6](#), [P1-62](#), [P2-117](#)
 Vyas, Avni [FC1.4](#)

W

Waaks-Stepień, Bogdan [P2-220](#)
 Wabitsch, Martin [P1-120](#), [P2-195](#), [P2-222](#)
 Wachter, Ulrich A. [P1-107](#)
 Wade, Laura [P2-58](#)
 Waheeb, Saber [P2-445](#)
 Waheed, Khawaja Ahmad Irfan [P2-64](#)
 Wajnrajch, Michael P. [P1-135](#), [P1-138](#),
[P2-300](#)
 Waksman, Yarden [P2-201](#)
 Walleczek, Nina-Katharina [P2-387](#)
 Walsh, Anna [FC4.4](#)
 Walton-Betancourth, Sandra [P2-263](#),
[P2-479](#)

- Wan, Mandy P1-15
Wang, Fengyun P1-141
Wang, Jian P2-414
Wang, Jinling [P1-34](#), [P2-177](#), [P2-178](#)
Wang, Kuan-Wen P2-215
Wang, Rong P2-176
Wang, Winston P2-379
Wang, Xiaoyan P1-141
Wang, Xiumin P1-156, P2-323, P2-414
Wang, Yirou P1-156, [P2-324](#), P2-414
Ward, Kate P1-195
Warr, Nick P1-49
Warren, Daniel P2-367
Wasniewska, Malgorzata P1-39, P1-43, P1-73, P1-97, P1-99, P1-153, P1-164, P2-176, P2-189, P2-196, P2-211, P2-357, P2-462
Wasserman, Jonathan P1-191
Waterland, Robert P1-195
Watson, Gillian FC10.5
Watson, Mando P2-110
Webb, Susan FC8.3
Weber, Michael P1-54
Webster, Matt FC2.2
Wei, Ge P2-303
Wei, Liya P2-393
Weintrob, Naomi FC7.3, [HDI1.1](#), P2-90
Weiss, Birgit P2-308
Welling, M.S. [P2-180](#), [P2-216](#)
Welling, Mila P2-191
Welsch, Sophie [P2-99](#)
Welsh, Kathryn [P2-221](#)
Welzel, Tatjana P2-453
Weng, Richard P1-125, P1-130
Weninger, Julia P1-44
Werner, Ralf P1-150
Wesley J. Goedegebuure P1-129
Whitaker, Martin J P2-17
Whitehead, Jennifer [FC8.5](#)
Whittaker, Danielle E. FC8.2
Wickramarachchi, Chandu P1-29
Wiegand, Susanna P2-17
Wiepjes, Chantal M FC5.1
Wijnand, Justine P1-166
Wikiera, Beata [P1-176](#)
Wilber, Ellen P2-182
Williams, Hywel J. FC8.2, P2-406
Williams, Jack P1-173, P1-179, P2-287
Williams, Rachel P2-182
Wilmot, Emma [S13.1](#)
Wilson, Aileen P1-111
Wilson, Louise P1-13
Wilson, Sarah P1-24
Win, Myat [P1-77](#)
Wit, Jan-Maarten [CON2.2](#), P1-134, P2-286, P2-308
Witchel, Selma P2-409
Witsch, Michael P2-103
Woelfle, Joachim P2-283
Wójcik, Małgorzata [P2-207](#)
- Wolf, Cordula P1-124
Wolffenbuttel, Katja P. P1-48
Wolter, Nikolaus P1-191
Wong, James P2-150
Wong, Jeanne S.L. P2-412
Wong, S.C. [P2-9](#)
Wong, Sze Choong [P1-11](#), [P2-5](#)
Wood, C. P2-9, P2-450
Wood, Ruth P2-450
Woodhead, Helen P1-96
Woodland, Clare FC4.4
Worth, Chris [FC1.4](#), [P1-24](#), [P1-25](#), [P1-61](#), [P2-125](#)
Wright, Katherine [P2-160](#)
Wright, Samantha P2-233
Wu, Haiying P1-141
Wudy, Stefan A. [WG4.2](#), P1-107, P2-107, P2-176, P2-196, P2-247, P2-326
Wulf, Kristina P1-9
- X**
Xargay-Torrent, Silvia P1-152, P2-232, P2-236, P2-240
Xie, Rongrong P1-141
- Y**
Yaacov, Hadar P2-201
Yakovovitch Gavan, Michal P1-59, P2-170, P2-201, P2-386
Yaghmaei, Parichehreh P1-37
Yakovovich-Gavan, Michal P1-171
Yaman, Akan P1-2
Yaman, Ali P1-102
Yamna, Kriouile P2-392
Yan, Claudia P2-126
Yanar, Eda [P2-18](#)
Yaneva, Natasha P2-109
Yang, Jaejin P2-447
Yang, Li P2-379
Yang, Ningjing [P2-83](#)
Yang, Yu P2-379, P2-393
Yanowski, Jack FC2.2, P1-31
Yaralı, Oğuzhan P2-25
Yasar, Elif P2-353
Yatsenko, Svetlana P2-409
Yatsuga, Shuichi [P2-10](#)
Yau, Daphne P1-25, P1-68, P2-125
Yavas Abali, Zehra P1-18, P1-19, [P1-102](#), P2-25, P2-278, P2-432
Yavas, Zehra FC1.2, P1-6, P1-43
Yde, Sonny P1-193
Ye, Feng [P2-393](#)
Yegen, Berrak Caglayan P2-371
Yenhovotova, Viktoria [P2-139](#), [P2-169](#)
Yeow Hua Hong, Janet P2-143
Yesil, Gozde P1-49
Yesil, Sule P2-383
Yesiltepe Mutlu, Gul P2-14
Yesilyurt, Ahmet P1-78, P2-361
Yesquen, Pamela [P2-129](#)
- Yeste, Diego P1-119, P1-143, P1-200, P2-72, P2-129, P2-186, P2-402
Yi, Kyung Hee P1-63, P2-171
Yi, Kyung Hee
Yıldırım, Ahmet P2-144, [P2-422](#)
Yıldırım, Zeynep Yıldız P1-38
Yildiz, Melek P1-2, P1-41, [P1-127](#)
Yilmaz, Duygu P2-62
Yilmaz, Uğur Cem P1-67
Yinanç, Mehmet Ali P2-385
Yonan, Chuck P1-3
Yong, James P2-118
Yoo, Suk Dong P2-336
Yoon, Jong Seo [P1-63](#), [P2-171](#)
Yoon, Ju Young [P2-336](#)
Yordanova, Nikolinka P2-15, P2-20, P2-258, P2-259
You, Cheng P2-379
Young, Jacques FC7.1
Youssef, Michael P2-215
Yu, Jeesuk [P2-447](#), [P2-472](#)
Yuan, Guojun FC2.1, FC2.2, FC2.3, P1-31, P2-222
Yuan, Xuewen P2-379
Yuditskiy, Anton [P2-217](#), [P2-249](#)
Yuen, Kevin C.Y. P1-135
Yüksek Acinikli, Kübra P1-64, P2-4, P2-353
Yuksel, Deniz P2-28, P2-473
Yunes, José A FC1.6
Yung, Zoe P2-233
- Z**
Zachurzok, Agnieszka [P2-207](#)
Zaharova, Svetlana P2-490
Zamanipoor Najafabadi, Amir H. P1-89
Zambon, Antonella P2-346
Zammitt, Nicola FC10.5
Zangen, David FC5.5, P1-184
Zantour, Baha P2-340
Zapletalova, Jirina P2-297, P2-309
Zarante, Ignacio P2-485
Zarate, Yuri P2-332
Zdravković, Vera YI1.1
Zebian, Bassel FC8.3
Zeithofer, Petra P2-429
Zelinska, Natalia P1-43, P1-66, P2-139, P2-169
Zema, Attilio P2-211
Zemkova, Daniela P2-297, P2-309
Zenger, Gülberil P2-156
Zenker, M. P1-124, P2-317
Zerah, Michel P1-185
Zerrouki, Dounia P2-382
Zeryouh, Nabila P2-57
Zevker, Emine Gokcehan P2-254
Zeytun, Hikmet P2-422
Zghal, Mohammed Ali P2-491
Zhan, Shumin P2-393
Zhang, Dandan [P1-141](#)

Zhang, Jun FC3.2, P2-53, [P2-83](#), [P2-225](#),
P2-319, [P2-394](#)
Zhang, Qianwen [P1-156](#), P2-323
Zhang, Ying P2-332
Zhao, Jian P2-126
Zheng, Rujiang P2-53
Zhong, Yan P2-379
Zhong, Zhu Xuan [P2-182](#)

Zhu, Min P2-393
Zhu, Yun Fei P2-126
Zhukouskaya, Volha [P1-58](#)
Zimmermann, Marius P1-7, P2-7
Zineb, Imane P2-392
Zirilli, Giuseppina P2-211
Zoccolillo, Matteo P2-286
Zoidakis, Jerome P1-106

Zoog, Stephen P2-66
Zorkot, Zeinab [P2-409](#)
Zorn, Stefanie P1-120, [P2-195](#)
Zouridaki, Christina P2-451
Zubicaray, Josune P2-281
Zucchini, Stefano P2-208, P2-295
Zwaveling-Soonawala, Nitash [P1-91](#),
P2-446, [P2-448](#), P2-449, P2-452