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Neonatal hypocalcaemia revealing maternal calcium metabolism disorder

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Background: During pregnancy, the fetus maintains high blood calcium levels, thanks to an active transport across the placenta. At birth, with the cord clamping, he is abruptly disconnected from the maternal supply of calcium and becomes dependent of the intestinal calcium intake and the skeletal reserves. Besides, the newborn Vitamin D status is directly related to his mother’s Vitamin D status. Thus, the slightest abnormality in the maternal calcium metabolism may have severe consequences in the newborn calcium regulation.

Objective: To determine the relation between hypocalcaemia in newborns and their mother’s mineral status.

Methods: Mother of newborns presenting with symptomatic hypocalcaemia were tested to detect either vitamin D deficiency or hyperparathyroidism.

Results: 7 mother-newborn couples were identified. The mean age was 8.3 days (3-27). There was one female and six males. All the newborns but one were referred for general seizures. All mothers but one wore the veil (3 wore integral veil). None of the mothers had a known calcium metabolism disorder. All newborns but one had severe hypocalcaemia (<60 mg/l). The evaluation of the mothers revealed:

- Severe Vitamin D deficiency in 4 mothers, one of them had an asymptomatic hypocalcaemia
- Unknown maternal hyperparathyroidism due to parathyroid adenoma in 2 mothers (one had two children).

All patients were given calcium supplements and alfacalcidol. Evolution was favorable for all of them.

Conclusions: Testing for calcium metabolism and Vitamin D status during pregnancy should be mandatory. It would allow to detect rare cases of asymptomatic maternal hyperparathyroidism, and especially to screen for Vitamin D deficiency. Recent publications have reported the increasing frequency of maternal Vitamin D deficiency in Muslim countries. Therefore, we suggest that vitamin D supplementation should be systematically considered after proper screening in those countries.

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Bone mass and quality in juvenile systemic lupus erythematosus (JSLE)

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Introduction: There are few data on bone mass and quality in patients with Juvenile Systemic Lupus Erythematosus (JSLE). However, there are few data comparing bone mass and quality determinants using dual energy X-ray absorptiometry (DXA), peripheral quantitative computed tomography (pQCT), and quantitative ultrasound (QUS) in JSLE.

Design: To evaluate, through a cross-sectional and longitudinal study, bone mass and quality determinants in JSLE young adolescent and adults, and to assess the prevalence and to identify the main predictors of reduced Bone Mineral Density (BMD) and bone quality using these techniques.

Methods: Fifty-six JSLE patients (46 females, 10 males, mean age 21.5 +/- 6.1 years) were evaluated. In all subjects DXA scan at the lumbar spine, radius pQCT, and phalangeal QUS were performed. Of these, forty-six consecutive females with JSLE were followed-up longitudinally with a second DXA, pQCT and QUS evaluation. The data obtained were compared with 80 ages- and sex-matched healthy subjects.

Results: JSLE patients showed a reduced spine BMAD SDS (p < 0.001), TrabBMD (p < 0.0001), Muscle CSA (p < 0.005), SSIp (p < 0.05), AD-SoS (p < 0.05), and QUS z-score (p < 0.005), but not CortBMD and CBA respect to controls. However, fat CSA were significantly increased (p < 0.0001). These data were confirmed in longitudinal evaluation. SSIp longitudinal evaluation showed that JSLE patients presented no more significantly lower levels than controls.

Conclusions: Patients with JSLE have a low bone mass, not reaching the normal condition over time despite the current more effective drugs, with the high risk of osteoporosis in early adulthood. To reduce the risk, a close monitoring of BMD, a better control of disease activity, physical activity, and a dietary intake of calcium and vitamin D are advocated to ameliorate the bone mass.

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A novel de-novo mutation of PHEX gene in a patient with X-linked hypophosphataemic rickets with severe bone lesions

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Background: X-linked Hypophosphatemic Rickets (XLHR) is the most common familial form of HR, caused by inactivating mutations of the PHEX gene (Phosphate-regulating gene with Homologies to Endopeptidases on the X chromosome), which encodes a zinc-dependent endopeptidase involved in bone mineralization and renal phosphate reabsorption.

Objective and hypotheses: Case report of a 2-year old female referred to us for a dwarfism due to XLHR, initially misdiagnosed as impaired growth caused by interventricular defects.

Methods: Gene analysis was performed by extraction of genomic DNA and total RNA from leukocytes. The PHEX gene was amplified from DNA by PCR and analyzed by Denaturating High Performance Chromatography (WAVE-MD, Transgenic) and the amplicons were directly sequenced by 3130xl Genetic Analyzer (Applied Biosystems).

Results: We report on a female with XLHR harboring a novel heterozygous duplication of 5 nucleotides (c.2049_22053dupCTTCT, Ensembl Gene ID ENSG00000102174) at exon 20 of gene PHEX, which leads to a stop codon and gives rise possibly to a truncated PHEX protein. Physical examination at time of diagnosis showed severe disproportionate short stature, enlarged wrists, knocked knees and bowed legs. Radiographs of wrists and legs showed the classical rickets bone changes. Laboratory evaluation revealed normal serum calcium levels, hypophosphatemia, low 1,25(OH)2D3, low alkaline phosphatase activity and phosphaturia. For 18 months the child has been being treated with phosphate supplements and calcitriol with a slight normalization of biochemical parameters but without improvement in clinical signs. DNA analyses of all family members were normal Conclusions: We report a novel nonsense mutation of PHEX gene, gaining an insight into the molecular genetic of this disorder. This case report emphasizes the importance of early diagnosis and treatment in order to improve bone growth and skeletal deformities. PHEX gene mutation could be useful for prognosis even if the timing of treatment may have a key role in improving bone lesions.

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Vitamin D deficiency in children with cerebral palsy: what kind of a problem?

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Background: Children with cerebral palsy (CP) have risks for vitamin D deficiency.

Aim: Aimed to make the child neurology and emergency units be more alert in case children with CP are presented with seizures apart from attributed to known CP.

Methods: Mean age 10.2 ± 5.0 years 94% girls of 29 patients with CP evaluated as vitamin D deficiency. Vitamin D status defined according to serum 25OHDL levels as insufficiency, deficiency and severe deficiency, respectively (25OHDL<20, 15-20 and <5 ng/ml). Rickets diagnosed based on the clinical and biochemical parameters.

Results: Mean diagnosis age of CP was 13 ± 1.6 month. Sixty percent of 23 patients who used anti epileptic treatment were given nonenzyme-inducing drugs. Anthropometric data showed many of patients were underweight (75%...
of patients weight z score < -2.5 and %50 BMI z score <-2.5. Vitamin D insufficiency, deficiency and severe deficiency found in 59% (n = 17) of patients, respectively [%57, %38, %4]. Eleven patient (38%) diagnosed as rickets, 7% of them had osteomalacia. Secondary hyperparathyroidism (iPTH=65 pg/ml) was observed in 24%. Two patients with rickets whose weight z score -5.3 and -2.4 had hypocalcemia (serum Ca 7.4 -6.3 mg/dl) and seconder hyperparathyroidism (iPTH 178,174 pg/ml), although their serum ALP levels were normal and this were explained due to malnutrition.

Conclusions: • It is shown that one of five children with CP had rickets and every quarter had seconder hyperparathyroidism in which effects bone health adversely.  
  • We recommend at least 400 U/day and if necessary a higher dose vitamin D supplementation and closely monitored for vitamin D deficiency &hypocalcaemia should not be overlooked.

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Vitamin D status in obese children and adolescents
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Background: Some reports have indicated that vitamin D level is inversely associated with obesity.

Objective: To assess the association between vitamin D status and obesity in our region (latitude: 40 N).

Population and methods: We measured serum levels of 25-hydroxyvitamin D [25(OH)D3], parathyroid hormone (PTH), alkaline phosphatase (AP), calcium, and phosphorus of 66 obese children (girls/boys: 40/26), aged 11-18 years. We classified vitamin D status as deficient [25(OH)D3 levels <10 µg/l], insufficient [25(OH)D3 10-29,9 µg/l], or sufficient [25(OH)D3 ≥30 µg/l]. We obtained anthropometric variables and blood samples at the end of the winter (spring, girls/boys: 22/18) and at the end of the summer (autumn, girls/boys: 18/6). The control group consisted of healthy peers (n=746).

Results: The mean age, body mass index (BMI) and 25(OH)D3 levels of the obese children were 14.3±1.9 yr, 29.5±4.1 kg/m2, and 11.9±6.7 µg/l, respectively. There was no difference between the obese girls and boys in terms of the vitamin D levels. In the obese children and the controls, 25(OH) D3 levels were 10.7±7.4 µg/l vs 11.5±5.6 µg/l in spring (p=0.05) and 13.8±5.1 µg/l vs 16.3±7.9 µg/l in autumn (p=0.05).

There was a negative correlation between vitamin D and PTH levels in both obese children and controls (p<0.01). Vitamin D levels were significantly lower in obese children than those with BMI<25 (p=0.01). Vitamin D levels were significantly higher in autumn (16.2±4.3 µg/l) than spring (11.4±3.9 µg/l) in boys (p<0.05).

In the obese children and controls, the frequencies of vitamin D deficiency and insufficiency were 63% vs 49% and 27% vs 51%, respectively in spring; and 63% vs 49% and 27% vs 51% in autumn.

Vitamin D levels were lower in obese children than those with BMI<25 (p=0.01). Vitamin D levels were significantly lower in obese children than those with BMI<25 (p=0.01). Vitamin D levels were significantly lower in obese children than those with BMI<25 (p=0.01). Vitamin D levels were significantly lower in obese children than those with BMI<25 (p=0.01). Vitamin D levels were significantly lower in obese children than those with BMI<25 (p=0.01). Vitamin D levels were significantly lower in obese children than those with BMI<25 (p=0.01). Vitamin D levels were significantly lower in obese children than those with BMI<25 (p=0.01). Vitamin D levels were significantly lower in obese children than those with BMI<25 (p=0.01). Vitamin D levels were significantly lower in obese children than those with BMI<25 (p=0.01). Vitamin D levels were significantly lower in obese children than those with BMI<25 (p=0.01). Vitamin D levels were significantly lower in obese children than those with BMI<25 (p=0.01). Vitamin D levels were significantly lower in obese children than those with BMI<25 (p=0.01). Vitamin D levels were significantly lower in obese children than those with BMI<25 (p=0.01). Vitamin D levels were significantly lower in obese children than those with BMI<25 (p=0.01). Vitamin D levels were significantly lower in obese children than those with BMI<25 (p=0.01). Vitamin D levels were significantly lower in obese children than those with BMI<25 (p=0.01).

Conclusion: Vitamin D levels were lower in obese children than those healthy controls. The present study confirmed that obesity was a risk factor for vitamin D deficiency. Our results indicate that vitamin D supplementation is necessary for obese children with a higher dosage in winter time.

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Continuous glucose monitoring, oral glucose tolerance, and insulin – glucose parameters in adolescents with simple obesity
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Background: In obese children pancreatic beta-cells may not be able to cope with insulin resistance leading to hyperglycemia and type2 diabetes (T2DM).

Objectives: To assess oral glucose tolerance, 72-h continuous blood glucose concentrations (CGM) and calculate homeostatic model assessment (HOMA), and the quantitative insulin sensitivity check index (QUICKI) in 13 children and adolescents with simple obesity (BMI<SDS ≥ 4 ± 1.06).

Subjects and methods: The study was conducted on thirteen obese adolescents with BMISDS > 2SD. A standard OGTT was performed (1.75 g of glucose solution/kilogram body weight to a maximum of 75 g). The CGMS sensor was inserted subcutaneously and interstitial fluid (ISF) glucose levels were measured by the glucose oxidase reaction for 24 hours. Insulin resistance was estimated by homeostatic model assessment (HOMA) and QUICKI (quantitative insulin sensitivity check index) was calculated.

Results: OGTT performed in 13 obese adolescents (13.9 ± 2.2 years) revealed 3 cases (23%) with IFG (> 5.6 mmol/L), 4 cases (30%) with IGT (> 7.8 < 11.1 mmol/L), and none with diabetes. Using the CGMS, IFT was detected in 4 cases, the maximum BG (2h or more after meal) was > 7.8 and < 11.1 mmol/L (IGT) in 9 children (69%) and ≥ 11.1 mmol/L (diabetes) in one case (7.6%). Five cases had a minimum BG recorded of < 2.7 mmol/L (hypoglycemia). No glycemic abnormality was detected using HbA1C (5.7± 0.3 %). 11/13 patients had HOMA values > 2.6 and QUICKI values > 0.35 denoting insulin resistance. Beta cell mass percent (B %) = 200 - 94.8 % and insulin sensitivity (IS) = 50.4 ± 45.5% denoting insulin resistance with hyper-insulinemia and preserved beta cell mass.

Conclusion: In obese children and adolescents; CGMS is superior to OGTT and HbA1C in detection of the glycemic abnormalities, which appears to be secondary to insulin resistance.
Clinical spectrum and outcome of pandemic influenza A (H1N1) virus in diabetic pediatric population

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Background: The 2009 H1N1 Influenza virus was the first infectious pandemic of the 21st century which spread rapidly throughout the world.

Aim: This is observational study of cases admitted to pediatric hospital, Ain Shams University in 2011 with suspected influenza A (H1N1) virus infection.

Methods: We investigated clinical characteristics, rate of virus identification and complications with special interest in those developing diabetes and in known diabetic children. Patients were tested for H1N1 virus on pharyngeal brush/nasal aspirates, using a RT-PCR assay to confirm infection.

Results: Ninety three cases admitted suffered from influenza H1N1 like symptoms among the diabetic group of which thirty patients (32.2%) H1N1 viral RNA was detected in their nasopharyngeal specimens. The mean age of this group was 9.94 ± 4.06 years, 73.3% were males. The most common symptoms were: flue (57.8%), gastrointestinal (22.2%) and neurological manifestation (20%). Overall, 14 patients were newly diagnosed; five (16.6%) children presented with ketoacidosis (DKA) while nine (30%) had diabetic ketoacidosis (DK) as the onset manifestation of type 1 diabetes. For the known diabetic patients (11.68%) presented with DK while 2 presented with DKA (12.5%). All patients received oseltamivir, but eventually the mortality rate was 3.3% (one newly diagnosed) where H1N1 infection was associated with severe DKA at presentation. Abnormalities in chest radiography were detected in 43.9%, lymphopenia in 65.6%, and high C-reactive protein in 58.4%. Independent risk factors for RT-PCR positivity included high HbA1c and low lymphocytic count (P = 0.001 and 0.021 respectively).

Conclusion: Clinicians should be aware of complications of H1N1 virus infection, particularly in patients with risk factors. H1N1 virus seems in some way involved in the pathogenesis of type 1 diabetes. Rapid diagnosis of influenza by RT-PCR and early treatment with oseltamivir should be considered in diabetics and/or DKA patients with flu-like symptoms.

Insulin secretion and its association with physical activity, fitness and sedentary behavior in children

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Background: Understanding the association of moderate to vigorous physical activity (MVPA), fitness and sedentary behavior (SB) on insulin secretion (ISct), beyond their association to insulin sensitivity (IS), is essential to developing effective preventive strategies against type 2 diabetes in youth.

Objective and hypotheses: Determine the cross-sectional independent associations of MVPA, fitness and SB to ISct.

Methods: Caucasian youth (n=630) aged 8 to 10 years, with at least one obese biological parent, were studied (QUALITY cohort). Fasting ISct was measured using HOMA2%-beta; 1st-phase secretion by AUC I/Gt120min and 2nd-phase secretion by AUC I/Gt120min over 2h. Fitness was measured by VO2peak, percent fat mass (PFM) by DXA and 7-day MVPA using accelerometry. SB indicators included average hours daily of self-report screen time (SBst), and average minutes daily at <100 counts/minute from accelerometry (SBt). Multivariable linear regression models were adjusted for age, sex, season, puberty and IS. The association between ISct and IS was modeled using non-parametric smoothing splines.

Results: In multivariable models, PFM was strongly associated with ISct: for every 1% increase in PFM, ISct increased from 0.3 to 0.88% across indices. MVPA was negatively associated with HOMA2%-beta (p<0.05), but not with OGTT-derived ISct measures. Fitness was negatively associated with AUC I/Gt120min (p=0.05) with SBst in the model, p=0.07 with SBacc in model. Fitness was not associated with HOMA2%-beta or AUC I/Gt120min, SBst showed a trend to be positively associated with HOMA2%-beta in girls (p=0.061).

Conclusions: In children with an obese parent, lower ISct requirements are associated with lower adiposity, higher MVPA (faster ISct), better fitness (2d phase secretion) and possibly reduced SBst (faster ISct). Strategies targeting these lifestyle factors might prove beneficial to the prevention of type 2 diabetes in youth.

Transition to adult diabetes care - results from the DPV database

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Background: Transition from pediatric to adult diabetes care still remains an issue especially regarding dropout of medical treatment. Only few data are available from patients that are followed after transition to adult treatment centers. Controversial data are reported about metabolic control and acute complications like hypoglycemia and ketoacidosis during and after the transition process.

Methods: The German DPV database (Diabetes Patienten Verlaufsbeobach- tung) accumulates data form pediatric and adult diabetes treatment centers (370 centers). These data allow to analyse a subgroup of patients that were treated in pediatric centers and were transferred to adult clinics. We analysed all available patients 2 years prior and 2 years after transition regarding metabolic control, documented acute complications and microvascular complications.

Results: We found 775 patients that where followed at least 2 years prior and 2 years after transition. Mean diabetes duration at transition was 5.6 years. HbA1c 1 year before transition was 8.4±1.86% and 8.5±1.88%. However, the rate of severe hypoglycemia with (5.40±2.5 vs. 7.73±1.6) and without coma (41.5±9.1 vs. 21.5±5.2) was more frequent after transition. There was a more than 20% increase in usage of short and long acting analogues in adult treatment. Patients injected insulin more frequent after transition to adult centers (5.5±2.2/d vs. 5.1±1.9/d) Lipid lowering drugs and antihypertensive medication also increased after transition. Only a slight increase in microvascular complications was noted in the 2 years of follow up.

Conclusion: Our data show a large group of patients followed a long time in pediatric and at least two years in adult treatment. 2 years after transition we could find a slight increase in HbA1c and rate of sever hypoglycaemia. Treatment was intensified not only regarding insulin but also regarding complications.

Incidence of type 1 diabetes mellitus (T1DM) in children in Russian Federation within the years 2001-2010

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Background: The incidence of type 1 diabetes mellitus (DM1) annually increases in children’s population both in the world and in Russian Federation (RF). The territory of RF is large and submitted by 8 Federal districts (FD): Northwest (NWD), Central (CD), Volga (VD), North Caucasus (NCD), South (SD), Ural (UD), Siberia (SD), Far East (FED), where live more than 100 nationalities.

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Objective and hypotheses: The aim of this study was to estimate the incidence of T1DM among the children’s population of RF within 2001-2010 years.

Methods: The incidence was studied at children with T1DM during the period 2001-2010 years. The information was received from National Register of DM and annual statistical reports from regional endocrinologists. The incidence was calculated on 100.000 the children’s population. The confidential interval was 95%. The age standardized incidence rates were obtained using the direct method with a standard population consisting of equal members of children in each of three subgroups defined by age (0-4, 5-9 and 10-14 years of age).

Results: On 01.01.2011 year there were 17519 children with T1DM, 2911 of them were new diagnosed. During 2001-2010 years the average incidence of T1DM among children in RF was 10,74 (95% CI : 10.08 -11.4) on 100000 children’s population. The average annual gain of incidence is 2.7 %. Age standardized incidence rate was 10.86 (95% CI: 10.02-11.6) on 100000 children’s population. Significant distinctions in incidence level were marked between FD, located in various geographically-defined areas of RF. The maximum incidence level constantly registered in NW: 15.39/100000 (in 2010 year). Incidence rate was considerably below in SD: 6.89/100000 (in 2010 year).

Conclusions: In 2001-2010 years the average and standardized incidence of T1DM are increased in children’s population in RF. Annual incidence gain is 2.7%. The decrease of incidence was observed in a direction from north on a south of RF.

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Care of children newly diagnosed with type 1 diabetes: a survey of UK paediatricians
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Background: The DCCT study showed that patients managed with intensive insulin regimens and support achieved better clinical outcomes than those managed on conventional regimen. A UK wide survey in 2005 showed that majority of paediatric diabetes teams (92%) managed children newly diagnosed with type 1 diabetes on conventional twice daily regimen. No team in that survey offered continuous subcutaneous insulin infusion at diagnosis. In 2011, we carried out a UK wide survey in order to document current practice.

Methods: Data was collected in 2011 using email questionnaires sent to Paediatricians and paediatric diabetes nurse specialists (PDSN) working in 173 hospitals across the United Kingdom (UK). They were identified from database held by the Association of Children’s Diabetes Clinicians (ACDC), UK.

Data was analysed using Minitab® (Minitab Inc., USA) and compared to the 2005 survey.

Results: 80/173 (46%) teams responded. The most popular insulin initiation dose was 0.5units/kg/day (57.5%). 87.5% of teams now offer basal bolus regimen at diagnosis with 11.3% offering continuous subcutaneous insulin infusion to children aged less than 3 years at diagnosis. There was no significant difference between teams working in tertiary hospitals compared to secondary care hospitals in the choice of insulin regimen or dose of insulin at initiation (p>0.05). Compared to results of 2005 survey, staffing had improved, with mean patients per PDSN of 89 (2005: 103), with 53 (66%) centers having a ratio of < 100 (2005: 45%).

Conclusion: Majority of UK teams now offer intensive insulin regimen at diagnosis. Results of the National Diabetes audit will be used to study whether this has led to improved outcomes.

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Early postnatal growth in children with HLA-conferred susceptibility to type 1 diabetes
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Background: The role of HLA haplotypes conferring risk for type 1 diabetes (T1D) in the association between T1D and increased linear growth is unclear.

Objective and hypotheses: To study early linear growth in children with different HLA haplotypes conferring risk for T1D in two countries with a three-fold difference in the incidence of T1D. We hypothesize that the association between increased linear growth and HLA risk haplotypes is stronger in the country with higher incidence of T1D.

Methods: The linear growth in 425 children with HLA haplotypes conferring increased risk for T1D in Estonia and Finland was monitored at the age of 3, 6, 12, 18, and 24 months. Length SD score (SDS) for age and sex was assessed using the WHO growth reference data. According to their HLA haplotypes the participants were divided into three risk groups for T1D. The linear growth in 425 children with HLA haplotypes conferring risk for type 1 diabetes mellitus (DM1).

Results: Mean height SDS at 18 and 24 months was significantly lower in the high-risk group compared with the moderate-risk group (0.01, 95% CI: 0.4;0.4 vs. 0.4, 95% CI 0.2;0.5; p=0.001 and -0.2, 95% CI -0.6;0.2 vs. 0.3, 95% CI 0.1;0.5; p=0.002 respectively) and at 24 months also lower than in the low-risk group (-0.2, 95% CI -0.6;0.2 vs. 0.3, 95% CI 0.2;0.5; p=0.004). When Estonian and Finnish cohorts were analysed separately similar trends were observed but there was a statistically significant difference remained only in the Estonian cohort at the age of 24 months.

Conclusions: Contrary to our hypothesis children with HLA haplotypes conferring the highest risk for T1D had the slowest linear growth during their first 24 months. The absence of any difference in growth pattern between these two countries suggests that HLA itself rather than the environment may play the primary role in the observed association.
Background: Health-related quality of life (HRQOL) is an important health outcome and a well-known indicator of the long-term consequences of chronic diseases that affect the quality of life (QOL).

Objective and hypotheses: Aim of our study was to investigate general and HRQOL of children with type 1 diabetes (T1DM) and subjects with coeliac disease (CD) compared to healthy controls.

Methods: We studied 101 outpatients: 35 children with T1DM (12.8±2.85 yr, duration of T1DM 60.5±33.4 months), 32 subjects with CD (9.60±2.61 yr, duration of CD 52.0±47.9 months), and 34 controls children matched for age and sex. All subjects were assessed using the Paediatric Quality of Life Inventory (PedsQL) GENERIC Core Scales to measure HRQOL with 23 items included in 4 scales.

Results: T1DM patients showed a satisfactory metabolic control HbA1c (8.06±0.75%). Twenty-one out of 32 CD subjects showed a strict dietetic control. We demonstrated that social functioning (fx), school fx, psychosocial health fx, and total scale were significantly different between groups; the major concern was related to emotional fx (Table. Kruskal-Wallis ANOVA; * vs. controls; " vs. T1DM).

Conclusions: Our results demonstrate that children and adolescents with chronic disease, despite a good adherence to therapy, have impairment in psychosocial health fx. Our data disagree with common opinion that children with CD have a better adaptation and functioning. These findings contribute significant information on the effects of pediatric chronic conditions on generic QOL from the perspectives of children. It is conceivable that a multidisciplinary approach to patients with T1DM can be responsible for this differences.

<table>
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<th>T1DM</th>
<th>CD</th>
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<td>Physical Health fx</td>
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<td>73.0±11.7&quot;&quot;</td>
<td>83.2±22.2</td>
<td>0.94</td>
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</tr>
<tr>
<td>Total scale</td>
<td>77.9±11.7&quot;&quot;</td>
<td>74.5±11.9&quot;&quot;</td>
<td>83.9±15.8</td>
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**P2-d1-495** Diabetes and Insulin 3

**Increased ischaemia-modified albumin levels in children with diabetic ketoacidosis**

**Mehtem Emin Atabek; Nazli Alptekin; Beray Selver Ekloglu; Sevil Kurbani**

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**Background:** During acute ischemic conditions, the metal-binding capacity of albumin to transition metals is reduced, leading to the generation of a metallo-variant of the protein, commonly known as ischaemia-modified albumin (IMA). Most studies agree that IMA starts to increase within minutes of the onset of ischaemia. It is known ischaemia and myocardial cell damage occur in diabetic ketoacidosis (DKA).

**Objective:** In our previous study, we have shown that cardiac troponin I, known as a marker of myocardial ischaemia, was elevated in children with DKA. The aim of the present study was to determine the IMA levels, known as a sensitive marker for the diagnosis of myocardial ischaemia in children with DKA.

**Methods:** The study included 33 diabetic children with DKA (13 males and 20 females; mean age 8.62± 4.70 years) and 33 healthy controls (10 males and 23 females; mean age 7.92±4.55 years). IMA levels were measured on admission and after 24 hours in diabetic patients and compared with controls.

**Results:** The diabetic children had significantly higher IMA values than the controls on admission and 24 hours later (0.780±0.198 vs 0.425± 0.076; p<0.001) and (0.485±0.159 vs 0.425 ± 0.076; p=0.01) respectively. Also the difference of IMA values on admission and 24 h later significantly different in diabetic children (0.780±0.198 vs 0.485±0.159; p=0.04). Although IMA levels inversely correlated with blood pH, it wasn’t statistically significant.

**Conclusions:** According to our findings, IMA levels elevated in children with DKA. We suggested that IMA may be marker of myocardial ischaemia in DKA.

**P2-d1-497** Diabetes and Insulin 3

**Increased sonic hedgehog signaling and regeneration in pancreases of carboxyl-ester lipase MODY patients**

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**Background:** Carboxyl-ester lipase (CEL)-MODY (maturity-onset diabetes of the young type 8, MODY8) is a human monogenic disease model of pancreatic beta cell failure and exocrine dysfunction characterized by severely defective insulin secretion (Raeder, Nat Gen, 2006 and Raeder, Diabetes, 2007). The mechanism(s) for beta cell failure is however unknown. Sonic hedgehog (SHH) signaling and beta cell dysfunction was recently linked in an animal model (Landsman et al, PNAS, 2011).

**Objective and hypotheses:** Define signaling features involved in the disease mechanism in CEL-MODY.

**Methods:** We used immunohistochemistry to examine pancreatic tissue from two MODY8 patients; one autopsied pancreas and one specimen from a non-tumoral pancreas of a patient undergoing surgery for pancreatic ductal adenocarcinoma.

**Results:** We show that in CEL-MODY patients acinar tissue is replaced by fat and fibrous tissue infiltrated by leucocytes and the remaining acinar cells display features of endoplasmic reticulum stress. The islets have irregular shape but show no evidence of apoptosis or proliferation. The ductal compartment is expanded and contains metaplastic duct cells, which display various regenerative features including positive staining for Ki67 (proliferation), insulin (neogenesis of beta cells in ducts) and SIHH (regeneration). The SHH+ cells surrounding insulin+ cells suggest paracrine signaling.

**Conclusions:** In conclusion, our data implicate a pancreatic injury model with regeneration and sonic hedgehog signaling in CEL-MODY patients.
Clinical presentation of Maturity-onset diabetes of the young (MODY) 2 in children and adolescents - single centre observations

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Background: MODY 2 is the most common monogenic subtype of diabetes mellitus (DM) in Caucasian population characterized by an autosomal dominant inheritance with high penetrance. Because of its asymptomatic course and omitting data from family history, MODY 2 is mistakenly diagnosed as Type 1 or Type 2 DM at first.

Objective and hypotheses: To analyze clinical features of children and adolescents with genetically confirmed mutation of glucokinase (GCK) characterized MODY 2.

Methods: Twenty one patients (pts): 9 girls and 12 boys 3.8 - 18.3 years old, mean 13.1 years with MODY 2 treated in our diabetic centre were included into the study during 2011 year. Retrospective analysis of clinical data was performed.

Results: Pts with MODY 2 constituted 3% of all DM pts in our center. All were asymptomatic. Before MODY diagnosis 8 pts (38%) had an impaired fasting glucose (IFG), 6 (29%) had DM diagnosed on the basis of an oral glucose tolerance test, 5 (24%) had an IFG and an impaired glucose tolerance, and 2 (10%) had no data. Five pts (24%) were treated with daily insulin < 0.5 U/kg b.w, one of them additionally with metformin. 14 (67%) with diabetic diet, and 4 (19%) did not receive any treatment. Sixteen pts (76%) had detected GCK mutation as first members of own families. Only one patient (5%) was obese and had positive autoantibodies typical for DM at diagnosis and negative two years later when his body mass was normalized. All had normal C-peptide levels and never presented diabetic ketoacidosis. All pts had family history of DM, most in previous two generations. After MODY 2 diagnosis diabetes diet and physical activity were recommended to all pts. HbA1c levels during the treatment period varied between 5.7–7.5%, (mean 6.3%). Any diabetes complications, autoimmune diseases, and additional abnormalities were observed in presented pts.

Conclusions: MODY 2 is a rare type of DM diagnosed mostly in non-obese in children and adolescents with IFG and positive family history. Results of its treatment only with the lifestyle modification are good.

Metabolic control with insulin pump therapy in Spanish children and adolescents with type 1 diabetes

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Background: Insulin pump therapy has been shown to be beneficial in pediatric patients with type 1 diabetes (T1D).

Objective and hypotheses: To report the effect of continuous subcutaneous insulin infusion (CSII) on glycemic control, severe hypoglycemia (SH) and diabetic ketoacidosis (KA) rates in prepubertal and pubertal patients with T1D.

Methods: Data of 78 children (29 prepubertal/42% males, 49 pubertal/48% males) treated with CSII in our pediatric diabetic unit from 2001. Hba1c (HPLC-Menarini 5.3±0.4%), insulin requirements (U/kg/day), number of basal rates, SMBG per day, SH and KA rates were collected at baseline, 1/12/24/36 and 48 months. Statistical analysis: SPSS program 20.0. Data expressed in percentage, mean±SD, median and interquartile range.

Results: Mean age at CSII: 11.36±4.9 years. Diabetes duration: 5±3.4 years. Average CSII duration: 3.1±1.6 years. Hba1c at onset of CSII: prepubertal 6.8% (6.4-7.6) and pubertal 7% (6.4-7.5). Both groups improved Hba1c during first year (prepubertal 0.1% and pubertal 0.2%). This good metabolic control controls persist in the remaining years. The insulin dose decreased significantly in both groups during the 4 years follow-up, without significant differences between groups. Incidence of SH in prepubertal patients: 6/9 events/100 patient-year; prepubertal patients 0.5% and pubertal (2%). This direct relationship between HbA1c improvement and SMBG/day (p=0.026) but not between basal rate and HbA1c.

Conclusions: CSII is an effective and safe therapy in children and adolescents with T1D. Glycemic targets can be achieved with low incidence of acute complications.

The relationship between insulin resistance and IL-6 and TNF-α levels in LGA born children in prepubertal period

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Background: It has been shown that there is a risk of insulin resistance in large for gestational age (LGA) born children even in childhood. Adipocytokines, that are affecting insulin sensitivity, are thought to be the markers of metabolic impairment in childhood.

Objective and hypotheses: We aimed to evaluate the insulin resistance and the relationship between insulin sensitivity and IL-6 and TNF-α in LGA born children in prepubertal ages.

Methods: Forty (19 female,21 male) LGA born prepubertal children (mean age 6.1±2.5 years) were evaluated with respect to glucose, insulin, TNF-α, IL-6 levels. Their data were compared to that of prepubertal 49 (25 female,24 male) appropriate for gestational age (AGA) children (mean age 5.4±1.8 years).

Results: LGA children were taller, heavier than AGA children but had similar body mass index (BMI) SDS , waist/hip circumference ratio as AGA born children. There were no significant differences in glucose(G), insulin(I) levels, G/I ratio, I/G ratio, quantitative insulin sensitivity check index (QUICKI) and homeostasis model assessment-insulin resistance (HOMA-IR) between children born LGA and AGA. TNF-α levels were lower and IL-6 levels were higher in children born LGA than AGA(p<0.000 for both). Univariate variance analysis revealed that the being born LGA and having a higher HOMA-IR(higher than 2.5) had significant interaction and was associated with a lower TNF-α level.

Conclusions: Increased IL-6 and decreased TNF-α levels in LGA born children in prepubertal ages points to a decreased insulin sensitivity in this group of children even in the absence of obesity. The close relationship between TNF-α levels and HOMA-IR shows that these cytokines might have a role in the development of insulin resistance.

High phenotype variability in Czech patients with MODY5 (Renal Cysts and Diabetes syndrome)

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Background: The RCAD (Renal Cysts and Diabetes) syndrome (MODY5) is caused by heterozygous mutations in the HNF1B gene leading to developmental kidney damage combined with diabetes mellitus.

Patients and methods: The HNF1B gene was investigated by direct sequencing and MLPA in A) 104 Czech patients (median age 16 years) with various cystic kidney diseases B) two patients with RCAD (aged 17 and 53 years) and C) 30 patients with MODYX (without nondiabetic kidney disease, without metabolic impairment in childhood). Their data were compared to that of prepubertal 49 (25 female,24 male) appropriate for gestational age (AGA) children. There were no significant differences in glucose(G), insulin(I) levels, G/I ratio, I/G ratio, quantitative insulin sensitivity check index (QUICKI) and homeostasis model assessment-insulin resistance (HOMA-IR) between children born LGA and AGA. TNF-α levels were lower and IL-6 levels were higher in children born LGA than AGA(p<0.000 for both). Univariate variance analysis revealed that the being born LGA and having a higher HOMA-IR(higher than 2.5) had significant interaction and was associated with a lower TNF-α level.

Conclusions: Increased IL-6 and decreased TNF-α levels in LGA born children in prepubertal ages points to a decreased insulin sensitivity in this group of children even in the absence of obesity. The close relationship between TNF-α levels and HOMA-IR shows that these cytokines might have a role in the development of insulin resistance.
hormone therapy, and impaired glucose tolerance was disclosed in a 10-year-old girl. Both patients with RCAD have whole-gene deletion and developed serious spontaneous hypomagnesemia as a sign of the RCAD. In a 25-year-old patient treated with insulin from 17 years (one out of 30 patients with MODYX) and her mother with diabetes was found novel mutation R235W.

**Conclusion:** Genetic investigation of HNF1B gene identified first Czech patients with various clinical phenotype: from patients with diabetes only, patients having the combination of diabetes with cystic kidney disease and hypomagnesemia to children having end-stage renal disease based on cystic kidney disease without diabetes. In contrast to other MODY genes is HNF1B gene mutations difficult to predict progress of the disease and ideal treatment.

**P2-d1-502 Diabetes and Insulin 3**

**Frequency of peripheral neuropathy in children with insulin-dependent diabetes**

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**Background:** Aim of prospective research was to establish, during the period of 4 years, the frequency of peripheral neuropathy in 57 children, 8–18 years old, who have diabetes mellitus type 1.

**Objective and hypotheses:** A possible pathogenetic mechanism of appearance of diabetic neuropathy is consequence of insulin and C-peptide deficit which correlates with the earlier influence of oxygen radicals due to nerves ischemia, and with oxidation and phosphorylation disorder which disrupts interaction of build units of axion myelin membrane.

**Methods:** The subjects were divided in two groups, those who perform in intense physical activity which includes intensified legs work and children who do not train a sport. The obtained results were based on neurological examination and on velocity of nervous implementation on median, which were conducted at the beginning of the research, and after two or four years.

**Results:** 20.05% children had pathologically changed velocity of nervous implementation after two years and 38.61% children had it after four years. Loss of sense of polyneuropathic type (distribution shaped as “gloves and socks”) was established in 8.35% subjects after two years and in 29.40% after four years but with a smaller percentage of damaged postural reflexes. The dominant clinical symptom were paresthesias in almost 90% of children. 75.83% of total number of children who showed signs of peripheral neuropathy were from the group of athlete children and only in 2.5% of them appeared syndrome of painful claudications of upper leg muscles.

**Conclusions:** In those subjects which were under higher body load it is possible that an increased release of damaged products of muscle work occurred; which in turn resulted in toxic effect on myelin membrane. Also, almost 90% of those with signs of peripheral neuropathy have illness duration longer than 7 years, while in only 5.91% of subject retinopathy was proven, nephropathy in 23.3% and higher blood pressure in 1.8% of the subjects examined.

**P2-d1-503 Diabetes and Insulin 3**

**Associations between glycaemic control and social family factors in children, adolescents and young adults with type 1 diabetes**

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2Charité - Universitätsmedizin Berlin, Institute for Biometrics and Clinical Epidemiology, Berlin, Germany.

**Background:** Achieving good glycaemic control in type 1 diabetes is crucial in order to prevent microvascular and macrovascular complications. Demographic and psychosocial factors are known to have a major impact on glycaemic control.

**Objective and hypotheses:** Aim was to evaluate the relationship between glycaemic control and social family variables in children, adolescents and young adults with type 1 diabetes.

**Methods:** A total of 222 children, adolescents and young adults with type 1 diabetes up to the age of 21 years participated in the cross-sectional study. Self-report questionnaires were used to assess social and family variables. Clinical data and HbA1c levels were collected during outpatient clinic visits. Risk factors were analysed by linear regression.

**Results:** Mean age of the study participants was 12.6±4.1 years, mean diabetes duration was 5.8±3.3 years, and mean HbA1c level was 8.4±1.4%. High socioeconomic status was significantly associated with better glycaemic control whereas middle and low socioeconomic status was associated with poor glycaemic control (HbA1c 8.0±1.0% vs 8.5±1.4% and 8.9±1.7%; p=0.006 and p=0.001). Glycaemic control was significantly better in subjects from one-child families compared to families with more than two children (HbA1c 8.2±1.4% vs 9.1±1.6%, p=0.011) as well as in subjects from two-parent families compared to single-parent families (HbA1c 8.3±1.4% vs 8.9±1.5%; p=0.002). In children and adolescents with younger mothers HbA1c levels were significantly higher compared to those children with mothers of higher age (p=0.033). Linear regression analysis identified longer diabetes duration, low socioeconomic status, and single-parent status as risk factors for poor glycaemic control.

**Conclusions:** Diabetes duration, socioeconomic status, and family status are significant risk factors for glycaemic control.

**P2-d1-504 Diabetes and Insulin 3**

**Thiamine resolved anaemia and improved diabetes control in a child with SLC19A2 (S143F) gene mutation**

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Sian Elbard2, Abdelrah M Habe2
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**Background:** Mutations in the thiamine transporter gene SLC19A2 are associated with a triad of early onset diabetes, anaemia and deafness which is referred to as Thiamine Responsive Megaloblastic Anaemia (TRMA) or Roger's syndrome.

**Aim:** To report a child with neonatal diabetes and deafness in whom anaemia was not megaloblastic and to describe our experience of thiamine therapy in this child.

**Methods:** The child had phenotypic, laboratory assessment including sequencing of SLC19A2 gene. The response to thiamine therapy was monitored over 18 month period.

**Results:** The girl was referred at 13 months with anaemia started at 4 weeks old and required multiple transfusions. She developed diabetes at 6 weeks old and started on insulin. Initial Hb was 6.8 g/l, MCV 88, WBC and platelets were normal Bone marrow biopsies were inconclusive. Her development was normal with no concern about hearing. Sequencing of SLC19A2 gene identified a known homozygous missense mutation (S143F) in exon 2 of the SLC19A2 gene, which was inherited from both parents. Subsequently formal hearing test revealed bilateral sensorineural deafness. Oral thiamine 25 mg normalized Hb within 4 weeks and 50 mg over further 2 months reduced insulin requirement by 40% and HbA1c% from 10.2% to 8.4%. Further improvement in HbA1c to 7.4% was achieved with 100mg but not beyond that dose. Hemoglobin and MCV remained normal but hearing test 6 months after treatment showed similar findings. There were no reported side effects of thiamine therapy over 18 months period.

**Conclusions:** In this child thiamine was safe and effective in resolving anemia and improving diabetes control but not deafness. The presence of normoblastic rather than megaloblastic anaemia in patient with neonatal diabetes and deafness should not preclude from testing for SLC19A2 mutations and the condition would be better named thiamine responsive anaemia with diabetes.
A novel homozygous EIF2AK3 missense mutation in a patient with Wolcott-Rallison syndrome

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Background: Wolcott-Rallison syndrome (WRS) is a rare autosomal recessive disorder characterized by an early-infancy-onset diabetes mellitus associated with skeletal dysplasia and growth retardation. Other manifestations including frequent episodes of acute liver failure, renal dysfunction, exocrine pancreas insufficiency, intellectual deficit, hypothryoidism, neutropenia and recurrent infections may be seen in these patients. WRS is caused by mutations in the gene encoding eukaryotic translation initiation factor 2a kinase 3 (EIF2AK3), also known as PKR-like endoplasmic reticulum kinase (PERK). To date, fewer than 60 cases have been described in the literature.

Case: A 3 year-old male presented with diabetic ketoacidosis at the age of three months. Neonatal diabetes was diagnosed and insulin treatment was initiated. On follow up, he had several episodes of acute liver failure. He had also attacks of neutropenia and frequent infections. Growth retardation and skeletal dysplasia was recognized within the second year of life. Molecular genetic testing revealed a homozygous novel EIF2AK3 missense mutation, p.R587L (c.1760G>T). The mutation affects a highly conserved residue and a different mutation at the same position has been previously reported in a different ethnicity. Genetic testing revealed a homozygous novel EIF2AK3 missense mutation, p.R587L (c.1760G>T). The mutation affects a highly conserved residue and a different mutation at the same position has been previously reported in a different ethnic group.

Conclusions: WRS should be kept in mind for the diagnosis of patients with permanent neonatal diabetes associated with skeletal dysplasia and/or episodes of acute liver failure. Molecular genetic testing is useful for the definitive diagnosis.

Novel p.Leu795Pro INSR gene mutation causing decreased insulin receptor autophosphorylation in a patient with Donohue syndrome

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Background: Donohue syndrome (former leprechaunism) is a rare, recessively inherited disorder of extreme insulin resistance due to mutation in the insulin receptor gene (INSR). The pathogenesis of insulin resistance is due to a cellular defect in insulin binding, receptor autophosphorylation and tyrosine kinase activity on insulin-stimulated biological activity.

Objective and hypotheses: To identify causative INSR gene mutation and to functionally characterize the postbinding defect of the insulin receptor signaling in a neonatal patient with Donohue syndrome.

Methods: Mutational analysis of the INSR gene was performed by direct sequencing. Functional characterization of insulin receptor in cultured fibroblasts from patient, patient’s mother and control individuals was performed with immunochemical analysis of cell insulin receptor autophosphorylation.

Results: We have identified novel homozygous missense mutation p.Leu795Pro located in the extracellular portion of the insulin receptor β subunit. Functional characterization showed that the mutation was causing decreased insulin receptor autophosphorylation and therefore resulting in the extreme insulin resistance in patient. Patient had neonatal hyperglycemia (12 – 16.6 mmol/l) with hyperinsulinemia (700 mU/l), characteristic dysmorphic features of leprechaunism, hypertrichosis and acanthosis nigricans, reduced subcutaneous fat, distended abdomen, enlarged external genitalia and severe progressive hypertrophic cardiomyopathy.

Conclusions: Novel p.Leu795Pro INSR gene mutation located in insulin receptor β subunit was causing extreme insulin resistance due to decreased insulin receptor autophosphorylation rather than insulin binding impairment.
P2-d3-509 Diabetes and Insulin 4

Does insulin pump therapy improve quality of life and satisfaction in children and adolescents with type 1 diabetes?
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Background: Insulin pumps are booming in pediatric diabetology.

Objective and hypotheses: The objective is to assess changes for children and adolescents using pump with type 1 diabetes about quality of life (QOL), satisfaction and glycosylated haemoglobin.

Methods: A retrospective self-evaluation questionnaire was distributed to 41 patients. It focused on general QOL, diabetes-specific QOL supplemented by specific pump’s questions and satisfaction. Clinical and biological parameters (glycated hemoglobin : HbA1c) were compared before and after pump use.

Results: The score for QOL with pump is positive, more if started early after diagnosis of diabetes (p<0.03) and with children under the age of 8 years (p<0.02). These positive results are mainly related to the characteristics of the pump, “insulin management” and “injections”, and also “diabetes management”, “behaviours”, “schooling”, “family life”, “daily life” and “physicals activities”. On the other hand, the improvement wasn’t significant for the item “life in society and encourage”.

Discussion: The injections’ decrease and the flexibility of meals were the most positive points. The HbA1c is improving as the pump is indicated before starting (p<0.005) and is constant during 4 years (p<0.05). Omissions of injections, comments on diabetes and technical problems appeared to be exceptions. The pump changes the body’s perception because of ambivalent feeling with normality (more freedoms) and difference (visibility and reminiscence of the disease).

Conclusions: The benefits of quality of life and glycemic control with pump are indissociable and can only be considered, surrounded by paramedical and medical assistance. Improving QOL in short and long term by reducing the risk of further complications is the daily challenge of families and diabetologists.

P2-d3-510 Diabetes and Insulin 4

Effects of treatment with vitamin D on glucose metabolism in subjects with type 1 diabetes mellitus
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Background: Clinical and experimental data suggest that vitamin D can be one of the important environmental factors responsible for the increased incidence of autoimmune diseases in people who have a particular geographical, climatic and ethnic background.

Objective and hypotheses: The aim of this study is to demonstrate that, in children with Type 1 Diabetes treated with insulin therapy, vitamin D can positively influence glucose metabolism.

Methods: Our study involved 298 children, among these we selected those of 1 type at the age from 7 to 16; 24 of them have the debut of the disease (1 group) and 24 children have suffered the disease more than 5 years (2 group). In order to estimate SSVP there was used apparatus programmed complex, to evaluate the state of VNS «VNS – spectrum» (Neurosoft) with VNS block for 2 minutes of life and satisfaction in children and adolescents with type 1 diabetes. The study of SSVP showed some differences between the children with diabetes and without it.

Conclusions: The benefits of quality of life and glycemic control with pump are indissociable and can only be considered, surrounded by paramedical and medical assistance. Improving QOL in short and long term by reducing the risk of further complications is the daily challenge of families and diabetologists.

P2-d3-511 Diabetes and Insulin 4

The prevalence, epidemiologic and clinical features of type 2 diabetes mellitus in children and adolescent with obesity
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Objectives: The aim of the study was determining the prevalence of type 2 diabetes mellitus (T2DM) in obese Turkish children and describing the epidemiologic and clinical features of patients.

Material and method: Data obtained from hospital records of patients diagnosed as T2DM between January 2007 and December 2011. 2181 children (2-18 years old) diagnosed as obesity in 2011 in our outpatient clinic. Results: 24 patients diagnosed as T2DM in 2011. The total prevalence of T2DM was 1.1%. Increased prevalence was found in male 15-19 years group (2.43% vs 1.70%). 44 patients (29 F, mean age F:M=13.5±1.7 vs 12±3.2) were included. 14 mothers and 10 fathers had T2DM. 31 mothers and 15 fathers were obese. Girls had advanced puberty (F:M= Tanner V 2.22 vs Tanner II n=7). Vaginal candidiasis was present in 9 girls. At admission 22 patients had hyperglycemia (291±108 mg/dL) and 22 patients were diagnosed with OGTT. Fasting C-peptid (3.7±2.9 vs 6.8±5.5, p=0.027), fasting glucose (131±17 vs 291±10, p<0.000) and HbA1c (6.7±3 vs 10.9±2.7, p<0.000) was significantly different. Autoantibodies (ICA, GAD, AIA) were positive in 11 of 37 patients. Hypercholesterolemia was found 11 of 42, hypertyglycideridemia in 16 of 42, increased LDL in 14 of 40 and decreased HDL in 27 of 40 patients. 4 patients had microalbuminuria. C-peptid was significantly correlated with blood pressure (SBP = p<01, DBP = p<0.05), BMI (p=0.004, r=0.452), AST (p=0.004, r=0.488) and ALT (p=0.003, r=0.482). HOMA-IR was significantly correlated with AST (p=0.022, r=0.488) and ALT (p=0.001, r=0.991). Hyperlipidemia was determined in 87.5% of patients. PCOS was shown in 66.6% of 18 girls by USG. All patients were being treated with metformin (M). Insulin glargine was prescribed in 24 patients and regular insulin in 14.

Conclusion: T2DM is increasing in late adolescence with obesity. Hyperlipidemia, hyperglycemia and obesity are associated with increased risk of cardiovascular disease.

P2-d3-512 Diabetes and Insulin 4

Apparatus programmed testing in diagnostics of diabetic vegetative neuropathy in children
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Background: The diagnostics of diabetic vegetative neuropathy is an actual problem of children diabetology.

Objective and hypotheses: To study the early manifestations of DNV by means of apparatus – programmed analysis of SSVP in children with diabetes mellitus (DM) of I type.

Methods: There were examined 80 children (64 girls and 16 boys) with DM of I type at the age from 7 to 16; 24 of them have the debut of the disease (1 group); 32 children with the duration of the disease from 1 to 5 years (2 group) and 24 children have suffered the disease more than 5 years (3 group). In order to estimate SSVP there was used apparatus programmed complex, to evaluate the state of VNS «VNS – spectrum» (Neurosoft) with VNS block for investigation of SSVP. The basis of this method is the recording of elderly activity as the response to the stimulus. Latent period (LP), amplitudes (A1, A2), duration of ascending phases (S1, S2) were evaluated.

Results: The compensation of carbohydrates metabolism (HbA1C 7%) was revealed in all patients of the 1 group; subcompensation (HbA1C 7.5-11) was revealed in all patients of the 2 group; subcompensation (HbA1C 5.5-8) was revealed in all patients of the 3 group.
in 6 patients from II group and 5 patients – from III group; decompensation (HbA1C 7.5%) in 10 patients from II group and 7 – from III group. In I group the readings of SSVP were normal. In II and III groups there was noted statistically significant decrease of LP=2.32± 0.09 with (p< 0.05) and 3.19±24 with (p< 0.05) correspondingly. More statistically significant decrease of amplitudes was noted in children from III group; A1 = 0.17± 0.08 mwt (p <0.05) and A2 =0.28± 0.06 mwt (p< 0.05). Significant increase of duration of ascending phases was recorded in III group: S1 = 1.71 ±0.26 with (p<0.05), S2 =40±0.35 with (p<0.05) correspondingly in comparison with the readings in II group (1.4±0.28 and 2.15±0.12) correspondingly.

Conclusions: SSVP allows diagnosing DNV in children in preclinical stage. She reading of SSVP becomes worse with the increase of the duration of the disease and degree of carbohydrates metabolism decompensation.

**P2-d3-513 Diabetes and Insulin 4**

**Vitamin D status in childhood type 1 diabetes mellitus: analysis of 212 diabetic children in regard to the age onset**

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2Kasimpasa Military Hospital, Department of Pediatrics, Istanbul, Turkey;
3Ministry of Health Bakirkoy Maternity and Children Education Hospital, Department of Pediatrics, Istanbul, Turkey;
4Istanbul University, Cerrahpasa Medical Faculty, Department of Metabolic Diseases, Istanbul, Turkey

**Background:** Epidemiological studies convincingly implicate a link between vitamin D and Type 1 diabetes mellitus (T1DM). Furthermore, diabetes with onset before 5 years of age suggests a major role for genetic factors.

**Objective and hypotheses:** To present vitamin D status in diabetic children regarding to age onset and investigate vitamin D effect on insulin treatment of T1DM.

**Methods:** A total of 212 children with T1DM were investigated by screening serum 25(OH)D from December 2009 to April 2010. Daily insulin doses and HbA1c levels were obtained. Two groups were composed; a) patients >5 years of age in DM 1 group (n: 159), b) patients ≤ 5 years of age in DM 2 group (n: 53). Additionally, 52 healthy siblings of diabetic patients were evaluated, due to the similarity of life conditions.

**Results:** Only 32.1% of cases in DM 1, 43.4% of DM2, 36.5% of the siblings were determined to have 25(OH)D levels of ≥30 ng/ml (vitamin D sufficiency) (Table 1). There was no statistical difference between these groups about vitamin D status. Although similar daily insulin doses were used in patients with vitamin D deficiency [25(OH)D of <20 ng/ml], HbA1c levels were found significantly higher in DM 1 group (Table 2).

**Conclusions:** Vitamin D deficiency is common in diabetic children independent from possible genetic and environmental factors. Particularly, vitamin D should be screened especially for insulin therapy in T1DM.

<table>
<thead>
<tr>
<th>Vitamin D status</th>
<th>DM1 (n=159)</th>
<th>DM2 (n=53)</th>
<th>Siblings (n=52)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficiency (&lt;20 ng/ml)</td>
<td>71 (44.7%)</td>
<td>20 (37.7%)</td>
<td>24 (46.2%)</td>
<td>0.74</td>
</tr>
<tr>
<td>Insufficiency (21-29 ng/ml)</td>
<td>37 (23.3%)</td>
<td>10 (19.2%)</td>
<td>9 (17.3%)</td>
<td></td>
</tr>
<tr>
<td>Sufficiency (30-99 ng/ml)</td>
<td>51 (31.2%)</td>
<td>23 (43.4%)</td>
<td>19 (36.5%)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 1.** Comparison of vitamin D status between groups in regard to vitamin D deficiency, insufficiency, and sufficiency

**P2-d3-514 Diabetes and Insulin 4**

**Investigation of relation between three adipokines (adiponectin, leptin, resistin) and type 1 diabetes mellitus**

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**Background:** Adipose tissue is not only a storage organ for lipids because it also hormonally active tissue, producing adipokynes which may influence activity of other tissues. Adiponectin, leptin and resistin are popular adipokynes and they play a significant role in regulation of lipid and carbohydrate metabolism especially in patients with type 2 diabetes but little is known about the relation with type 1 diabetes mellitus.

**Objective and hypotheses:** The aim of this study was to measure serum adiponectin, leptin, and resistin levels in patients with T1DM and investigate their relationship with type 1 diabetes mellitus.

**Methods:** Fifty children and adolescents with T1DM (21 boys and 29 girls) and thirty three healthy control subjects (18 boys and 15 girls) were participated in the study. All patients followed in Pediatric Endocrinology and Metabolism Unit of Gaziantep University Faculty of Medicine and control subjects had no hypertension, obesity, hyperlipidemia, anemia and infection. Adiponectin, leptin and resistin levels were analyzed with ELISA.

**Results:** There were no statistically significant differences related with age, sex, BMI distribution between diabetic group and control group. The variables were in the equation. Resistin levels were significantly higher in diabetic group compared to controls (5.26 ± 3.15 ng/ml vs. 3.50 ± 1.26 ng/ml; p< 0.01). There were no significant differences in mean adiponectin and median leptin levels in diabetic group and control group.

**Conclusions:** Only resistin was associated with type 1 diabetes mellitus between three adipokynes. Therefore, resistin may play role in process of inflammation and also pathophysiology of T1DM.

**P2-d3-515 Diabetes and Insulin 4**

**Partial remission period in pediatric patients with type 1 diabetes mellitus: which is the best definition?**

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**Background:** Type 1 diabetic (T1D) patients with partial remission (PR) have easier metabolic control and protection for chronic complications. The definition of PR has varied from the conventional definitions based on stimulated C-peptide levels and insulin doses to the new one based on insulin dose and HbA1c levels (Mortensen 2009). It would be useful to have an easy clinical measure of PR.
Objective and hypotheses: To compare different definitions of PR in T1D pediatric population.

Methods: Prospective study of 45 patients with T1D from diagnosis. We analyzed: 1) at diagnosis: age and HbA1c [HPLC-Menarini, nv 5.3±1.31%]; 2) after one-two months: C-peptide response to intravenous glucagon stimulation test (GST, 15µg/kg, maximum 1mg) (PR >0.9mg/ml; 3) after 6 and 12 months: insulin dose and HbA1c (PR ≥0.5ug/kg/day, HbA1c ≤7.5% or HbA1c<4*insulin-dose) [%]. Statistical analysis: SPSS program, version 15.0, non parametric tests; data expressed in percentage, median and range (percentile 25-75).

Results: Mean age at T1D diagnosis: 9.7 years (4.0-13.1), 51% males. Mean HbA1c: at diagnosis 10.8% (9.6-11.9), 6 months 6.2% (5.9-6.9) and 12 months 6.3% (6.2-6.7). Different definitions of PR were analyzed:

<table>
<thead>
<tr>
<th>C-peptide response</th>
<th>Insulin dose</th>
<th>HbA1c levels</th>
<th>HbA1c&lt;4</th>
<th>HbA1c&lt;4*insulin-dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>12 months</td>
<td>6 months</td>
<td>12 months</td>
<td>6 months</td>
</tr>
<tr>
<td>40%</td>
<td>53%</td>
<td>31%</td>
<td>93%</td>
<td>44%</td>
</tr>
</tbody>
</table>

There was good relation between C-peptide response, insulin dose and HbA1c<4*insulin-dose levels 6 and 12 months after diagnosis (p<0.05), not with HbA1c alone. Six and 12 months after diagnosis, patients with positive C-peptide response had lower insulin dose (0.32 vs 0.6 and 0.44 vs 0.72ug/kg/day, respectively) and lower HbA1c<4*insulin-dose levels (7.3 vs 9.4 and 8.2 vs 9.1, respectively) (p<0.05). Moreover, they had lower HbA1c levels at 6 months (5.9 vs 6.5%, p<0.05), not at diagnosis neither 12 months later.

Conclusions: The new definition of partial remission in T1D is simple and has a good correlation with conventional definitions.

Wolfram syndrome epidemiology: a hot-spot area in north-eastern Sicily

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Background: According to the few available epidemiological studies Wolfram syndrome (WS) prevalence ranges from 1:100 000 in North-America to 1:805 000 in North India.

Objective and hypotheses: The main purpose of this study was to ascertain WS prevalence in a district of North-eastern Sicily, i.e. a geographic area where consanguineous unions are not very unusual, particularly in the mountain villages of the hinterland.

Methods: Prevalence rates were calculated by considering both the total population of our district (653 737) and the populations included within the 0-30 year age range (202 681). Furthermore, we also estimated the relative prevalence of WS among patients with youth-onset insulin-dependent DM of the Messina district who are currently aged under 30 years (256). To compare different definitions of PR in T1D pediatric population.

Results: According to our findings, the global WS prevalence in our district (1:65 000) has a good correlation with conventional definitions.

There was good relation between C-peptide response, insulin dose and HbA1c<4*insulin-dose levels 6 and 12 months after diagnosis (p<0.05), not with HbA1c alone. Six and 12 months after diagnosis, patients with positive C-peptide response had lower insulin dose (0.32 vs 0.6 and 0.44 vs 0.72ug/kg/day, respectively) and lower HbA1c<4*insulin-dose levels (7.3 vs 9.4 and 8.2 vs 9.1, respectively) (p<0.05). Moreover, they had lower HbA1c levels at 6 months (5.9 vs 6.5%, p<0.05), not at diagnosis neither 12 months later.

Conclusions: The new definition of partial remission in T1D is simple and has a good correlation with conventional definitions.

Heparin treatment for severe hypertriglyceridaemia in a child with new-onset type 1 diabetes mellitus presenting with diabetic ketoacidosis

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Background: Diabetic ketoacidosis (DKA) is severe complication of type 1 diabetes and can be associated with severe hypertriglyceridaemia, exposing the patient to the risk of pancreatitis. However, diabetic ketoacidosis-induced severe hypertriglyceridaemia and its treatment in children have been rarely reported in the literature.

Objective: To report a patient with severe hypertriglyceridaemia in DKA treated successfully with heparin.

Methods: We report on a 10-year-old male patient with new-onset type 1 diabetes mellitus presenting with severe DKA and severe hypertriglyceridaemia.

Results: On admission, physical examination revealed signs of severe dehydration, with no cutaneous signs of hyperlipidemia, nor an abdominal tenderness on abdominal examination. Blood drawn for investigation appeared milky which suggested a lipemic state. Findings from laboratory tests showed a severe ketoacidosis (pH 7.03, bicarbonate level of 5.0 mmol/l), glucose level of 26.7 mmol/l, normal almylase level. Hemoglobin A1c level was 14.6%. Lipid levels could not be measured due to the milky serum. The patient was admitted to the intensive care unit and treated with intravenous fluids and insulin infusion. Over the next 30 hours resolution of diabetic ketoacidosis was noted. However, at 30 hours of treatment, his blood still showed milky appearance and triglyceride (TG) level measured for the first time was 190.3 mmol/l, and total cholesterol was 22.9 mmol/l. Although insulin drip was con-
timed even after DKA resolution, there was not the improvement of severe hyperlipidemia and intravenous regular heparin treatment was started at 500 U/h, 30 hours after initiation of insulin treatment. At 6 hours of heparin treatment decline in TG level to 81.9 mmol/l was noted. Heparin was stopped in 3 days with TG dropped to 14.9 mmol/l. The patient had normal lipid profile on outpatient follow-up.

Conclusion: Heparin can be considered a safe treatment modality for rapidly reducing TG levels in children with severe hypertriglyceridemia and diabetic ketoacidosis.

P2-d3-519 Diabetes and Insulin 4
Structure of paediatric diabetes in Latvia
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Background: In 1993 the Latvian childhood diabetes register was established. All newly diagnosed diabetic patients <18 years have enrolled since 1993.

Objective: To describe the Diabetes incidence during the time period since 1993 to 2011 years.

Methods: Since 1 January 1993, all hospitalized incident cases have been reported on a special form. Childhood diabetes register data analysis. Population data were obtained from Latvian Statistics Agency.

Results: A total of 1003 children with type-1 diabetes < 18 years were diagnosed in 1993 – 2011. There were 589 boys and 414 girls. The mean increase in number of cases per year was 2.74/100,000 (CI 0.8 – 4.1%). A total 26 children with type-2 diabetes < 18 years were diagnosed 2002 – 2011, there were 16 girls and 9 boys. The age of the patients at the moment of diagnosis ranges from 9.5 years to 17 years. 24 of 25 patients have BMI to sex and age above 95th percentile. 2 patients diagnosed PNDM with clinical manifestation before 6 months of age and with detected heterozygous mutation R99C INS gene exon 3. We have a family with two children with TNDM (transient neonatal diabetes mellitus), who have not typical chromosome 6 abnormalities. The family will be tested for chromosome 15 mutations. We suspect DIADMOADs by one girl with atrophy of the optic nerve, deafness and diabetes mellitus, but the genetic tests are not done. In our register we have 8 patients with MODY and 1 patient with double diabetes.

Conclusions: There is a continuous increase of type-1 diabetes in Latvia. Incidence of type-2 diabetes is increasing in Latvia, but is still much lower than expected. The main risk factors of type-2 diabetes in our patients are: overweight (<91%, overweight in the family – 55%, diabetes in the family – 72%). We suspect, that not all children with type-2 diabetes are diagnosed, and further screening programs need to be work out. Sometimes it is not easy to determine the type of diabetes – type1, type2, MODY or maybe double diabetes, what is a really challenge for doctors to choose the best treatment.

P2-d3-520 Diabetes and Insulin 4
Epidemiology of the type 1 diabetes debut in children and people under the age of 15 in Navarre
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1 Complejo Hospitalario de Navarra, Pediatric endocrinology, Pamplona, Spain; 2 Complejo Hospitalario de Navarra, Diabetes, Pamplona, Spain

Background: There has been a clear increase in the incidence of type 1 diabetes in recent years, particularly among children under the age of 5 years.

Objective: To find out the epidemiological data and characteristics of type 1 diabetic patients under the age of 15 years at the time of onset who are cared for at a tertiary reference center in the Community of Navarre (461,295 inhabitants), between January 1990 and December 2011.

Methods: Retrospective study of children and young people diagnosed with type 1 diabetes between 1990-2011. Analyze the DKA at diagnosis after pre-diabetic period when the frequency of CAD at the time of diagnosis was unacceptable high in our population before DKA prevention campaign.

Results: From 1990 to 2011, 311 children and adolescents under the age of 15 years debuted in Navarre (171 males, 140 females) with a mean age of 8.65 years ± 3.8 SD (range: 1−15 years). No significant seasonal variation at the time of debut. Mean number of cases was 14.14/ year. The highest incidence is in the 10-14 year old age group (49.8%). The analysis per 5-year periods reveals that the mean incidence in young people was 15.5/100,000 from years 1990-1995 and 20.5/100,000 between 2006-2011, with an evident increase in recent years. 34% of the patients were diagnosed with DKA, most commonly (39.7%) in the 0-4 year old age group.

There were no significant differences per 5-year periods. Although there is a clear decrease in DKA incidence after the prevention campaign (21.4% in 2011).

Conclusion: The incidence of type 1 diabetes in the pediatric population has clearly increased in recent years in Navarre. The frequency of CAD at the time of diagnosis was unacceptable high in our population before DKA prevention campaign.

P2-d3-521 Diabetes and Insulin 4
Adipokine serum levels are affected by weight loss during short-term intervention in obese children
Julia Bilitz1; Isabel Wagner2; Kathrin Dittrich3; Julia Gesing1; Denisse Rockström1; Kathrin Landgraf1; Daniela Friebe1; Antje Berthold2; Firooz Ahmad1; Wieland Kiss1; Antje Körner1
1 University of Leipzig, University Hospital for Children and Adolescents, Leipzig, Germany; 2 Rehabilitation Centre Bad Frankenhausen, Rehabilitation Centre for Children and Adolescents, Bad Frankenhausen, Germany

Background: Adipokines are secreted by adipose tissue in relation to adipose tissue mass and may be a link between obesity, inflammation and cardio-vascular dysfunction. Only limited data are available on how adipokines and inflammatory markers are affected by short-term intervention focusing on dietetic treatment and therapeutic exercises.

Objective and hypotheses: The aim of this study was to analyze the effects of short-term intervention in obese children on adipokine patterns (chemerin, resistin, progranulin, FGF-21). We hypothesized that weight loss influences adipokine serum levels and positively affects cardio-vascular risk profile.

Methods: Blood samples and anthropometric data of 58 obese children and adolescents were assessed before and after up to six weeks of dietetic treatment and therapeutic exercises. Serum levels of the adipokines were measured by ELISAs (VC intra-assay 1.8-11.2%, VC inter-assay 0.7-2.8%).

Results: The intervention had positive effects on weight status (BMI-SDS -0.26±0.015, p<0.0001) and metabolic parameters. Concomitantly, serum chemerin (-18.44±3.02[ng/ml), p<0.0001) and resistin (-0.69±0.20[ng/ml, p<0.0001) levels decreased significantly. Furthermore, we observed significantly increased FGF-21 (+0.034±0.01[ng/ml, p<0.0007) serum levels after short-term intervention. In contrast, there was no difference in serum progranulin levels detectable.

Conclusions: Cardiovascular risk factors such as adipokines can be affected positively by dietary change and a higher level of physical activity in obese children. We conclude that already short-term intervention is beneficial in terms of improving the metabolic state and circulating adipokines as a surrogate marker for cardiovascular and metabolic health.

P2-d3-522 Diabetes and Insulin 4
Maturity onset diabetes of the young in a child with Prader-Willi syndrome
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1 IRCCS San Raffaele Scientific Institute, Department of Pediatrics, Endocrine Unit, Milan, Italy; 2 IRCCS San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Department of Pediatrics, Endocrine Unit, Milan, Italy

Background: Prader-Willi syndrome (PWS) is a relatively common multi-system disorder with a prevalence estimated in several studies to be in a range of 1 in 10,000 to 30,000 individuals. The main beneficial effect of GH therapy in PWS is promoting growth and muscular tropism, with consequent improvement in body composition, strength, agility, physical activity and cardiovascular function.

Case: We describe the case of a female, born at term from a pregnancy complicated by gestational diabetes mellitus, treated with insulin therapy from the 34th week of gestation. At the age of three years, for persistence of hypotonic -
ity, genetic test confirmed the diagnosis of PWS (deletion). At the age of five years, after performing a sleep study and blood tests, including oral glucose tolerance test (OGTT) and HbA1c which resulted normal, the child started GH therapy. Blood tests performed 4 months after the beginning of GH therapy showed a normal OGTT, with HbA1c in the upper normal range (6%). The following control showed an increase in HbA1c (6.3%). Consequently, GH therapy was reduced, for impaired glucose tolerance and persistent high values of HbA1c, GH therapy was therefore interrupted after 14 months. Despite two years of treatment interruption, the child still presents impaired glucose tolerance and HbA1c levels of 6.2%. Patient’s impaired glucose tolerance and history in first degree relatives for impaired glucose metabolism, suggested a genetic analysis of Maturity Onset Diabetes of the Young (MODY) 2, which resulted positive.

**Conclusions:** Coexistence of PWS and MODY, presented here for the first time to our knowledge, is a peculiar situation with managing difficulties arising from the fact that the only treatment available for the former is potentially dangerous for the latter. Moreover, the lack of studies on the effects of GH on glucose tolerance in patients affected by MODY make it difficult to determine whether the risks of GH are balanced by benefits of the same therapy on PWS.

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**P2-d3-524 Diabetes and Insulin 4**

**Comparative effects of oral honey vs. glucose tolerance test solutions on circulating glucose and insulin concentrations in obese prepubertal girls**

*Joanna Farakla 1; Eleni Kouli; Jessica Arditi; Paraskevi Moutatsiou 1*; Maria Dracopoulou 1; Ioannis Papassotiriou 1; George P Chrousos 1; Evangelia Charmandari 1

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**Background:** Honey is a composite biological carbohydrate solution that is regularly used as a natural sweetener and a traditional medicinal agent. Honey contains sugars (75%), protein (3%) and water (19%), as well as substances from the bees’ hypopharyngeal glands. Recent studies performed in adult healthy subjects suggested that honey has a beneficial effect on plasma glucose and serum insulin concentrations compared with monosaccharides and disaccharides.

**Objective and hypotheses:** To compare the effects of Oral Honey (OHTT) and Glucose Tolerance Test (OGTT) solutions on plasma glucose and serum insulin concentrations in obese prepubertal girls.

**Methods:** Seventeen healthy obese prepubertal girls aged 10.6 (± SE: 0.4) years with a body mass index above the 90th centile for age (26.8 ± 0.7 kg/m²) were recruited to participate in the study. All subjects underwent initially a standard OGTT and two weeks later an OHTT. Both solutions contained 75 g of carbohydrate. Plasma glucose and serum insulin concentrations were determined before the solution administration and at 30 min intervals thereafter for a total of 3 hours. Baseline biochemical and endocrine investigations were performed at time 0 min.

**Results:** Fasting plasma glucose (76.9 ± 1.7 mg/dL vs. 77.2 ± 1.4 mg/dL) and insulin (53.6 ± 19.9 ìIU/mL vs. 34.9 ± 14.5 ìIU/mL) concentrations did not differ between OGTT and OHTT. However, plasma glucose concentrations at 120 min were significantly lower following the OHTT (88.2 ± 2.1 mg/dL) than the OGTT (100.7 ± 3.5 mg/dL, P = 0.028). Similarly, serum insulin concentrations at 120 min were significantly lower following the OHTT (55.7 ± 8.1 ìIU/mL) than those of the OGTT (113.8 ± 21.2 ìIU/mL, P = 0.01).

**Conclusions:** Honey had a beneficial effect on stimulated plasma glucose and serum insulin concentrations compared with the standard OGTT solution. These data indicate that honey contains substances that might delay or prevent the development of insulin resistance, impaired glucose tolerance and/or diabetes in obese children.

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**P2-d3-525 Diabetes and Insulin 4**

**Severe lipoatrophy complicating insulin analogue treatment: first reported case of lipoatrophy complicating the administration of insulin aspart via continuous subcutaneous insulin infusion (CSII)**

*Jahnaky Suththanathan; Vijith Reddy Puthi; Sarah Walton*

Peterborough City Hospital, Paediatrics, Peterborough, United Kingdom

**Background:** Lipoatrophy is a rare complication of insulin administration. It is thought to be immunologically mediated and is associated with glycaemic flux and can be disfiguring. Lipoatrophy has been reported in only a small number of patients using insulin analogues. We would like report 2 cases with severe lipoatrophy with Insulin Aspart. To our knowledge this is the first reported case of lipoatrophy complicating the administration of Insulin Aspart via continuous subcutaneous insulin infusion (CSII).

**Objective and hypotheses:** To illustrate lipoatrophy complicating Insulin Aspart administration

**Method:** Two case reports: - The first, a 7-year-old girl with a 2½ year history of Insulin Dependant Diabetes Mellitus (IDDM) in whom lipoatrophy complicated the administration of Insulin Aspart via CSII. Her Glycosylated Haemoglobin (HbA1c) has worsened and a Continuous Glucose Sensor Monitoring (CGMS) showed worsening variability in glucose reading. In the litera-
ture only three cases report lipoatrophy in patients using Insulin Aspart, all of whom were on a Multiple Daily Injection (MDI). - The second, a particularly severe localized lipoatrophy measuring 7x10cm at an injection site in a 17-year old boy with IDDM, Hypothyroidism and Addison’s disease, who is on MDI involving Insulin Aspart at mealtimes and Insulin Glargine at night. His HbA1C had also worsened with recurrent hypoglycaemic episodes. His dose of hydrocortisone was adequate, and his lipoatrophy still continues to be a problem despite the cessation of injection in the site.

Results: Lipoatrophy is seen to complicate two cases of Insulin Aspart administration.

Conclusions: Insulin analogue treatment via CSII or MDI is commonplace amongst diabetic paediatric patients. Our cases highlight the need for vigilance for lipoatrophy when using CSII or MDI, regardless of which insulin is used. They also promote cautious interpretation of evidence in the literature for recovery of lipoatrophy following the use of CSII and/or short-acting insulin analogues.

P2-d3-s526 Diabetes and Insulin 4
Combined therapy with insulin and rGH in thirteen Italian patients with type 1 diabetes
(T1DM) and growth disorders
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Background: Combined GH and insulin therapy are rarely prescribed in pediatric pts because the association of GHD and T1DM is rare and maybe for the difficulties in managing a double therapy with opposite effects on glucose metabolism. Objective and hypotheses: To investigate on the attitude of pediatric endo-diabetologists in treating these pts. Methods: Data were collected from over 50 centres belonging to the ISPED. The inclusion criterion was based on the double therapy for at least 6 months with insulin due to T1DM, and GH, due to growth impairment. Results: Most centres stated that the use of combined therapy was considered uncomfortable and frequently avoided, whereas 10 centres reported the treatment of 13 pts (7M, 6F). In 7 pts T1DM was the first diagnosis (age at onset from 1.5 to 9.5 yrs) and they were treated with insulin (group 1) and with rGH subsequently (after 0.5-9.75 yrs) due to idiopathic GHD in 4 pts, Turner’s in 1 pt, Leri-Weill’s in 1 pt and bone dysplasia in 1 pt. In 6 pts rGH therapy was started first (age at start 2.5-12 yrs) due to idiopathic GHD in 4 pts, organic GHD in 1 pt and Turner’s in 1 pt. Height SDS at the start of rGH therapy ranged from -2.5 to 3.9. Longest duration of rGH therapy was 7 yrs and 5 pts are still treated. Insulin schedule was with MDI in 10 pts and with CSII in the remaining 3. In the 7 pts of group 1, mean insulin dose increased during the first 6 months after rGH start from 0.68 to 1.06 U/kg (p=0.03). HbA1c ranged from -2.5 to -3.9. Longest duration of rGH therapy was 7 yrs and 5 pts and 2.3 for 10-16 years group (n:22). The frequency of life events in diabetic children was 2.8 for 0-4 years group (n:14), 2.4 for 5-9 years group (n:20) and 2.3 for 10-16 years group (n:22). The frequency of life events in diabetic children was 2.8 for 0-4 years group (n:14), 2.4 for 5-9 years group (n:20) and 2.3 for 10-16 years group (n:22). The mean age of study group was 8.4±4.2 years, 53% (n:30) of the participants were girls. LCU score of the study group was higher than control group (78±36, 51±71, respectively), but the differences was not statistically significant. Sixteen percent (9/59) of the study group reported one life event during the last year. The mean number of experienced life event of diabetic children was 2.8 for 0-4 years group (n:14), 2.4 for 5-9 years group (n:20) and 2.3 for 10-16 years group (n:22). The frequency of life events in diabetic children was higher than control group. The experience of stressful life events was associated with a 1.6 fold increased the risk of developing diabetes. Conclusion: Stressful life events may be precipitating factor for developing diabetes. Large-scale studies are required to reveal the relationship between psychological stress and developing type 1 diabetes.

P2-d3-s528 Diabetes and Insulin 4
Atypical progeroid syndrome - case report
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Background: A typical progeroid syndrome is a very rare disease, from the group of congenital lipodystrophies. Until 2009 only 13 cases were described. The spectrum of clinical features is very wide. Methods: We describe a girl, who was born with a normal weight and length. At the age of six months, when “cafe au late” spots were noticed, she was diagnosed with neurofibromatosi type 1. At the age of seven years she was diagnosed with scurveriosis. She was initially treated with metoxetane, prednisolone, folic acid and alphaD3. At the age of 11 years, she was examined by nephrologist because of the dysuric problems and abdominal pain. She had mandibular hypoplasia, hyperthelorism, prominent eyes, beaked nose. Skin showed mottled hyper- and hypopigmentations on the extremities, telangictasies on the legs. There was generalized loss of subcutaneous fat, with prominent muscle. A very high insulin concentration (1408 mU/l). Genetic testing showed mutations in the LSX and LMC3 genes. The mean age of study group was 8.4±4.2 years, 53% (n:30) of the participants were girls. LCU score of the study group was higher than control group (78±36, 51±71, respectively), but the differences was not statistically significant. Sixteen percent (9/59) of the study group reported one life event during the last year. The mean number of experienced life event of diabetic children was 2.8 for 0-4 years group (n:14), 2.4 for 5-9 years group (n:20) and 2.3 for 10-16 years group (n:22). The frequency of life events in diabetic children was higher than control group. The experience of stressful life events was associated with a 1.6 fold increased the risk of developing diabetes. Conclusion: Stressful life events may be precipitating factor for developing diabetes. Large-scale studies are required to reveal the relationship between psychological stress and developing type 1 diabetes.

P2-d3-s527 Diabetes and Insulin 4
Is documented stress a factor in the development of type 1 diabetes?
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Background/aim: Emotional stress is considered as one of the precipitating factors in the development of type 1 diabetes. We aimed to evaluate the relationship between the stressful life events and development of diabetes in this study. Methods: The study group was comprised of the 56 children aged 0.8-16 years, diagnosed with type 1 diabetes in the last year. Participants were classified into 3 groups according to their age (0-4, 5-9, 10-16). Participants and the control group completed modified life change values (LCU) questionnaire consisted of 45 events. A control group was comprised of 51 healthy children whose age, gender, ethnicity and social status are similar. The participants were asked to answer the questions considering the last one year of diagnosis. The scoring was made according to age groups as predicted in LCU. Scores above 50 were considered significant. In addition, the number of stressful life events was determined. Results: The mean age of study group was 8.4±4.2 years, 53% (n:30) of the participants were girls. LCU score of the study group was higher than control group (78±36, 51±71, respectively), but the differences was not statistically significant. Sixteen percent (9/59) of the study group reported one life event during the last year. The mean number of experienced life event of diabetic children was 2.8 for 0-4 years group (n:14), 2.4 for 5-9 years group (n:20) and 2.3 for 10-16 years group (n:22). The frequency of life events in diabetic children was higher than control group. The experience of stressful life events was associated with a 1.6 fold increased the risk of developing diabetes. Conclusion: Stressful life events may be precipitating factor for developing diabetes. Large-scale studies are required to reveal the relationship between psychological stress and developing type 1 diabetes.
**P2-d3-529** Diabetes and Insulin 4

**Extremely elevated triglyceride blood concentration as a presentation of type 2 diabetes mellitus (T2DM) in childhood obesity**

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**Background:** T2DM is a chronic disease, tightly related to obesity characterized by a gradual increase in insulin insensitivity associated with a subsequent decline in insulin secretion. Treatment milestones of T2DM are diet, exercise and oral hypoglycaemic agents.

**Objective:** This case presentation shows that besides insulin insensitivity, insulin deficiency can be severe also in childhood T2DM, can cause extremely high serum lipid concentrations, and might require insulin treatment at onset.

**Results:** At the age 14 yr, a child was admitted for investigations for high TG and cholesterol concentrations (4294 mg/dL and 487 mg/dL, respectively) noticed during routine follow-up blood tests. Born at term, normal pregnancy, vaginal delivery, BW 4165 gr. Family history significant for hypothyroidism, T1DM, obesity and CVD.

The patient was obese since age 2yr and was diagnosed of primary non autoimmune hypothyroidism at age 3 yr. He had already developed stigma of the Metabolic Syndrome (hypertension, dyslipidemia, hepatic steatosis, insulin insensitivity and impaired glucose tolerance). Compliance with dieting and exercise had always been poor. On admission, based on standard criteria, the diagnosis of DM was immediately made, and the conditions were such that the protocol for diabetic ketoacidosis had to be applied.

Weight loss had occurred over the past 2 months. Intraocular insulin treatment was required for 24 hr with a reduction in TG concentrations from 4294 mg/dL to 533 mg/dL. Then subcutaneous insulin treatment was given for over 3 months, when the child was gradually switched to oral Metformin treatment. TG concentrations were normalized after 40 days of insulin treatment. The child is now in good glycaemic control on oral medication only. All markers for T1DM were negative, C-peptide was normal, and a diagnosis of T2DM was made.

Conclusion: T2DM onset in childhood obesity may present with extremely elevated triglyceride blood concentrations that require prolonged insulin treatment before oral hypoglycaemic drugs can be used alone.

**P2-d3-530** Diabetes and Insulin 4

**Use of metformin in the management of insulin resistance and metabolic syndrome in obese children**

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**Background:** The prevalence of obesity in childhood is increasing, including its complications such as metabolic syndrome. There is a high incidence of insulin resistance in obese children, which is a precursor to diabetes mellitus. As well as adopting a healthy lifestyle, drugs including metformin, have shown some benefit in improving metabolic syndrome.

**Objective and hypotheses:** To assess efficacy of metformin in children with insulin resistance and metabolic syndrome.

**Methods:** 31 children with metabolic syndrome were randomly selected from outpatient clinics. Patients were reviewed after >6months. These children had a BMI assessment before and after treatment, assessment of diet and physical activity, blood tests to analyse insulin resistance (HOMA), cholesterol, USS of liver, questionnaires to assess energy levels, concentration after treatment with metformin.

**Results:** 30 children were assessed, 13 were male and 17 female with a mean age of 12.4yrs (4-17). BMI was assessed in 21 patients (70%) after treatment with metformin. 12 (60%) had a reduction in BMI after 1 year and 9 (43%) had an increased BMI after 1-year. 22 patients had a liver USS at diagnosis of which 10 (45%) had fatty infiltration of the liver. 21 patients (91%) reported improvements in energy levels only 1 still felt tired whilst taking metformin. 18 patients (78%) felt happier and more positive and 10 (43%) reported to have better concentration. Insulin resistance was measured by the homeostasis model assessment of insulin resistance (HOMA) in 19 patients. HOMA scores improved in 9 (47%), worsened in 8 (42%) and remained the same in 2 (11%). There was a reduction in cholesterol levels in 10 patients (67%) on metformin.

**Conclusions:** Metformin therapy causes an improvement in BMI and insulin levels in those with insulin resistance. Hence metformin can be used for the prevention of type II diabetes in obese children with insulin resistance.

**P2-d3-531** Diabetes and Insulin 4

**IPEX syndrome: a Moroccan case**

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**Introduction:** IPEX is a rare pediatric syndrome, poor prognosis, secondary to a mutation in the FOXP3 gene on chromosome X (Xp 23.11 region-q 13.3). We report the case of an infant aged 8 months suffering from IPEX syndrome confirmed by the presence of a mutation in the FOXP3 gene.

**Observation:** This is YD from a non consanguineous marriage, who was hospitalized at the age of 5 days with acute dehydration and metabolic acidosis, and whose diagnosis of diabetes mellitus was made at day 11 to life after a misdiagnosis of neonatal infection and then congenital adrenal hyperplasia. Insulin therapy was then started. Laboratory tests found a C-peptide levels undetectable anti-GAD negative, normal liver function tests and osmosis. The initial genetic study has excluded common mutations responsible for neonatal diabetes (KCNJ11 mutation, mutation of ABCB8). The patient subsequently developed atopic eczema at the age of 3 months, then was hospitalized twice for dehydration in acute diarrhea mucous at the age of five and seven months. The child died at the age of 8 months in an array of severe growth restriction and dehydration. The review of his case, suggested the IPEX syndrome. The search of the FOXP3 gene mutation has returned positive, and the mother is a carrier of this mutation.

**Discussion:** IPEX is a Deregulation immune polyendocrinopathies, autoimmune enteropathy X-linked, which often manifests itself in a boy in the early neonatal period or before the age of 4 months for insulin-dependent diabetes, a profuse secretory diarrhea responsible for a significant failure to thrive, eczema, thrombocytopenia, anemia, thyroid dysfunction and recurrent infections. The evolution is often fatal, children with rarely exceed the first year of life.

**Conclusion:** IPEX is rare but one should think before a boy with neonatal diabetes that develops later any autoimmune disorder.

**P2-d3-532** Endocrine Oncology 2

**The development of endocrine dysfunction after aloigenic H SCT in children**

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**Background:** The mechanisms of endocrine dysfunction developing after hematopoietic stem cell transplantation (H SCT) in children remain not completely recognized. Toxicity of the conditioning regimen, especially total body irradiation, and immunologic mechanisms are most commonly postulated cause of endocrine abnormalities.

**Objective and hypotheses:** The aim of the study is evaluation of endocrine dysfunction after H SCT.

**Methods:** We prospectively evaluated the function of thyroid, gonads, pituitary and adrenals in 51 children, aged 1-18 years, who survived after transplantation. The reasons for bone marrow transplantation were: severe aplastic anaemia, acute lymphoblastic anaemia, inborn errors, acute myeloblastic leukaemia and others. The conditioning regimen included chemotherapy in 27 children and TBI in 8 patients. Every year we evaluated high velocity and sexual maturation of the children TSH, FSH, LH, prolactin, estradiol and testosterone, GH, glycaemia, lipids, insulin and glucose levels and circadian rhythm of cortisol secretion.

**Results:** In 8 children, autoimmune hypothyroidism was diagnosed. In 3 patients this feature was transient. One patient was diagnosed as having Graves' disease. Transient delay of growth velocity was observed in all the children in the first year after H SCT, in one girl was observed growth hormone deficiency, in 2 boys they were short stature observed; however the growth hormone
secretion was normal. In 4 hypergonadotropic hypogonadism and in 2 hy- pogonadotropic hypogonadism. The 3 children were treated for obesity with- out adrenal and pancreatic disorders. The endocrine disorders increased with age of the patients from 20% in first year to 48% in five years after HSTC. 

Conclusions: 1. Autoimmune thyroid diseases are a most frequent complication in children after HSCT. 2. The frequent complication is hyper- and hypogonotropic gonad disorders and short stature. 3. The children after HSCT need permanent observation in 

P2-d3-533 Endocrine Oncology 2
Long-term endocrine sequelae after therapy for acute lymphoblastic leukemia in Thai children
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Background: The survival rate of acute lymphoblastic leukemia (ALL) has improved substantially over the last few decades. However after the therapy ALL survivors are at risk of metabolic and endocrine complications including growth hormone deficiency (GHD), obesity, gonadal dysfunction, abnormal thyroid function, cortisol deficiency, and osteoporosis.

Objective and hypotheses: To determine the prevalence of hormonal ab- normalities, metabolic disturbances and low bone mass density in childhood ALL survivors in Thailand and to provide risk factors relevant to those abnormalities.

Methods: Thirty ALL survivors were determined for metabolic and en-ocrine abnormalities. Testing including growth hormone (GH) and cortisol by insulin tolerance test (ITT), IGF-1, IGFBP-3, thyroid function test, LH, FSH, estradiol or testosterone, FPG, lipid profiles and bone mineral density(BMD).

Results: Thirty patients of childhood onset ALL survivors were recruited in this study. Eight patients were over than 18 years old. Twenty-five patients (83.33%) received cranial radiotherapy. In accordance with complete endo- crine examination, most patients (90%) had endocrine abnormalities. Adult height was correlated to their genetic potential (mid-parental height, MPH) and was more deteriorated in female group (p=0.091). Ten patients with growth hormone deficiency (GHD) were detected; however, their IGF-1 and IGFBP-3 were between -2SD to 2SD. Early onset of ALL was the poten- tial risk factor (p=0.033). We found 20% with subnormal cortisol responses. Gonadal failure was found in one case experienced testicular irradiation. No diabetes insipidus was detected. Among 10 obese patients, 2 patients were probable metabolic syndrome and 1 was diagnosed diabetes mellitus. Low BMD was detected in the most of patients.

Conclusion: This study shows various endocrine and metabolic sequelae oc- curring in childhood onset ALL after completion of their therapy. Biochemi- cal and hormonal abnormalities should be regularly aware and monitor for prompt treatment.

P2-d3-534 Endocrine Oncology 2
Frequency and risk factors of endocrine complications in Turkish children and adolescents with sickle cell anemia
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Objective: To define frequency and risk factors of abnormalities in for puberty, puberty, thyroid, bone and carbohydrate metabolisms in children and adolescents with sickle cell disease (SCD).

Methods: Endocrine problems including height, puberty, thyroid, carbohy- drate, bone metabolisms and body measurements in 50 Turkish children and adolescents with SCD have been evaluated. Relationships between gender, disease type, blood transfusions, exchange and exacerbation frequency, fer- ritin levels and endocrine pathologies have been investigated.

Results: Age mean of study group was 13.1±2.9 years. Weights and heights of 12 participants (24%) were below - 2 standard deviations (SD), and 4 par- ticipants (8%) had malnutrition. Endocrine complication frequency was 50%: Hypergonadotropic hypogonadism in 3 patients (6%); hypogonadotropic hy- pogonadism in 1 female patient (2%), and small testicular volume in respect to age in 3 male (8.5%) patients. Growth hormone deficiency (GHD) was de- tected in 1 (2%) female patient, hypothyroidism was diagnosed in 3 patients (6%, 1 case with central, 2 cases with primary hypothyroidism). At vertebral level, 5 patients (21%) had osteoporosis, 1 patient (2.2%) had osteopenia, and 5 patients (11.1%) had osteopenia at femur neck level. 25-hydroxiva- min D [25 (OH) D] was deficient in 63.2%, and was insufficient in 18.4% of patients. Gender, disease type, blood transfusion frequency, exacerbation frequency, and ferritin levels were not related to endocrine pathologies. At the age was increased, SDS of femur neck bone mineral density (BMD) was decreased (r=-0.56; p<0.05). Vitamin D was lower in patient, whose weights and/or heights were below – 2 SD (p<0.05).

Conclusion: Endocrine organ dysfunctions are commonly detected in chil- dren and adolescents with SCD, and vitamin D deficiency is the most com- monly encountered endocrine disorder. Regular follow- ups of patients for endocrine complications starting from early ages of patients, and initiation of appropriate treatments will elongate expectancy and quality of life.

P2-d3-536 Endocrine Oncology 2
Induction of puberty by autotransplantation of frozen/thawed ovarian tissue in a girl with ovarian failure after treatment for Ewing sarcoma
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Background: Aggressive cancer treatment in children with high-dose che- motherapy and/or radiation often leads to premature menopause. Many parents now request cryopreservation of their children ovaries ovarian tissue prior to potential gonado- toxic treatment. Several children have been born after autotransplantation of ovarian tissue. Cryopreserved ovarian tissue may also have the potential to induce puberty.

Objective: To describe how cryopreserved ovarian tissue from a pre-pubertal girl with cancer has the capacity to induce puberty after autotransplantation years after gonadotoxic treatment.
Case story: A nine-year old girl was diagnosed with Ewing sarcoma of the pelvis. Prior to therapy, one ovary was removed and cryopreserved. The chemotherapy protocol included vincristine, ifosfamide, doxorubicin, etoposide, actinomycin, and cyclofosfamide. Subsequently, she underwent total surgical tumor resection. Postoperatively, she received a radiation dose of 41.17 Gy to the pelvis in 23 fractions. At the age of 13.4 years, the girl showed no signs of relapse. She had consistent high levels of follicle stimulating hormone (FSH) of more than 80 IU/L, and showed no clinical signs of puberty. Two pieces of ovarian cortex with histologically verified high density of primordial follicles were autotransplanted to the remaining small atrophic ovary. Three months after autotransplantation, FSH was reduced to 14 IU/L, luteinizing hormone (LH) was reduced from 19 IU/L to 8.6 IU/L, and the level of estradiol increased from undetectable to 70 pmol/l. She went into puberty stage B 3-4 and P-3 during the next year; at that time she had menarche. The next months she had six cycles. Up to 19 months after the graft, the gonadotrophins were suppressed, but then gradually increased.

Conclusion: This study showed that small amounts of frozen/thawed ovarian tissue from a pre-pubertal girl has the capacity to induce puberty and restore ovarian function. However, the ovarian function vanished after 19 months.

P2-d3-537 Endocrine Oncology 2
Fertility preservation in paediatric cancer patients, a multidisciplinary approach
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Background: Almost 80% of children diagnosed with cancer are alive five years after diagnosis and 1/650 young adults is a childhood cancer survivor. Due to cancer treatments, 23% suffer from gonadal insufficiency. Different fertility preservation options (FPO) are available for post-pubertal patients (embryo/oocytes and sperm cryopreservation (CP)). Only recently experimental options can be offered to pre-pubertal patients such as ovarian/testicular tissue CP. Once the patient is ready to conceive, two possibilities are available: auto-transplantation of the cryopreserved tissue (already performed in older women, potentially allowing a recovery of endocrine function/not reported for men) or still experimental in-vitro (iv) maturation of primordial follicles/spermatids followed by iv fertilization.

Objective: To offer FPO to pre-pubertal patients.

Method: In 2010, a multidisciplinary team was formed in two university hospitals of Switzerland, including specialists in pediatric oncology, endocrinology, gynecology, surgery, reproductive medicine, ethics and law. Monthly meetings take place to present new medical cases, debate recommendations and literature, complete the patient registry and later on analyse the long-term outcome of patients. The indication for FPO is discussed for every newly diagnosed oncological female patient with potentially gonadotoxic treatment. When indicated, the chosen FPO is proposed to the girl and her family. Before proceeding, FSH, LH, E2 and AMH are measured and antral follicles counted. The procedure for boys is still under elaboration.

Results: To date FPO indication was discussed for 20 girls, and 9 were realized (ages 3-17 years).

Conclusions: Fertility preservation techniques are nowadays proposed to both pre- and postpubertal pediatric cancer patients. As the methods available for fertility restoration are still experimental, accurate information should be provided to patients and their parents. In view of the paucity of cases, a multidisciplinary approach and the follow-up using a patient registry are indispensable.

P2-d3-538 Endocrine Oncology 2
Pre-cancerous thyroid lesions in a 14 years old girl with Cowden syndrome: would thyroid ultrasound screening start earlier than recommended?
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Background: Cowden syndrome (CS) is an autosomal dominant disease caused by germline mutations in the PTEN tumor suppressor gene. It is characterized by multiple hamartomatous lesions and an increased risk of benign and malignant tumors of the thyroid, breast and endometrium. Lifetime risk of thyroid cancer is estimated to be 10%. Recommendations suggest starting thyroid ultrasound screening at the age of 18 years or five years before the earliest age at thyroid cancer diagnosis in the family.

Hypothesis: Cases of thyroid cancer can be missed following these recommendations.

Method: We report the case of a girl addressed to our clinic at age 12 years. She had macrocephaly, an arterio-venous malformation at the ankle and a positive familial history for CS. As her father, brother and dizygotic twin sister, she also carried a PTEN mutation (c.697C>T, p.Arg233X). Her father underwent a hemi-thyroidectomy at the age of 34 years because of a multinodular goiter. Histopathology was benign. Her brother, now 24 years old, was followed for infracentemetric thyroid nodules starting at the age of 15 years. Thyroid ultrasound performed at the age of 12 years in our patient showed a multinodular thyroid, the largest nodule measuring 8x6x11 mm. Given the growth of the nodules upon follow-up, a fine needle aspiration was performed showing hypercellular and follicular lesions. Thyroid function was normal with the presence of anti-TPO and anti-TG antibodies. Subsequent ultrasounds showed a further significant growth of the nodules (maximum 17x15x13 mm), leading to a thyroidectomy at the age of 14 years.

Results: Histopathology of the thyroid revealed a macro- and microfollicular multinodular goiter with pre-cancerous lesions such as capsular invasion.

Conclusions: Precancerous nodules of the thyroid can be present in pediatric patients with CS even in the absence of thyroid cancer in affected family members. We therefore propose to start ultrasound screening earlier than recommended, that is at the age of 12-14 years.

P2-d3-539 Endocrine Oncology 2
Papillary thyroid carcinoma in a 15 month old child
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Background: Differentiated thyroid carcinomas constitutes 0.4% of all childhood malignancies. More than 70% of these cases are present between the ages of 11 to 17 and 85% to 90% of them are papillary thyroid carcinomas. Papillary thyroid carcinoma is very rare before the age of five and no case before the age of two is reported previously in the literature.

Results: Case: A 15 months old boy with no other previous medical conditions presented with a cervical mass. His parents noticed the mass when he was 3 months old but did not seek medical advice until four months ago, when the mass became enlarged. Ultrasonoraphic examinations showed a solid mass with dimensions of 50x27 mm on his right cervical region and he was operated in pediatric surgery department. Pathological examination of surgical specimen revealed a papillary thyroid carcinoma and the patient was consulted with pediatric endocrinology unit. The case is evaluated by a multidisciplinary team and after total thyroidectomy replacement therapy with L-thyroxin is commenced. The patient has been followed up at our pediatric endocrinology outpatient clinic.

Conclusions: We present a rare and possibly the youngest case of papillary thyroid carcinoma in a 15-month-old child. Rare malignancies can be seen in patients presenting with cervical masses. A multidisciplinary approach in experienced centers is necessary to deal with such cases.
MEN2B is still difficult, but is crucial for curative thyroid surgery. Because of its rareness and de novo occurrence, early diagnosis of complications in the RET oncogene. The pheochromocytoma was ruled out on the laboratory test results. Calcitonin 5.0 pmol/l (normal < 3.8 pmol/l) was slight elevated. Ultrasound of the thyroid gland was normal. CT-scan of upper thorax was without signs of metastases. Thyroidectomy was made without complication. Two foci of MTC were found, each 4 mm in size, respectively in the right and the left lobe. Lymph nodes were without metastases. After resection of cervical lymph nodes were performed, in which confirmed by histological findings and immunohistochemistry study the diagnosis of SETTLE.

Conclusions: A long term follow-up is recommended since these patients may present with delayed metastasis. With early diagnosis and prompt surgical intervention, this patient would be expected to have a favorable prognosis. Key Words: SETTLE; thyroid; metastasis.

Medullary thyroid carcinoma in a 9 year old boy with Multiple Endocrine Neoplasia type 2B (MEN2B)

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Background: MEN2B is the rarest and most aggressive form of MEN syndrome. MEN 2B patients manifest characteristic marfanoid body habitus, besides the presence of cell-derived tumors including medullary thyroid carcinoma (MTC), pheochromocytoma, mucosal neuroma, and ganglioneuromatosis of the gut. MTC develops early in life and is described as early as the first year of life.

Objective and hypotheses: A 9 year old boy was referred to the department of Pediatrics from the ophthalmological department, because corneal fibers had been demonstrated by a slit lamp examination and so MEN2B was considered. The boy appeared with big bumpy lips, gingiva and tongue with numerous mucosal neuromas, high-arch palate and marfanoid habitus. During early childhood he had been examined because of suspicion of Ehlers-Danlos, hypermobile joints and tendency to massive constipation without conclusive diagnosis.

Results: MEN2B was confirmed with genetic test showing a M918T mutation in the RET oncogene. The pheochromocytoma was ruled out on the laboratory test results. Calcitonin (5.0 pmol/l (normal < 3.8 pmol/l)) was slightly elevated. Ultrasound of the thyroid gland was normal. CT-scan of upper thorax was without signs of metastases. Thyroidectomy was made without complication. Two foci of MTC were found, each 4 mm in size, respectively in the right and the left lobe. Lymph nodes were without metastases. After surgery PTH and calcium remained in normal levels. Thyroid substitution was initiated. One year follow up with normal calcitonin and no signs of pheochromocytoma.

Conclusions: Ophthalmological and oral manifestations led to the diagnosis in our case. Because of its rareness and de novo occurrence, early diagnosis of MEN 2B is still difficult, but is crucial for curative thyroid surgery.

Vitamin D in obese children and adolescents. Relationship with insulin resistance parameters and adipocyte cytokines

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Introduction: Different experimental and clinical studies have associated vitamin D with insulin secretion regulation and sensivity. Low vitamin D levels have been related with the development of insulin resistance, glucose intolerance and the metabolic syndrome.

Aims: 1. To establish vitamin D levels in obese children and adolescents. 2. To determine the relationship of plasma vitamin D levels with BMI, insulin resistance indexes, adipocyte cytokines and metabolic syndrome (MS).

Patients and methods: Cross-sectional study of 272 obese Caucasian patients (137 males) aged from 8 to 18 years (mean: 12.5 ± 2.3), and the following BMI distribution: between +2 and +3 SD: 45.0%; between +3 and +4 SD: 33.6% and > +4 SD: 21.4%. All patients underwent an OTTG and WHO, IDF-2007 classification criteria. Vitamin D and PTH were determined by RIA, Adpt by ELISA, RBP4 by nephelometry and IL-6 by immunoassay.

Results: Mean vitamin D concentrations were 20.4 ± 7.3 ng/dl; 48.9% of patients presented deficient vitamin D values (<20 ng/dl) without season-related differences. Glucose intolerance prevalence was 8.7% (n=25). MS prevalence was 15% (n=43). Plasma 25OHD concentrations showed no statistically-significant differences in relation to glucose intolerance and MS. 25OHD correlated negatively and statistically with BMI (r=-0.16, p=0.01), waist perimeter (r=-0.20, p=0.001), insulin (r=-0.12, p=0.04), HOMA (r=-0.13, p=0.05) and PTH (r=-0.26, p=0.001), and positively with HDL-c (r=0.20, p=0.01).

Conclusions: A significant proportion of obese children and adolescents (87.8%) present vitamin D deficiency and insufficiency. Vitamin D deficiency in obese patients is associated with a greater degree of adiposity and its central distribution, a greater degree of insulin resistance and a more atherogenic plasma lipid profile. The absence of relationship between plasma adipocytokine concentrations and circulating vitamin D levels does not support a role of vitamin D in the regulation of proinflammatory activity present in obese children and adolescents.

No long-term weight reduction after gastric banding (LAGB) in obese patients with craniopharyngioma involving hypothalamic structures – Experiences from kraniopharyngem 2000

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Background: Craniopharyngiomas are embryogenic malformations which lead to eating disorders and morbid obesity due to hypothalamic involvement. Objective and hypotheses: The experience with laparoscopic adjustable gastric banding (LAGB) in obese craniopharyngioma patients is limited especially in regard to long-term effects and tolerability.

Methods: We are reporting on four patients with childhood craniopharyngioma diagnosed at age 2, 13, 12, and 20 years.

Results: Body mass index (BMI-SDS) at diagnosis was -0.9, +4.5, +4.7 and +2.3 SD. All patients developed morbid obesity (BMI-SDS: +10.8, +10.3, +11.4, +6.2) so that 11, 5, 9 and 3 years after diagnosis LAGB were performed. LAGB were well tolerated. During long-term follow-up, the nadir BMI SDS (+6.9, +9.5, +7.8, +4.9) were reached 2.0, 0.5, 1.0, 0.8 years after LAGB. At last evaluation 9.1, 5.3, 7.1, 7.1 years after LAGB, the patients BMI (BMI SDS at last evaluation: +10.2, +13.9, +10.2, +6.5) had increased again but remained at a constant level comparable with baseline BMI SDS at the time of LAGB. Quality of life was not decreased due to LAGB and tolerability was sufficient.

Conclusions: We conclude that LAGB is feasible and could have clinical relevant effects on long-term weight stabilization of obese craniopharyngioma patients with hypothalamic syndrome. However, a significant weight
significant differences were found between the levels of the Cd, Co and Ni in urine of obese children.

Conclusions: The imbalance in the level of nickel, cadmium and cobalt may be due to a changed cellular metabolism in the obese children. However, the results of our study reveal the significant differences in the concentration of these metals between patients with obesity and healthy children, which suggest that this fact may be related to environmental or occupational factors and therefore it requires further study.

**P2-d2-546** Fat Metabolism and Obesity 3

**Follow-up of a children's cohort from age 3-4 to 7-8 years: evaluation of overweight risk factors**

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Background: In 2008, 1043 children of 3-4 years were examined during school health assessment in Haute-Saône, France. 6.7% of the children were overweight according to the French national cut off (including 2.1% obese). Prevalence of early adiposity rebound (EAR) reached 35.5%.

Objective and hypotheses: In 2011, at age 7-8 years, this cohort was reassessed.

Methods: Evaluation included Body Mass Index (BMI) and EAR survey through individual analysis of the BMI curve. Parents filled a questionnaire specifying their anthropometric data, characterizing food intake and family lifestyle.

Result: 88.3% (n=921, male=52%) of the initial cohort could be seen again at the age of 7-8y. 15% of these children were overweight, including 5.1% of obese. The following risk factors of being overweight at the age of 7-8y were found: a high BMI in parents (p<0.0001), lack of sleep (p=0.012) and of daily physical activity (p=0.033), an early adiposity rebound at 3-4y and being overweight at 7-8y (p=0.0001). When focusing on EAR, we noticed that 74.3% of the overweight children at 7-8y had had an EAR at 3-4y. This confirms the importance of EAR diagnosis at age 3-4y to identify a population at risk, but 25.7% of overweight children at 7-8y didn’t present an EAR at 3-4y, suggesting that AR could occur later. On the other hand, 73.8% of the children with EAR at 3-4y had a normal corpulence at 7-8y. In these children, there might have been a physiological variation of the BMI curve rather than a real AR. That might also suggests that their family changed habits in order to normalize child’s BMI. Finally, a longer follow-up is required to verify that these children won’t become overweight when older than 7-8y.

Conclusions: These data confirm the importance of BMI curve supervision in all the children, especially from age 3-4y that appears adequate to identify children at risk. Finding an EAR at 3-4y thus warrants a subsequent individuated follow-up, without moralizing nor alarming the parents. The follow up of this cohort will be further continued.

**P2-d2-547** Fat Metabolism and Obesity 3

**Distributions of serum lipid levels, prevalence of dyslipidemia, and prevalence of potentially qualified for pharmacological treatment among korean children and adolescents ages 10—18 years**

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Background: Dyslipidemia is one of the important risk factors for cardiovascular disease. The reduction of dyslipidemia might reduce cardiovascular morbidity and mortality in adulthood. Recently, American Academy of Pediatrics (AAP) updated guideline on lipid screening in childhood. Thus, it is important to know the lipid distributions and prevalence of dyslipidemia among Korean children and adolescents based on other risk factors such as obesity, hypertension, smoking, and diabetes.

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Horm Res 2012;78(suppl 1) 169
Methods and results: Data from 2,438 examinees aged 10 to 18 years in Korea National Health and Nutrition Examination Survey IV (2007—2009) were used. The reference values of each lipid profile were made according to age and sex. The mean serum level for total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TGs), and high-density lipoprotein cholesterol (HDL-C) were 158 mg/dL, 91 mg/dL, 90 mg/dL, and 49 mg/dL, respectively. The 95th percentiles for TC, LDL-C, and TGs were 204 mg/dL, 129 mg/dL, and 186 mg/dL. The 5th percentile for HDL-C was 36 mg/dL. Depending on the cut points used, the prevalence of dyslipidemia of TC, LDL-C, TGs, and HDL-C were 6.7%, 4.8%, 10.1%, and 7%, respectively. Considering risk factors, approximately 0.95% of children and adolescents were potentially eligible for pharmacological treatment according to AAP guideline.

Conclusion: These findings provide the lipid distribution, prevalence of dyslipidemia, and prevalence of pharmacological treatment among Korean children and adolescents. This information might be useful not only Korean but also Asian in planning programs for the prevention of cardiovascular disease through lipid control from childhood.

Body composition analysis is useful to identify early puberty girls with high body fat. We found that a given normal BMI could reflect very large differences in body fatness in school children similar to DXA scans although with lower values. Conclusions: Body composition analysis is useful to identify early puberty girls with high body fat percentage. It should be applied in monitoring lifestyle modification intervention effect in EP girls to prevent obesity complications.

Background: Earlier onset of puberty is observed in association with increasing the prevalence of obesity.

Objective and hypotheses: The purpose of this study was to analyze the body composition and growth state in central precocious puberty (CPP) and early puberty (EP) girls. Our hypothesis was EP girls have higher fat component in body composition compare to CPP girls with similar height and weight.

Methods: Data of 105 girls were obtained, who visited our hospital with early onset of breast budding and performed GnRH stimulation test. We defined subjects in two-groups by the level of peak leuteinizing hormone (LH), peak LH level ≥5 mIU/L is CPP (n=49), peak LH level <5 mIU/L is EP (n=56). Height and weight were measured and body mass index (BMI) was calculated. For body composition component, fat mass (FM) and fat-free mass (FFM) were measured by bioelectric impedance analysis and fat mass index (FMI), fat-free mass index (FFMI) and percent of body fat (PBF) were obtained.

Results: There is no difference of height, weight, height z-score between CPP and EP groups. But weight z-score (p=0.045), BMI (p=0.015), BMI z-score (p=0.006), PBF (p=0.018), FM (p=0.047), FMI (p=0.017) were significantly higher in the EP group than CPP group.

Conclusions: In EP girls, increased BMI were attributed to increased FMI. Body composition analysis is useful to identify early puberty girls with high FM component. It should be applied in monitoring lifestyle modification intervention effect in EP girls to prevent obesity complications.

Methods and results: Five patients (4 male) aged 14-16 years (mean age 15.25) underwent bariatric surgery. Mean pre-operative BMI was 60.3 kg/m² and BMI SDS +4.3. Comorbidities included hypertension, insulin resistance, obstructive sleep apnoea, limited mobility and psychosocial issues. All 5 patients had prior involvement with local weight management services. Three patients had tried drug treatment with orlistat and/or sibutramine. Three laparoscopic gastric bypass procedures, 1 laparoscopic gastric banding (patient had a gastric balloon prior to band) and 1 laparoscopic sleeve gastrectomy was performed. No major post operative procedural complications were noted (one patient had a port rotation).

Results: Mean percentage of weight loss as a percentage of total body weight at 3 months and 6 months was 11% and 13.25% respectively. Three year data for 1 patient showed 15% weight loss but disappointingly at 5 years, this has not been sustained. Mean BMI at 3 months post procedure was 53 kg/m2 and BMI SDS +4.1. Mean BMI and BMI SDS at 6 months was 51 and +4.0. Resolution of hypertension, increased physical activity and improved school attendance were some of the other benefits noted. No patient developed T2DM.

Conclusion: Recent systematic reviews and meta-analyses suggest that bariatric surgery results in sustained and clinically significant reduction in BMI in adolescents. There were no significant changes recommended in the 2011 review of the previous NICE guideline. Short term follow up data on our cohort of patient’s shows initial significant weight loss but less than suggested from previous data with longer term outcomes awaited. The surgical option should continue to be exercised with extreme caution and only in severely obese adolescents.

Background: Body mass index (BMI) may not be a very good measure of body fat in children if the aim is to predict future disease risk. Body fat percentage derived from DXA scans is widely recognized as a better measure when evaluating fatness; however this method is often not available for clinical purposes.

Objective and hypotheses: We aimed to provide a reference material for fat percentages of healthy Danish children, and to investigate correlations between body fat percentages calculated from skinfold-measurements, DXA scans and BMI in children.

Methods: Height, weight, and skinfolds were measured in a large longitudinal cohort of Danish children (n=2500) at age 0, 3, 18, 36, months once, at age 4-9 years, and again twice at age 6-14 years (12850 examinations). DXA scans were performed once at age 6-14 (n=1116). We calculated body fat percentages from skinfold-measurements (Slaugther et al) and gender/age specific BMI Z-scores.

Results: Reference curves for fat percentage were constructed. BMI and BMI Z-score correlated positively with fat percentages (r= 0.776, P<0.001). Fat percentage calculated from skinfolds correlated strongly with DXA fat %, (n=1078, r=0.872, P<0.001). Fat percentage from skinfolds was generally 15% lower than fat % from DXA. A child with a normal BMI for gender and age (BMI Z-score between -1 and 1) had body fat between 6-35 % (boys) and 9-27 % (girls) measured by DXA and between 6-28 % and 9-27 % respectively when evaluated with skinfolds.

Conclusions: Fat percentages derived from skinfolds appear to reflect “true” fatness in school children similar to DXA scans although with lower values. Corresponding to the well known clinical entity of “skinny fat” individuals, we found that a given normal BMI could reflect very large differences in body fat percent.
Background: Obesity is associated with an accumulation of macrophages in adipose tissue. This inflammation of adipose tissue is a key event in the pathogenesis of several obesity-related disorders, particularly insulin resistance.

Objective and hypotheses: We sought to develop an in vitro model of inflamed adipose tissue to study the interaction of adipocytes and macrophages.

Methods: Human THP-1 monocytes were differentiated into macrophages by incubation with 125 ng/ml phorbol 12-myristate 13-acetate for 48 h. Macrophage differentiation was controlled by flow cytometry. Macrophage-conditioned media (MacCM) were collected after 48 h. Human SGBS adipocytes and adipocytes were either cultured with MacCM or directly cultured with THP-1 macrophages. Adipogenic differentiation, insulin-stimulated glucose uptake as well as lipogenesis, and the secretion of adipokines was studied.

Results: Incubation with 10% MacCM or co-culture of SGBS cells and macrophages at a ratio of 1:1 completely blocked adipogenic differentiation as seen by inhibition of triglyceride formation. Insulin-stimulated glucose uptake was robustly inhibited by MacCM (inhibition by 50% at insulin 10 nM and MacCM 10%). Consequently, insulin-stimulated de novo lipogenesis was blocked to a similar extent accompanied by reduced phosphorylation of Akt. Treatment with MacCM shifted the expression of adipokines towards a pro-inflammatory profile with increased expression of IL-6 and IL-8 and reduced expression of adiponectin.

Conclusions: Perfectly mimicking the biology of inflamed adipose tissue in vivo, this in vitro model is a useful tool to study adipose inflammation in vitro. It can be easily extended for usage with human primary macrophages and fat cells.

Background: The WHO predicts that by 2015 approximately 2.3 billion adults will be overweight (OW) and more than 700 million will be obese (O). In 2005, at least 20 million children (Ch) under the age of 5 were OW. O is determined by a complex interaction of prenatal, perinatal, genetic, and other factors.

Objective and hypotheses: The aim of the study is to investigate different maternal risk factors in pregnancy (P) and delivery (D) for development OW and O in childhood.

Method: Target group: elder Ch and adolescents 10-18 y.o.: Gr.1 - 30 OW Ch, Gr.2 - 65 O Ch. Diagnostic criteria: Body mass index (BMI) over the 85th percentile for OW Ch, BMI over 95-th for O Ch for age and sex (CDC, 2000). Control group (C.Gr) - 35 healthy Ch with normal BMI. The association between medical history of P and D, maternal risk factors and childhood OW and O was investigated.

Results: Non-physiological P was observed in 54.17% of Gr.1 and in 72.73% Gr.2 compared to 24.14% patients from C.Gr. In many cases first trimester gestosis (Gr.1 – 25.00%, Gr.2 – 29.55%) and risk of miscarriage (Gr.1 – 29.17%, and Gr.2 – 25.00%) were observed. Excessive increase in a body weight during P is a big risk factor for OW or O in a child. Mothers of O and OW Ch during P were more likely to have edema (Gr.1 -8.33%, Gr.2 – 22.73%), P hypertension (Gr.1 4.17%, Gr.2 9.09%), gestational pyelonephritis (Gr.1 0.00%, Gr.2 9.09%), intrauterine fetus hypoxia (Gr.1 0.00%, Gr.2 9.09%), iron-deficiency anemia (Gr.1 16.67%, Gr.2 27.27%) compared to mothers of Ch from C.Gr.

Mothers of OW and O Ch more often have premature D or to deliver after 42 gestational weeks, and have pathological labor period either an accelerated or powerless labor.

<table>
<thead>
<tr>
<th></th>
<th>Gr.1 (n=30)</th>
<th>Gr.2 (n=65)</th>
<th>C. Gr. (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminated pregnancy</td>
<td>75.06</td>
<td>74.91</td>
<td>96.55</td>
</tr>
<tr>
<td>Cesarean sections</td>
<td>8.34</td>
<td>2.27</td>
<td>10.34</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>12.51</td>
<td>13.62</td>
<td>3.45</td>
</tr>
<tr>
<td>Delivery after 42 gestational weeks</td>
<td>8.34</td>
<td>13.62</td>
<td>-</td>
</tr>
<tr>
<td>Accelerated labor</td>
<td>25.00</td>
<td>20.45</td>
<td>-</td>
</tr>
<tr>
<td>Powerless labor</td>
<td>8.34</td>
<td>18.18</td>
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</table>

Conclusions: Non-physiological pregnancy and pathological delivery period are both risk factors for development of OW and O in Ch and adolescents. Investigation of P and medical history should be taken into consideration during investigation of Ch with normal BMI as a predicting factor of development of excessive weight.
Background: The prevalence of obesity in children is increasing all over the world.

Objective and hypotheses: To investigate the changes of clinic and laboratory variables of obese children between 2002-2010, in our center.

Methods: 1054 patients who presented to Pediatric Endocrinology Clinic for obesity between 2002-2010 years were included to the study. Patients were evaluated according to admission date (2002-2005 and 2006-2010). Laboratory and clinical data of the patients were obtained from the hospital records.

Results: 1054 children (577 female, 477 male) aged between 5.6 to 18 years were included in the study. The mean age was 11.8 years, body mass index(BMI) was 27.8 kg/m2, relative BMI was 147.9%. Patients who had family history of obesity were more obese and had higher waist and hip circumferences and fasting glucose levels. The frequencies of dyslipidaemia, hepatosteatosis, hypertension, were 38.1%, 39.9%, and 63.9% respectively. Metabolic syndrome rate in children above 10-year-old was 7.0%. Dyslipidemic patients had higher age, relative BMI, systolic and diastolic blood pressure, waist and hip circumferences, insulin, ALT levels and HOMA-IR score. Patients with hepatosteatosis had higher age, relative BMI, systolic and diastolic blood pressure, waist and hip circumferences, fasting insulin, triglyceride, ALT levels, HOMA-IR score; lower HDL cholesterol level. The frequency of hypertension was higher and the frequency of hepatosteatosis was lower in girls. The patients who admitted the last four years although didn’t have any differences in age and relative BMI, they had higher waist and hip circumferences, waist/hip ratio, ALT levels; lower HDL cholesterol levels than the first five years. Hepatosteatosis and dyslipidaemia had seen increased rates in the last four years.

Conclusions: Our results suggested that, obesity-related metabolic disorders are getting worse, although obesity severity and admission age didn’t change. We thought that childhood obesity will be more problematic in the future.

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Factors affecting the timing of adiposity rebound

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Background: The age of adiposity rebound (AR), when body mass index (BMI) starts to rise after infancy, is thought to be an origin of obesity in later life. We have already reported that children who exhibited an earlier AR were associated with the higher BMI value and atherogenic metabolic status at 12 years of age. We investigated which factors influenced on an earlier AR, birth weight, initial feeding, family history, meals or exercise.

Methods: A total of 533 children in the community were enrolled in the study. Serial measurements of BMI from 4 months to 12 years were carried out prospectively. We calculated the age of AR, defined as the age which the lowest BMI occurred during this period. The subjects were divided into 2 groups according to BMI at 3 years is bigger than at 1.5 years (earlier AR group) or not (later AR group). We asked the answering to the question sheet about the question sheet about weight at birth, initial feeding (breast-feeding, bottle-feeding or mixed feeding), family history, meals, and exercises of their parents when children were at 3 years old. We also analyzed which BMI predicted the obesity at 12 years old, 4, 8, 12, 18 month or 2, 3, 4, 5 or 6 years by using ROC analysis.

Results: Weight at birth was associated with earlier AR if birth weight was over 3500g, but was not associated with the timing of AR if it was between 1500g and 3000g. Initial feeding was not related to the timing of AR and the frequency of obesity at 2 years old. None of the breast-feeding subjects showed severe obesity at 12 years old. The factors as follows were associated with later AR; eating breakfast everyday, not eating snacks, non-obese father, the first baby, going to kindergarten. Contrary to expectation the habits of drinking sweet beverages and playing outside were not related to earlier AR.

BM1 at over 2 years old predicted to the obesity at 12 years old, but BMI in the infantile periods did not.

Conclusions: This study showed that obesity at 12 years old was associated with weight gain over 2 years old, but not with the weight gain during infantile period.

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Adipocyte aquaglyceroporin 7 (AQP7) protein expression: a comparative study of lean and obese children, adolescents and adults

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Background: Adipocyte AQP7 expression in three isoforms, 41,37 and 34kDa, plays a pivotal role in adipocyte glycerol efflux.

Objective and hypotheses: To compare AQP7 expression of lean and obese children, adolescents and adults to determine aits physiological changes with increasing age and b)its involvement in obesity.

Methods: AQP7 protein expression was investigated by Western Immunoblotting in primary adipocyte cultures from surgical biopsies of subcutaneous adipose tissue from 41 obese (BMI>95%) and 61 lean (BMI<85%) prepubertal children and adolescents, and 9 morbidly obese (BMI=45) and 6 lean(BMI=27) adults. The children were divided into two prepubertal groups, Group A:2mos-7yrs and Group B:8-12yrs and into pubertal Group C(10-15yrs).

Results: AQP7 in the mature adipocytes showed that: 1)the 34kDa isoform was significantly increased in lean and obese adults (p<0.05), whereas the 37kDa isoform was significantly increased in the lean adults vs. the lean children of Groups A and B (p=0.016;p<0.005) respectively, 2)the 34kDa isoform decreased significantly(p<0.008) in the obese adults vs their lean, 3)the 41kDa isoform was more frequently expressed in the obese children than in the obese adults, and 4)its 34kDa isoform was equally present in the lean adults and children. Most of the morbidly obese adults lacked the 41kDa isoform of AQP7.

Conclusions: In the lean groups, the AQP7 37 and 34kDa isoforms appear to increase with age, especially in the lean adults,whereas the 34kDa isoform decreases in the obese, possibly resulting in glycerol accumulation in the lipid droplet, contributing to their adipocyte hypertrophy. On the contrary, in the pubertal children, the 41kDa isoform shows a higher frequency of expression and is decreased in the obese adolescents possibly indicating its importance in the glycerol metabolism of the developing child. The lack of the highly glycosylated 41kDa AQP7 in the morbidly obese adults, may reflect their higher risk for developing the comorbidities of central obesity.

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Rapid-onset obesity, hyperventilation, hypothalamic dysfunction, autonomic dysregulation, and neural tumor (ROHHADNET) syndrome in two Italian patients: clinical characterization and exome sequencing analysis

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Background: ROHHADNET syndrome is often misdiagnosed. Finding the gene responsible for ROHHADNET pathogenesis will allow molecular diagnosis and genetic counseling.

Objective and hypotheses: We present our preliminary results of exome sequencing analysis in two patients with ROHHADNET syndrome.
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**Neck circumference and waist to height index are good predictors of blood pressure levels in school children**

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**Background:** Hypertension is a major health problem, under-diagnosed in children. Early identification of children at risk for high blood pressure levels is important to prevent cardiovascular complications. Excess body fat, particularly central adiposity, are recognized as important predictors of hypertension. Considering that body mass index (BMI) does not adequately describe regional adiposity, other indices of body fatness have been explored.

**Objective and hypotheses:** To investigate the ability of different anthropometric parameters (BMI, neck circumference, waist circumference and waist to height index) in predicting blood pressure (BP) levels in children from a middle city in southeast of Brazil.

**Methods:** A total of 320 children aged 6 to 13 years were evaluated. Weight, height and waist and neck circumferences were measured. BP levels were measured three times and converted to standard deviation scores (SDS) adjusted for sex, age and height. Hypertension was defined following the criteria of the 2004 Task Force Report on High Blood Pressure in Children and Adolescents.

**Results:** The prevalence of high BP was 6% (3% pre hypertensive and 3% hypertensive children). Among those who were obese, this prevalence increased to 11%. Systolic blood pressure (SBP) SDS were significantly related to BMI SDS (p = 0.003) and waist to height index (W/H-I) (p < 0.001). Diastolic blood pressure (DBP) SDS showed linear association with BMI SDS (p = 0.005), W/H-I (p = 0.008) and neck circumference (p = 0.004). The best individual predictor of SBP was the W/H-I (R² = 0.037). Neck circumference was superior to both BMI and W/H-I in predicting DBP, explaining 2.6% of observed variability.

**Conclusions:** BMI, waist to height and neck circumference are useful tools to predict BP levels in children. Neck circumference is a simple measurement which has been undervalorized, and may be used as a valuable screening method for diastolic blood pressure.

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**Increase in maximal isometric grip force (MIGF) is associated with increase in insulin sensitivity in obese children and adolescents during lifestyle intervention**

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**Background:** Obesity is a risk factor for impaired insulin sensitivity. Physical activity increases muscle force and should increase insulin sensitivity.

**Objective:** Aim of the study was to investigate muscle force and insulin sensitivity in obese children and adolescents during a short term intervention.

**Patients and methods:** We investigated 86 obese children and adolescents (43 females) before and after 6 months of a short term uncontrolled lifestyle intervention (increase in physical activity, e.g. strength training, nutritional recommendations). Mean (SD) age of patients was 12.3 (2.8) yrs and BMI SDS was 2.9 (0.5). In all patients serum insulin levels were measured with a commercial assay. MIGF was measured with a hand dynamometer (JAMAR LMS) at start and after 6 months. Values were transformed in age and gender related SDS.

**Results:** Initial mean MIGF SDS and insulin levels were 1.2 (1.4), and 146 (81) pmol/L. All patients had normal fasting glucose levels. After 6 months mean MIGF SDS and mean insulin level did not change significantly. Patients with the lowest initial MIGF SDS had the highest initial insulin levels (R² = -0.32, p = 0.0016). After six months, this group of patients (n=22) showed a significant increase of their MIGF SDS. In patients with highest MIGF at
start of intervention, we observed the opposite (R=−0.50, p<0.001). Changes in MIGF were correlated negative with changes in insulin levels (R=−0.24, p=0.015).

Conclusions: Mean MIGF SDS and mean insulin levels did not change in obese children and adolescents after an uncontrolled intervention. However, a subgroup of patients, who had initially high insulin levels and low MIGF SDS, increased their MIGF SDS due to increase in physical activity (strength training). This change was associated with a decrease of insulin levels. The measurement of MIGF is a cheap and easy tool to measure the adherence to physical activity interventions (strength training) in obese children and adolescents.

Background: Diet management is important in children with Prader-Willi Syndrome (PWS).

Objective and hypotheses: To investigate the effect of growth hormone (GH) treatment on energy intake in children with PWS, in relation with body composition and resting energy expenditure (REE).

Methods: We evaluated energy intake with use of 5-day dietary records in 47 children with PWS, in a randomized controlled GH trial. Body composition was measured by DXA. REE was calculated by the equation of Müller. Baseline characteristics were expressed as mean ± SD. Results were analyzed with repeated measures ANOVA.

Results: Infants (age 2.4 ± 0.9 yr, n=19) treated with GH demonstrated significantly higher increase in energy intake after 12 months compared to untreated infants (230 ± 40 vs. 76 ± 48 kcal/d, P=0.02), whereas no significant changes were observed between GH treated and untreated pre-pubertal children (age 7.0 ± 2.4 yr, n=28). Change in energy intake after 12 months was inversely related with change in body fat percentage SDS in all infants (r=−0.6, P=0.03) and all pre-pubertal children (r=−0.6, P<0.01), especially during GH treatment in pre-pubertal children (r=−0.8, P=0.01). Adiponectin levels increased after 12 and 24 months were positively correlated with the increase in energy intake (r=0.6, P<0.01, n=10 and r=0.8, P<0.01, n=12). Increases in energy intake by GH treatment did not show a significant correlation in REE changes (r=0.1, P>0.66).

Conclusions: In this study we found a protective role of GH treatment in relation to obesity in infants and children with PWS. Infants treated with growth hormone have a significant increase in energy intake with a significant decrease in body fat percentage. During GH treatment, changes in energy intake are inversely related to the fat mass and positively correlated with adiponectin. Increasing adiponectin levels are in line with high insulin sensitivity in PWS.

Effects of growth hormone treatment on dietary energy intake, body composition and resting energy expenditure in children with Prader-Willi Syndrome

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Prevalence of non alcoholic fatty liver disease (NAFLD) in obese children and the role of uric acid on the development of insulin resistance and hepatosteatosis

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Results: Mean age of obese patients was 12.1±2.1 and mean age of controls was 12.2±2.0 (p=0.28). NAFLD was detected in 94 (46.3%) of 203 obese children and adolescent, the frequency of obesity and metabolic syndrome is increasing in parallel. Nonalcoholic fatty liver disease (NAFLD) is a common liver disease that often coexists with other features of the metabolic syndrome. Uric acid level is a simple, cheap and widely available routine biochemical parameter. Hyperuricemia increases the risk of NAFLD and several metabolic disorders such as insulin resistance in obese subjects.

Objective and hypotheses: To determine the prevalence of NAFLD in obese children and to investigate the role of uric acid on insulin resistance and development of NAFLD.

Methods: Study included 203 exogenous obese children and 69 healthy age-matched controls. Serum uric acid level, lipid profile, fasting glucose and insulin level were measured in all patients and control. A standart oral glucose tolerans test was performed to obese subjects to evaluate glucose metabolism. Hepatosteatosis was graded as grade-I, grade-II and grade-III according to hepatobiliary ultrasound findings. Patients was divided into 3 groups; control(group A), obese NAFLD(-) (group B) and obese NAFLD(+) (group C).

Conclusions: We evaluated energy intake with use of 5-day dietary records in 47 children with PWS, in a randomized controlled GH trial. Body composition was measured by DXA. REE was calculated by the equation of Müller. Baseline characteristics were expressed as mean ± SD. Results were analyzed with repeated measures ANOVA.

Results: Infants (age 2.4 ± 0.9 yr, n=19) treated with GH demonstrated significantly higher increase in energy intake after 12 months compared to untreated infants (230 ± 40 vs. 76 ± 48 kcal/d, P=0.02), whereas no significant changes were observed between GH treated and untreated pre-pubertal children (age 7.0 ± 2.4 yr, n=28). Change in energy intake after 12 months was inversely related with change in body fat percentage SDS in all infants (r=−0.6, P=0.03) and all pre-pubertal children (r=−0.6, P<0.01), especially during GH treatment in pre-pubertal children (r=−0.8, P=0.01). Adiponectin levels increased after 12 and 24 months were positively correlated with the increase in energy intake (r=0.6, P<0.01, n=10 and r=0.8, P<0.01, n=12). Increases in energy intake by GH treatment did not show a significant correlation in REE changes (r=0.1, P>0.66).

Conclusions: In this study we found a protective role of GH treatment in relation to obesity in infants and children with PWS. Infants treated with growth hormone have a significant increase in energy intake with a significant decrease in body fat percentage. During GH treatment, changes in energy intake are inversely related to the fat mass and positively correlated with adiponectin. Increasing adiponectin levels are in line with high insulin sensitivity in PWS.

Prevalence of non alcoholic fatty liver disease (NAFLD) in obese children and the role of uric acid on the development of insulin resistance and hepatosteatosis

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children (grade I in 53, grade II in 38 and grade-III in 3 patients respectively). Serum uric acid level was higher in obese NAFLD+ patients than in obese NAFLD- controls (Figure; p=0.0001). Patients in group C had higher HOMA-IR than of group A and group B (HOMA-IR were 1.3±0.7; 3.2±2.1; 4.8±2.6 in group A,B and C respectively, p<0.0001). There was positive correlation between uric acid level and HOMA-IR (r=0.50; p<0.0001).

Conclusions: In present study in a large cohort we showed that NAFLD affects approximately half of obese children. Uric acid level is a valuable marker for NAFLD and insulin resistance in obese children.

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Gastric banding procedure for morbidity in adolescents: results of 12 months follow-up

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Background: Last year we presented the first results of a pilot study concerning the chirurgical approach (gastric banding procedure - GBP) to severe obesity in young adolescents. Preliminary results supported that GBP may be an alternative to the classical approach in young obese. Nevertheless, no definitive conclusion can be stated before an adequate period of follow-up (1).

Objective and hypotheses: Aim of the study was to evaluate the efficacy, safety and quality of life in our cohort of obese patients after a 12 months follow-up.

Methods: From the initial cohort of 14 patients (10 F/4 M), 12 were followed up to 12 months. All patients had a tightening of gastric banding between month 3 and month 6 in case of insufficient weight loss, according to study protocol.

Results: Two patients (two girls) were lost at follow up (at month 1 and 6, respectively) and one of them had her gastric banding removed due to slipping of the band. All but one patient presented a significant weight loss, ameliorating their BMI. Mean weight at the time of the surgery was 106.29 ± 9.76 kg versus 87.53 ± 13 after 12 months, representing a variation of BMI from 38.95 ± 3.52 to 31.15 ± 4.36 (from 4.28 ± 0.54 to 3.061 ± 0.98 in terms of kg versus 87.53 ± 13 after 12 months, representing a variation of BMI from 38.95 ± 3.52 to 31.15 ± 4.36 (from 4.28 ± 0.54 to 3.061 ± 0.98 in terms of

Conclusions: GBP procedure confirms its reliability after a 12 months follow-up. Results after a long-term follow up (i.e. five years) will allow a definitive

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The role of sleeping efficacy and sedentary time on obese children's health

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Background: Children obesity is a growing disorder leading to a reduced quality of life during childhood and adolescence and to an increase of metabolic-related diseases. Primary aim of this study was improving our knowledge about its causes.

Objective and hypotheses: The aim of the study was to observe the relationship of spontaneous physical activity and aerobic fitness with some metabolic indicators of health in obese children.

Methods: Twenty-seven prepubertal overweight-obese children (9.73±1.57 yrs, 26.86±3.71 BMI) were recruited by the Regional Center of Auxology and Pediatric Nutrition at the “S.Liberatore” Hospital of Atri (Italy). Body composition, blood pressure, plasma values of glucose, insulin, glutamic oxaloacetate transaminase (GOT), glutamate pyruvate transaminase (GPT), total cholesterol, high-density lipoprotein cholesterol and tryglicerides were investigated. Insulin sensitivity was measured through the quantitative insulin sensitivity check index (QUICKI). Spontaneous physical activity of participants was measured through a multisensor device (i.e. Sensewear Armband) for 7 consecutive days, and 6-min walking test (6MWT) was used to measure aerobic fitness.

Results: Linear regression model showed that sleeping efficacy (i.e. nocturnal sleep to nocturnal lying down) is related, through an inverse relationship, to BMI (p=0.01) and mean arterial blood pressure (p=0.006), and to QUICKI (p=0.02), through a direct relationship, whereas it was inversely correlated with sedentary time (r=-.965, p<.001). Linear regression analysis also showed that 6MWT (p=.02) and sedentary time (p=.03) predicted plasma values of GPT, throught negative and positive relationship respectively.

Conclusions: Our preliminary data suggest the importance of increasing aerobic capacity for its relation with GPT and reducing the children’s sedentary time, giving its relation with sleeping efficacy, which was in turn correlated with BMI, blood pressure and QUICKI.

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Laboratory and imaging studies in obese children: is there a correlation with a family history of obesity, cardiovascular disease and/or type 2 diabetes?

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Background: Excess body weight in children predisposes to cardiovascular disease, dyslipidemia, impaired glucose metabolism. Parental obesity is an important predictor of childhood obesity.

Objective and hypotheses: The aim of this study was to determine the relationship between biochemical and imaging characteristics of obese children and a family history (FH) of cardiovascular disease (CVD) and/or type 2 diabetes (T2D).

Methods: 48 obese children (22 boys, 26 girls) underwent auxology (weight (Wt), height (Ht), aist circumference (WC), Body Mass Index (BMI), blood pressure (BP)). An oral glucose tolerance test (OGTT) was performed, fasting blood samples were obtained for lipid and liver profile. Insulin resistance (IR) was determined by the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR). Non-alcoholic fatty liver disease (NAFLD) was assessed by liver ultrasound and an alanine aminotransferase (ALT). FH of CVD disease and/or T2DM, parental BMIs were recorded.

Results: Children’s mean age was 8.98 years old (range 2.2-13.5). All had BMI>97th percentile, WC>90th percentile for age and sex. The children with systolic BP (SBP)≥90th centile (27%), lower high-density lipoprotein cholesterol (LDL);≥130mg/dl (6.2%), lower high-density lipoprotein cholesterol (HDL);≥40mg/dll (37.5%), high triglycerides (TG)≥150mg/dl(31.2%), fatty infiltration of the liver (18.7%) and dysglycaemia (29.1%) were more likely to have a positive FH of CVD disease and/or T2DM (p<0.05). 4 children had impaired fasting glucose≥100mg/dl,10 impaired OGTT. 20.8% of all children showed insulin resistance (HOMA, IR index>2.5), 53.8% a positive FH of CVD and/or T2DM, were positive in 67.3%, 50% and 32.6% of the children respectively. Parents were overweight in 23.3%, obese in 44.3% (class I 27.7%, II 11.1%, III 5.5%). One child had a raised ALT (>40UL) and fatty infiltration of the liver.

Conclusions: Obese children with positive FH history of overweight/obesity, CVD disease and/or T2DM are at more risk to develop higher SBP, impaired glucose tolerance and abnormal lipid profiles than those with negative family history.

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Evidence of impaired endothelial and oxidative stress markers across rising categories of "normal" 2hr glucose levels in obese youths

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Background: Obese youths with high normal 2-hour (2hr) post OGTT glucose levels already display defects in both insulin secretion and sensitivity. The aim of the study was to evaluate the serum concentration of selected adipokines: adiponectin, leptin, resistin, retinol binding protein 4 (RBP-4) in obese children with special regard to correlations between their levels and the ultrasound grade of the liver steatosis.

Objective and hypotheses: We sought to determine whether obese youths with high "normal" 2hr post OGTT glucose levels also display impaired endothelial and oxidative stress markers, well known risk factors for cardiovascular disease (CVD).

Methods: A group of 94 obese youths and 37 healthy (12.1±3.1 and 11.4±3.3, years) matched peers were recruited. Fasting blood and urine samples were obtained for the evaluation of insulin, blood glucose and lipid profile. Adiponectin, leptin, resistin, retinol, Dimethylarginine (ADMA), serum and urinary Nitric Oxide (s- and u-NO) were determined as markers of endothelial dysfunction and hs-CRP, ezRAGE, sRAGE, and urinary PGF-2α/PAF as oxidative stress indexes. HOMA-IR was calculated as index of insulin sensitivity. An OGTT was performed, in all obese subjects, and according to the 2hr glucose levels, subjects were divided into three groups (<100, 100-119, 120-139, mg/dl). Differences across controls and 2hr categories were evaluated by ANCOVA adjusting for age, gender and pubertal stage.

Results: BMI and BMI-SDS were higher in obese compared to controls (all P<0.001), while no difference was documented across the 2hr glucose levels groups (all P>0.05). HOMA-IR values significantly increased across the four groups (P for trend <0.001). ADMA levels significantly increased (P for trend <0.001) while s-NO (P for trend <0.001) and u-NO (P for trend <0.04) decreased across the four groups. Similarly, hs-CRP (P for trend <0.001) and PGE-2/PAF (P for trend <0.001) concentration significantly increased while ezRAGE (P for trend <0.001) and sRAGE (P for trend <0.001) decreased across the control and 2hr glucose levels groups (P for trend <0.001).

Conclusions: Across rising categories of normal 2hr glucose levels, obese youths exhibit already progressive impairment of markers of endothelial dysfunction and oxidative stress, defining an increased risk for adulthood CVD.

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Serum concentration of adiponectin, resistin, retinol binding protein 4 and leptin in obese children with non-alcoholic fatty liver disease

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Objective and hypotheses: The aim of the study was to evaluate the serum concentration of selected adipokines: adiponectin, leptin, resistin, retinol binding protein 4 (RBP-4) in obese children with special regard to correlations between their levels and the ultrasound grade of the liver steatosis.

Methods: In this study, 148 pubertal children aged between 8-18 years (12.2±3.225) with a BMI of over 95th percentile regarding sex and age were evaluated. The control group included 63 sex-, age- and pubertal stage-matched non-obese healthy subjects without liver steatosis. After a minimum of 12-14 hours fasting samples for fasting blood glucose, lipid profile (TG, LDL, VLDL, HDL, total cholesterol) leptin, adiponectin, resistin, RBP-4 and insulin levels were taken. Ultrasonographic examination of liver was performed by an experienced radiologist.

Results: Sixty three children (42.5%) had a liver steatosis: 44 of them (69.8%) score1-2 (mild liver steatosis) and 19 children (32.2%) had an advanced steatosis (score 3). The concentration of adiponectin and resistin was significantly lower in children with advanced liver steatosis (p<0.05). The concentration of RBP-4 was significantly higher in children with advanced liver steatosis (p<0.0001). Adiponectin, resistin and RBP-4 ability to differentiate the children with an advanced and liver steatosis from those with mild steatosis was found significant (AUC=0.809±0.0573, p<0.0001; 0.661±0.0765, p<0.005; 0.782±0.0557, p<0.0001, respectively). A serum adiponectin level (cut-off) above 2.56 µg/ml had sensitivity of 84.21% and specificity of 63.64%, serum resistin level (cut-off) above 5.2 ng/ml had sensitivity of 36.8% and specificity of 95.5%, and serum RBP-4 level (cut-off) above 35 µg/ml had sensitivity of 84.20% and specificity of 68.20%. Leptin was not a good predictor of the ultrasonographically diagnosed liver steatosis.

Conclusions: In conclusion, these data suggest a role of both adiponectin, resistin RBP-4 and leptin in the pathogenesis of NAFLD in obese children.

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Health consequences of obesity and outcome of group-based treatment among obese children and adolescents

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Background: The increasing prevalence of obesity and its complications have been a concern around the world. Does obesity have an influence on intellectual capacity?

Objective and hypotheses: A 1-year prospective study was conducted to determine the prevalence of adverse health outcomes of obesity among obese children and adolescents and to evaluate the effectiveness of group-based treatment focusing on a healthy lifestyle and parental involvement on weight control and obesity complications.

Methods: Participants aged 8-18 years old with percent weight for height ≥120% were recruited and evaluated for metabolic disorders, abnormal liver function presumptive of non-alcoholic steatohepatitis (NASH), obstructive sleep apnea (OSA), microalbuminuria, and orthopedic complications. Participants and their parents were provided knowledge on healthy diet, appropriate exercise, and healthy lifestyle as a group-based session at 1, 2, 3, 6, and 9 months. Participants were reevaluated at 12 months after intervention.

Results: One hundred and twenty six participants (67 male and 59 female, mean age 12.3±3.1 years, percent weight for height 182.9±20.8, BMI 33.9±7.2 kg/m2) attended the study. Dyslipidemia (57.9%) was the most common adverse health outcomes, followed by NASH (28.6%), and OSA (26.2%). Type 2 diabetes, pre-diabetes, and metabolic syndrome were found in 2 (1.6%), 24 (19.0%), and 22 (17.5%) participants, respectively. Four participants had orthopedic complication and one participant had microalbuminuria. One hundred and fifteen participants completed a 1-year intervention program in which their percent weight for height and percent body fat decreased significantly (both p<0.001). Improvement in insulin resistance, lipid levels, and liver function were seen (all p<0.05). Numbers of participants with pre-diabetes, dyslipidemia, and NASH reduced significantly from baseline (all p<0.05).

Conclusions: Obese children and adolescents are at risk of developing complications of obesity. Group-based treatment was effective and resulted in improvement of obesity complications.

P2-d3-570 Fat Metabolism and Obesity 4

Does obesity have an influence on intellectual capacity?

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Background: Overweight and obesity may be associated with impaired mental function in the elderly. However, little information is available on whether there is an association between BMI and cognition in children and adolescents.

Hypothesis: Overweight and obesity may lead to metabolic alterations which influence cognition.

Objective: To study if there is an association between BMI and intellectual performance and to analyse whether birth characteristics will have modifying effect.

Methods: The study was performed as a retrospective cohort study of young males (n= 612 994) born 1973-1988 and conscripted for military service in 1991-2006. Birth characteristics were collected from the Swedish Medical Birth Registry and data on intellectual performance and BMI were obtained from the Swedish Conscript Register.

Results: A BMI above 30 kg/m2 was associated with an odds ratio (OR) of 1.95 (CI 95%, 1.89-2.01) for subnormal intellectual capacity at conscription.
In addition, ORs for subnormal intellectual capacity were consistently higher among obese subjects, regardless of birth characteristics. However, for those with low birth weight and obesity at conscription, the risk was even more pronounced (OR 3.04 CI 95%, 2.45-3.81).

Conclusions: A high BMI at conscription is associated with an increased risk of subnormal intellectual capacity. The risk is even more pronounced for obese subjects, who were born with a low weight for gestational age.

P2-d3-571 Fat Metabolism and Obesity 4
Severe obesity and cardiovascular risk factors in a cohort of Italian children and adolescents
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Background: The frequency of children with severe obesity (OBsev) is rising and has a high risk of tracking to adulthood.

Objective and hypotheses: We evaluated the frequency of OBsev among the obese patients referring to specialist paediatric outpatients clinic and analyzed the association with cardiovascular risk factors (RF).

Methods: 2943 obese subjects (1502 males), aged 5-18 years and followed at 15 care centers for obesity affiliated to ISPED/SIEDP were enrolled. Moderate obese (OBmod) were defined the subjects with BMI >95th percentile for age and gender according to the curves ISPED/SIEDP and OBsev people with BMI >99th percentile. The following conditions were considered indicative of cardiovascular risk: waist circumference > 90 percentile, systolic (SBP) and diastolic (DBP) blood pressure > 95th percentile for age, sex and height, triglycerides > 95th percentile, HDL cholesterol < 5th percentile, fasting glucose > 100 mg/dl.

Results: OBsev was present in 59.9% of patients, without gender difference (males 58.8%, females 61.1%). The age distribution was highest at 5 (83%) and 16 years (86.9%) and lowest at 11 years (45.5%). All cardiovascular RF, except hypertriglyceridemia, were significantly higher in patients with OBsev compared to OBmod.

Conclusions: OBsev represents the 60% of cases of obesity followed at specialist centres and presents more cardiovascular RF than OBmod. Since the management of children and adolescents with OBsev requires significant professional contact time with a trained multidisciplinary team, it is necessary to enhance the specialized centers dedicated to the care of Pediatric obesity in order to deal with the load relief that this disease causes and prevent or reduce the associated co-morbidities.

P2-d3-572 Fat Metabolism and Obesity 4
Obesity and asthma in iranian adolescents
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Background: Both asthma and obesity have become more common in western societies during the recent decades and several studies have shown a correlation between presence of asthma and obesity.

Objective and hypotheses: Many studies show that increased obesity is a risk factor for asthma however, there have been few studies on this subject in developing countries such as Iran.

Methods: The aim of this study was to evaluate the frequency of allergy and asthma in overweight and obese students. In this study, 2900 pupils (1700 females and 1200 males) attending 20 secondary schools, distributed all over Tehran, were questioned about asthma and allergy. Height and weight were measured using standard procedures and the BMI of each student was determined and adjusted for age- and sex-specific tables. The students were classified to normal, overweight, and obese.

Results: Prevalence of asthma in obese students was 14.7%, while it was 6.1% in normal students. 8.8% of overweight students reported asthma. Therefore asthma was significantly more frequent in obese and overweight students (P Value=0.05). The prevalence of allergy symptoms was not significantly different in overweight and obese students.

Conclusion: This study confirms earlier findings of an increased prevalence of asthma in obese and overweight patients. Increased obesity is thus a risk factor for asthma, which probably contributes to the high prevalence of asthma in recent years. Further research is needed on the associations between asthma and both obesity and being underweight, and on the benefits of weight loss in asthmatics.

P2-d3-573 Fat Metabolism and Obesity 4
Clinical observations, molecular genetic analysis, and treatment of homozygous LDL receptor defect in children
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Background: The clinical observation and treatment of children with homozygous LDL receptor defect has rarely been reported.


Results: The p.C308Y mutation was the most common mutation and was found in 31% of studied alleles. Four patients whose pretreatment serum total cholesterol levels were around 500 mg/dl had a fair response to high-dose HMG-CoA reductase inhibitor therapy (total cholesterol levels decrease to lower than 240 mg/dl). The other patients who had higher pretreatment total cholesterol levels had poor response to HMG-CoA reductase inhibitor therapy. Two patients of the poor responders received liver transplantation with good outcomes.

Conclusions: The relationship between genotypes and phenotypes, clinical manifestations and responses to different types of treatments in these patients are presented in this report.
**P2-d3-574 Fat Metabolism and Obesity 4**

**Vitamin D levels in a paediatric population of normal weight and obese subjects**

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**Introduction:** Vitamin D plays an important role on musculoskeletal composition, but new evidences highlight others possible pleiotropic effects on many tissues and also metabolic functions. Vitamin D insufficiency should be associated with all-cause mortality, in particular with cardiovascular disease and metabolic syndrome. International studies suggested that 25(OH)D level sufficiency should be established at 30 ng/ml, insufficiency between 30 and 20 ng/ml and deficiency lower than 20 ng/ml.

**Methods:** To evaluate vitamin D status, we studied vitamin D levels in a population of normal weight (NW) and obese (OB) children: 113 were NW children, 105 M and 8 F, 46 prepubertal and 67 pubertal children and 444 were OB, 219 M and 225 F, 299 prepubertal and 145 pubertal children.

**Results:** Only 28.3% of NW children showed normal levels of vitamin D, 40.6% showed vitamin D insufficiency while 22.1% showed a clear vitamin D deficiency. Among vitamin D deficient children, 8.8% demonstrated vitamin D levels lower than 14.5 ng/ml. Obese children showed a higher percentage of subjects with normal levels of vitamin D, 36.7% of subjects with vitamin D insufficiency and 44.4% of subjects with a status of vitamin D deficiency. Among these, 23.2% showed vitamin D levels lower than 14.5 ng/ml. Mean vitamin D levels in NW children (27.3 ± 1.2 ng/ml) resulted higher than in OB children (21.8 ± 0.6 ng/ml). No differences have been found between prepubertal and pubertal children in terms of vitamin D levels.

**Conclusions:** Our pediatric population demonstrates a low percentage of vitamin D levels sufficiency. In particular obese children show only 19% of subjects with normal levels while almost half of this population show a clear insufficiency. Further studies are needed to support these results and to evaluate the possible metabolic consequences.

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**P2-d3-576 Fat Metabolism and Obesity 4**

**Effect of weight reduction on leptin, total ghrelin and obestatin concentrations in prepubertal children**

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**Introduction:** There have been several studies reporting the role of insulin (I), leptin (L), ghrelin (Ghr) and obestatin (Obe) on energy homeostasis through control of appetite and energy expenditure. The published data concerning the possible relationships between childhood obesity and levels of Ghr, Ob and L at baseline and after an intervention program are conflicting. The aim of the study was to evaluate fasting levels of glucose, I, L, total Ghr and Obe in a group of prepubescent obese children before and after weight loss.

**Subjects and methods:** We enrolled 64 prepubescent obese children, but only 35 completed the study (mean age 7.6 ± 0.9 years, 19 females; BMI 25.5 ± 0.3 SDS) and 20 normal-weight prepubescent controls as children (BMI 0.1: 1.0 SDS). Fasting plasma concentration of glucose, I, HOMA-IR, L, Ghr and Obe levels were measured at baseline and after a 6 month lifestyle intervention (i.e. improved nutrition and increased physical activity). Hormone concentrations were assessed for all children by commercial Kits.

**Statistical analysis was performed.**

**Results:** At baseline, obese children showed significantly (p<0.001) higher L (44.6±6.7 vs 9.1±3.4 ng/ml) and Obe levels (134.9±10.6 vs 93.3±12.6 ng/ml), and lower Ghr concentrations (408.0±38.9 vs 672.2±106.0 ng/ml) than control subjects. Weight loss significantly (p<0.001) diminished plasma L (19.1±5.5 ng/ml) and I levels (7.1±4.4 µU/ml) and increased Ghr (438.4±47.2 ng/ml) and Obe concentrations (191.8±21.5ng/ml). At the end of follow-up, waist circumference correlated positively with T6 HOMA-IR (r=0.380; p=0.021) and at regression analysis there was a significant dependence on basal HOMA-IR (β=0.276; p=0.025).

**Conclusions:** Weight loss in prepubescent children is associated with a significant change in L, Ghr and Obe concentrations. These results confirm the hypothesis that levels of these hormones are closely associated with obesity in childhood and might take part, as consequence but not as a cause, in glucose, fat, and energy metabolism.

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**P2-d3-575 Fat Metabolism and Obesity 4**

**How reliable are HOMA-IR and fasting insulin in determining the insulin resistance in obese adolescents?**

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**Background:** In adolescents, HOMA-IR is frequently used to define insulin sensitivity.

**Objective and hypotheses:** The aim of the present study was to investigate IR in obese adolescents who have normal fasting insulin and HOMA-IR. A total of 97 obese adolescents (mean ages 14.0±2.2 years) who had values of HOMA-IR less than 3.16 and insulin levels less than 18 µU/ml were included in the study.

**Methods:** A standard OGTT was performed for all subjects. We divided the subjects into two groups: subjects with and without IR by using an insulin peak of ≥150 µU/ml and/or ≥75 µU/ml in 120 min after glucose charge. IR risk factors were defined as family history of diabetes mellitus, AN, and HS. Results: IR was detected in 61 patients (62.9%). There was no significant difference in the median values of HOMA-IR and mean levels of fasting insulin between IR and non-IR group. The IR group had significantly more frequent AN when compared to the non-IR group (p: 0.0001). Although the frequency of IR was higher in obese adolescents with HS or with family history of type 2 diabetes mellitus, that difference was not statistically significant. As the number of risk factors increased, the frequency of IR also increased (from %26.8 up to %80). These differences were found statistically significant (p: 0.01). Conclusions: Our results suggest that HOMA-IR is not reliable in determining IR. OGTT should be performed in order to decide the presence of IR, especially in obese adolescents with the above mentioned risk factors of IR. Ir: Insulin resistance AN: Acanthosis nigricans HS: Hepatic steatosis HOMA-IR: homeostasis model assessment for insulin resistance.
thyroid-stimulating hormone. There were no significant changes over time in insulin resistance or lipid profile in the whole study group or by treatment and no correlation between mean dose or treatment duration and auxological characteristics and fasting metabolic profile. All patients had a normal pattern of puberty and linear growth.

**Conclusions:** Long-term therapy with VPA or CBZ has no significant clinical or endocrinological effect on male children and adolescents with epilepsy, except for an increase in body weight during the first 6 months of treatment, with a decline thereafter. Further, longer prospective studies are required to corroborate our findings.

**P2-d3-578** Fat Metabolism and Obesity 4

**Prevalence of elevated TSH and autoimmune thyroiditis in obese children and adolescents**

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**Background:** The association between obesity and thyroid function is still under evaluation. Aim of the study was to assess the prevalence of elevated TSH levels in obese children and adolescents and to determine the prevalence of positive anti-thyroid antibodies among obese children and adolescents with raised TSH.

**Patients and methods:** Data from 230 children and adolescents with BMI>97th centile, aged 6-16 years, were examined retrospectively and compared to data from 230 age and sex matched controls with BMI within normal ranges. All children had their thyroid function assessed (fT4 or â4 and TSH).

**Results:** Elevated TSH>5 IU/ml levels, were found in 21 (9%) of obese children and adolescents, whereas only in two (0.95%) in the control group. In the group of 21 obese with raised TSH, only five were prepubertal, the rest of them being Tanner II-V. Among the pubertal obese children with raised TSH, four (25%) had positive anti-thyroid antibodies. Mean TSH levels of these four children (9.5 IU/ml), was higher than the mean value of the rest 17 of the group of obese children with raised TSH (5.7 IU/ml).

**Conclusion:** An increased prevalence of raised TSH levels was observed in obese children and adolescents. In some of them, especially during puberty, this finding can be attributed to autoimmune thyroiditis. However, in the majority of them it may be due to the obesity.

**P2-d3-579** Fat Metabolism and Obesity 4

**Overweight and obesity prevalence in children and adolescents between 2 and 16 years old**

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4Torrecárdenas Hospital, Pediatrics, Almería, Spain

**Background:** Obesity and overweight in children are public health problems. It is of crucial importance to identify their exact prevalence in order to plan for the resources needed to deal with them.

**Objective and hypotheses:** To calculate obesity and overweight prevalence in children and adolescents in our city and to research into associated factors.

**Methods:** Cross-sectional study. 1317 children and adolescents aged between 2 and 16. By means of a multistage probability sampling 3 groups of subjects were selected: 411 including individuals aged 12 to 16, 504 aged 6 to 12, and 402 aged 2 to 6. Body Mass Index was calculated and obesity and overweight were diagnosed using the threshold levels by International Obesity Task Force for children and adolescents. Parents were asked about eating habits, health, social and demographic aspects. Results are shown using percentages (95% confidence interval). The relation between obesity and overweight and the different variables was studied using multiple logistic regression. Adjusted Odd Ratio (OR) was calculated.

**Results:** 9.5% (8.0%-11.0%) of individuals aged 2 to 16 are obese and 22.4% (23.3%-24.6%) are overweight. In the group including individuals aged 12 to 16, 8.5% (5.9%-11.2%) are obese and 20.5% (16.7%-24.3%) are overweight. In the group of age between 6 and 12, 11.6% (8.9%-14.3%) and 31.0% (27.0-35.0) and in the group aged between 2 and 6, 8.0% (5.4%-10.6%) and 13.6% (10.3%-16.9%) respectively. Being obese or overweight is associated with age (OR 1.21; p<0.001), mother’s obesity (OR 10.99; p=0.008), weight at birth higher than 4 kg (OR 2.91; p=0.002) and formula feeding (OR 1.82; p=0.005).

**Conclusions:** Obesity and overweight in children and adolescents are highly prevalent problems in our city.

**P2-d3-580** Fat Metabolism and Obesity 4

**The association of overweight and obesity with kidney stone disease in children**

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**Background:** The prevalence of obesity and overweight has risen dramatically in the past decade in parallel with the increase in kidney stones in children. Health consequences of excess weight such as hypertension, diabetes mellitus, cardiovascular disease and chronic kidney disease are well known. Findings from few studies in adults show that obesity might increase the risk of kidney stone disease.

**Objective:** The purpose of this study was to evaluate the relationship between overweight and obesity and urolithiasis risk factors in children. Population and methods: The main kidney stones risk factors in urine such as calcium concentration, oxalate concentration, pH of urine as well as BMI (body mass index) and lipid profile in blood were analyzed in 249 overweight and obese children (study group) and in 281 children with normal weight (control).

**Result:** In the study group the mean oxalate concentration was significantly higher than in control (0.52±0.48 vs 0.26±0.12; p<0.05). The mean calcium concentration of overweight/obese patients was higher than those of normal body weight and the difference was close to statistically significant (3.23±2.55 vs 2.58±1.59; p=0.0537). The mean urine pH in the study group was 6.28±0.46 and was significantly lower (p<0.05) than the mean urine pH in control which was 6.40±0.47. We observed correlation between BMI and urine calcium concentration (r=0.29; p<0.05) in overweight/obese individuals. Urine pH was inversely related to BMI (r=-0.16; p<0.05) and weight (r=-0.18; p<0.05) as well as LDL-cholesterol in blood (r=-0.22; p<0.05) among overweight/obese patients.

**Conclusions:** Our results suggest that obesity or overweight at young age is associated with an increased risk of kidney stones. Weight loss might be explored as a potential treatment to prevent kidney stone formation.

**P2-d3-581** Fat Metabolism and Obesity 4

**The association of serum lipocalin-2 levels with metabolic and clinical parameters in obese children**

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**Background:** In vivo and in vitro studies have shown that lipocalin-2 is an dipokine secreted from adipose tissue and it is associated with insulin resistance in obesity. It has been reported that lipocalin-2 also play a role in body fat mass distribution, lipid metabolism and thermoregulation in experimental rat and adult studies. In obese children only two studies have been reported on lipocalin-2 and their results are conflicting.

**Objective:** We aimed to evaluate the association between serum lipocalin-2 level and clinical and metabolic parameters in obese children. Methods: The study included obese children with a body mass index (BMI) greater than 95 p who applied to Kecioren Teaching and Research Hospital with the complaint of weight gain and healthy children with a BMI under 85p. The height and weight of the patients were measured for compartment of anthropometric
P2-d3-582 Fat Metabolism and Obesity 4

Hypovitaminosis D and nocturnal hypertension in obese children: an interesting link
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Background: Hypovitaminosis D is an independent risk factor for cardiovascular morbidity. In adults, low levels of vitamin D are associated with hypertension. The prevalence of hypertension is increasing in childhood especially in obese children.

Objective: The aim of this study was to evaluate the relationship between 24-hour blood pressure patterns and vitamin D levels in obese children. Outcome Measures and Subjects. We recorded anthropometric parameters, took blood samples for 25-hydroxi-vitamin D measurements and monitored ambulatory blood pressure (ABP) in 32 obese children (M/F: 21/11, age 7-16 years).

Results: Hypovitaminosis D was diagnosed in 84.4% of the study group children. Subjects in the lower tertiles had higher HOMAIR, nighttime systolic and diastolic ABP, nighttime systolic and diastolic ABP load, 24-h ABP index and nighttime systolic and diastolic ABP index than those in the higher tertile. Vitamin D correlated negatively with 24-hour and nighttime systolic ABP, 24-h systolic ABP load, nighttime systolic and diastolic ABP load, 24-h systolic ABP index and nighttime systolic ABP index. The percentage of subjects with pathological 24-h SBP load, nighttime SBP load, nighttime DBP load, nighttime SBP index and nighttime DBP index increased progressively as the vitamin deficiency categories increased (+2 10.26, p < 0.05; ±2 16.34, p < 0.01; ±2 10.23, p < 0.05; ±2 10.38, p <0.01; ±2 10.06, p <0.01).

Conclusions: Low levels of vitamin D in obese children were associated with a higher BP burden, especially at night. Prospective studies and vitamin D supplementation trials could confirm a cause-effect relationship between vitamin D and BP also in children/adolescents.

P2-d3-584 Fat Metabolism and Obesity 4

Advantages of oral glucose tolerance test (OGTT) derived indexes over HbA1c or HOMA as predictors of metabolic derangement in obese children
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Background: Insulin resistance (IR) is the basis of metabolic derangement in obesity. The best clinical approach for its estimation is under discussion. Objective and hypotheses: To compare HOMA and HbA1c with insulin secretion during the OGTT as predictors of metabolic impairment in obese children.

Methods: Fasting glucose, insulin, HbA1c, lipid profile and uric acid were studied in 673 patients (49% girls/51% boys); BMI >+2SDS (3.9±1.4), age: 10.7±3.2 years (0.5-17.5), 51.3% prepubertal, with 465 undergoing an OGTT (1.75 g/kg; maximum 75g). Parameters: HOMA; Impaired fasting glucose (IFG); glycemia>100mg/dl; impaired glucose tolerance: glycemia-120´>140mg/dl. IR: fasting insulin>15, 30/60´>150 and/or 120´>75µU/ml (0 to 4 alterations). Area under the curve (AUC): 0.25×fasting+0.5×30´+0.75×60´+0.5×120´.

Results: Obesity and HbA1c differed among patients with IGT (n=42), IR (n=74), IR (n=185) or with no alteration (Table1A). HOMA was correlated with IR (rho=0.3; p<0.05), BMI (rho=0.32; p<0.05) and HOMA correlated with BMI (rho=0.5; p<0.05), but not with HbA1c. As there was not statistically significant difference in serum lipocalin-2 levels among the two groups, we suggest that serum lipocalin level could not be used as a predictor of obesity complications.

P2-d3-583 Fat Metabolism and Obesity 4

Influence of obesity on growth rate, bone maturation and adult height prediction in children and adolescents
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Background: Obesity influences growth rate in children. However, the precise role of gender, race, age at onset and severity of obesity and hyperinsulinemia on adult height is insufficiently characterized.

Objective and hypotheses: To study the pattern of growth and the reliability of the Bailey&Pineau (B&P) method for adult height prediction (based on Greulich & Pyle’s [G&P] bone age) in obese children according to their age, sex, race, pubertal stage and serum insulin levels.

Methods: A retrospective study of 673 obese children [BMI >+2 SDS (3.9±1.4); age: 10.7±3.2 years (0.5-17.5), 49% girls, 51% boys; 51.3% prepubertal, 48.7% pubertal; 77.3% Caucasians, 18.3% Latinos] was carried out. Parameters studied: Chronological and bone age (G&P), sex, race, pubertal stage (Tanner), height, BMI, target height (mid-parental height +/−6.5 cm boys/girls, respectively), adult height prediction (B&P), and adult height (growth <1 cm/year; n=114) were recorded.

Results: Obese children showed advanced bone age (+0.76±1.19 years; p<0.001) that positively correlated with BMI-SDS and insulin levels (both p<0.001) and was influenced by sex (females: 1.0±1.2 vs. males: 0.6±1.2; p<0.01); puberty (prepubertal: 0.9±1.2 vs. pubertal: 0.6±1.12; p<0.01) and race (Latinos: 0.9±1.1 vs. Caucasians: 0.7±1.2; p<0.05). Standardized height at diagnosis exceeded target height (+0.94±1.09 vs. -0.43±0.97 SDS; p<0.001), with the B&P prediction overestimating the target height (+0.23±1.26 DE) over the final height reached by the patients (+0.35±1.02 SDS; p<0.001), although the later was still above the target height (+0.56±1.07 SDS; p<0.001). These findings were most evident in male and Latino patients (p<0.001), although the later showed no gain in final height.

Conclusions: Obesity is associated with an accelerated of skeletal maturatation in children that is influenced by sex and race. This results in transient overgrowth but has minimal impact on adult height, which leads to the overestimation of final height by B&P.

Poster Presentations
The evaluation of the waist-to-height ratio in screening the cardio metabolic risk in 6 to 10 year old children

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Background: Childhood obesity is a worldwide problem and followed by an increased risk of cardiovascular and metabolic disturbances.

Objective and hypotheses: This study aims to compare the performances of waist-to-height ratio (WHHR) and the 2007 World Health Organization (WHO) body mass index (BMI) in screening the cardio metabolic and inflammatory disturbances, in 6-10-year-old children.

Methods: A cross-sectional study was undertaken including 175 subjects, selected from an outpatient Reference Center for Treatment of Children and Adolescents. The subjects were classified according to 2007 OMS reference as non obese (BMI z score > 1 and < 1) and overweight/obese ones (BMI z score > 1). The analyzed cardio metabolic variables were systolic (SBP) and diastolic blood pressure (DBP), fasting glycosmia, low (LDL) and high-density lipoproteins (HDL), triglyceride (TG), ‘homeostatic model assessment’ (HOMA-IR), leukocyte count and ultra-sensitive C–reactive protein (CRP).

Results: There were correlations between the WHHR and BMI z score (r = 0.88, p < 0.0001), SBP (r = 0.51, p < 0.0001), DBP (r = 0.49, p < 0.0001), LDL (r = 0.25, p < 0.0008), HDL (r = 0.28, p < 0.0002), TG (0.26, p < 0.0006), HOMA-IR (r = 0.83, p < 0.0001) and CRP (r = 0.51, p < 0.0001). The WHHR area under the curve was equivalent to that of the BMI in the diagnosis of all cardio metabolic variables. The WHHR cut-off higher than 0.47 was sensitive to screen insulin resistance and any one of the cardio metabolic disturbances.

Conclusions: The WHHR was as sensitive as the 2007 OMS BMI in screening the cardio metabolic and inflammatory risk in 6-10 year old children, even in the normal weight ones. The message ‘keep your waist to less than your height’ is effective in preventing the cardio metabolic disturbances in primary pediatric care.

P2-d3-586 Fat Metabolism and Obesity 4

Screening marker for obesity complications in children and adolescents: using haemoglobin A1C

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Background: Hemoglobin A1c (A1C) is recommended to diagnose and to identify subjects at risk for developing diabetes in the future.

Objective and hypotheses: The aim of this study was to investigate the difference of the A1C according to the degree of obesity, difference in clinical features between the groups by A1C 5.7% and to evaluated the contributing factors.

Methods: Data from 168 children and adolescents (M/F 93/75, age 10.2±2.6) who visited our hospital for obesity screening were included. Body mass index (BMI), percent weight for height (PWH), height z score (HTZ), weight z score (WTZ) and BMI z score (BMIZ) were calculated by the measured height and weight. Glucose, insulin, total cholesterol, triglyceride, HDL cholesterol, AST, ALT, IGF-1 and IGFBP-3 were analyzed. Confirm cases of diabetes and endocrine disease were excluded. We analyzed the difference of the A1C between the groups based on the BMIZ 2.0 and PWH 2.0, and the clinical findings according to the A1C 5.7%. Correlation analysis between A1C and metabolic parameters were conducted and contributing factors for A1C were evaluated with regression analysis.

Results: A1C was greater in subjects with impaired fasting glucose. A1C and HOMA-IR were not significantly different between the groups based on BMIZ 2.0. Based on PWH 2.0, HOMA-IR were significantly different, however A1C were not significantly different. TG, HDL, AST and ALT levels showed significant difference between the groups divided by the A1C 5.7%. There were positive correlations between A1C with height, weight, BMI, AST, ALT, glucose and HOMA-IR, however no significant correlation with HTZ, WTZ, BMIZ. The contributing factors for A1C were gender, BMI and IGFBP-3.

Conclusions: A1C level is associated with metabolic syndrome parameters, however, not correlated with obesity degree. Along to A1C and other factors should be considered to evaluate the risk of obesity complication in obese children and adolescents.

Increased body weight, fat mass and leptin levels due to neonatal over-nutrition in rats is associated with decreased circulating levels and adipose mRNA levels of interleukin 1β at 10 days of life

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Background: Early over-nutrition has long-term effects on metabolism. However, little is known regarding the mechanisms underlying these long-lasting modifications.

Objective and hypotheses: We hypothesized that early onset obesity modifies cytokine levels, both systemically and centrally, that could induce these long-term effects.

Methods: At birth, Wistar rats were organized into litters of 4 (neonatal over-nutrition; NON) or 12 (control; Ct) pups and sacrificed on day 10. Serum levels of leptin, insulin, interleukins (IL) 6 and 1β and TNFα were measured with a multiplexed bead immunassay and mRNA levels in adipose tissue, liver and the hypothalamus by real-time PCR.

Results: Neonatal over-nutrition increased body weight and subcutaneous fat mass (SC), with SC increasing more in females. Serum glucose, leptin and insulin levels were increased in NON rats, but serum IL1u levels were decreased, with no change in IL6 or TNFα. The increased leptin and decreased IL1β in serum corresponded to modifications in their mRNA levels in SC adipose tissue (see table), with no modification in IL1β mRNA in the hypothalamus or liver.

Screening marker for obesity complications in children and adolescents: using haemoglobin A1C

Background: Hemoglobin A1c (A1C) is recommended to diagnose and to identify subjects at risk for developing diabetes in the future.

Objective and hypotheses: The aim of this study was to investigate the difference of the A1C according to the degree of obesity, difference in clinical features between the groups by A1C 5.7% and to evaluated the contributing factors to A1C in obese children and adolescent.

Methods: Data from 168 children and adolescents (M/F 93/75, age 10.2±2.6) who visited our hospital for obesity screening were included. Body mass index (BMI), percent weight for height (PWH), height z score (HTZ), weight z score (WTZ) and BMI z score (BMIZ) were calculated by the measured height and weight. Glucose, insulin, total cholesterol, triglyceride, HDL cholesterol, AST, ALT, IGF-1 and IGFBP-3 were analyzed. Confirm cases of diabetes and endocrine disease were excluded. We analyzed the difference of the A1C between the groups based on the BMIZ 2.0 and PWH 2.0, and the clinical findings according to the A1C 5.7%. Correlation analysis between A1C and metabolic parameters were conducted and contributing factors for A1C were evaluated with regression analysis.

Results: A1C was greater in subjects with impaired fasting glucose. A1C and HOMA-IR were not significantly different between the groups based on BMIZ 2.0. Based on PWH 2.0, HOMA-IR were significantly different, however A1C were not significantly different. TG, HDL, AST and ALT levels showed significant difference between the groups divided by the A1C 5.7%. There were positive correlations between A1C with height, weight, BMI, AST, ALT, glucose and HOMA-IR, however no significant correlation with HTZ, WTZ, BMIZ. The contributing factors for A1C were gender, BMI and IGFBP-3.

Conclusions: A1C level is associated with metabolic syndrome parameters, however, not correlated with obesity degree. Along to A1C and other factors should be considered to evaluate the risk of obesity complication in obese children and adolescents.

Increased body weight, fat mass and leptin levels due to neonatal over-nutrition in rats is associated with decreased circulating levels and adipose mRNA levels of interleukin 1β at 10 days of life

Pilar Argente Arizón; Esther Fuente Martín; David Castro González; Francisca Díaz; Vicente Barrios; Laura M. Frago; Jesús Argente; Julie A. Chowen
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Background: Early over-nutrition has long-term effects on metabolism. However, little is known regarding the mechanisms underlying these long-lasting modifications.

Objective and hypotheses: We hypothesized that early onset obesity modifies cytokine levels, both systemically and centrally, that could induce these long-term effects.

Methods: At birth, Wistar rats were organized into litters of 4 (neonatal over-nutrition; NON) or 12 (control; Ct) pups and sacrificed on day 10. Serum levels of leptin, insulin, interleukins (IL) 6 and 1β and TNFα were measured with a multiplexed bead immunassay and mRNA levels in adipose tissue, liver and the hypothalamus by real-time PCR.

Results: Neonatal over-nutrition increased body weight and subcutaneous fat mass (SC), with SC increasing more in females. Serum glucose, leptin and insulin levels were increased in NON rats, but serum IL1u levels were decreased, with no change in IL6 or TNFα. The increased leptin and decreased IL1β in serum corresponded to modifications in their mRNA levels in SC adipose tissue (see table), with no modification in IL1β mRNA in the hypothalamus or liver.

Conclusions: Neonatal over-nutrition induces rapid modifications in body composition associated with a state of insulin resistance and hyperleptinemia, even at a very early age, but not systemic inflammation. Rapid modifications in cytokines such as IL1β and leptin could be involved in the long-term effects reported on the development of both adipose tissue and hypothalamic metabolic circuits.
**P2-d3-S88** Fat Metabolism and Obesity 4

**Anthropometric parameters and sex steroids – the impact on insulin sensitivity during preschool age**

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**Background:** Adiponectin is an indirect marker of insulin sensitivity (IS) and levels are decreased in obesity. An oral glucose tolerance test (OGTT) measuring glucose at 120-minutes is a simple and recognized method to evaluate IS. Little is known about the longitudinal changes in adiponectin and IS during preschool years.

**Objective and hypotheses:** To investigate if IS changes over time and if it is dependent of body composition or sex steroids during preschool age. Hypothesis: Sex steroids and anthropometry influence IS already at preschool age.

**Methods:** A longitudinal study was conducted in healthy children (57 boys/48 girls) at 5 and 7 years of age. Body mass index (BMI) ranged between 12.8 and 21.5. Variables examined included height, weight, BMI, waist-to-height ratio (WHR), plasma-glucose at 120 minutes with OGTT, testosterone, estradiol, adiponectin. Truncal fat percentage (%) was measured by DXA. The Pearson's correlation coefficients were calculated to assess the associations between variables.

**Results:** In boys, mean ±SD adiponectin was 9.62 ±3.4 and 9.37 ±3.7 at 5 and 7 years, and in girls 9.88 ±4.4 and 9.50 ±4.0, respectively. Mean 120-minutes glucose was 5.8 ±1.0 and 6.1 ±1.5 in boys, and 6.0 ±1.0 and 6.0 ±0.9 in girls. Adiponectin levels correlated negatively to 120-minutes glucose during OGTT at 7 years in girls (r = -0.35, p=0.05 respectively) and in boys (r = -0.38, p=0.05). Neither adiponectin nor glucose levels during OGTT did correlate to anthropometry in boys. In 7-year old girls, adiponectin correlated to WHR (r = -0.33, p=0.05). In 7-year old boys, a correlation was found between estradiol and 120-minutes glucose (r = 0.32, p=0.001), but not significant in girls (r = 0.34, p = 0.08).

**Conclusions:** In 7 year old children, IS correlated to sex steroids only in boys, whereas IS correlated to anthropometry only in girls.

**P2-d3-S89** Fat Metabolism and Obesity 4

**Usefulness of triglyceride to high density lipoprotein cholesterol ratio to identify endothelial dysfunction in obese pre-pubertal children**

Tommaso de Giorgi; Valentina Chiavaroli; Cosimo Giannini; M. Lovredana Maroccio; Ebe D’Adamo; Francesco Chiarelli; Angelika Mohn

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**Background:** Childhood obesity represents an important risk factor for the development of cardiovascular disease. Studies in adults have demonstrated that triglyceride to high density lipoprotein (HDL)-cholesterol ratio represents a useful marker able to predict cardiovascular risk. However, no data are available on the potential relationship between TG-to-HDL ratio and early signs of atherosclerosis in youths.

**Objective and hypotheses:** Our aim was to assess the relationship between TG-to-HDL ratio and carotid intima media thickness (cIMT) in pre-pubertal children.

**Methods:** In 50 obese (27 boys, age 7.8±1.5yrs) and 37 (20 boys; age 7.3±1.5 yrs) healthy pre-pubertal children, anthropometric measurements, oxidative stress markers (urinary prostaglandin F2α [PGF-2α], endogenous secretory receptor for advanced glycation end products [esRAGE] and soluble RAGE [sRAGE]) and insulin resistance indexes (HOMA-IR and WBISI) were evaluated. Lipids profile was assessed and TG/HDL ratio was calculated. In addition, high-resolution ultrasound was performed to assess cIMT.

**Results:** Obese children showed significantly higher values of TG-to-HDL ratio and cIMT (0.42±0.06 vs 0.31±0.07, p=0.001 and 2.01±1.24 vs 1.2±0.59, p=0.002, respectively) compared to controls. By dividing the study population in tertiles of TG-to-HDL ratio (<1.0, 1.04-1.67, >1.67), cIMT (0.35±0.08, 0.37±0.08, 0.43±0.06, p<0.009), HOMA-IR (p<0.001) and PGF-2α (p=0.002) progressively increased from the lower to the upper tertile, whereas WBISI (p=0.003) and sRAGE (p=0.05) progressively decreased. In a multiple regression model, TG-to-HDL ratio was directly associated with cIMT (r=0.758, beta=0.432, p<0.001), independently of IR, oxidative stress indexes and SDS-BMI.

**Conclusions:** In conclusion, TG-to-HDL ratio represents an independent marker of cardiovascular risk and endothelial dysfunction even in obese pre-pubertal children. Thus, TG-to-HDL ratio could be considered a useful marker to detect early signs of atherosclerosis in clinical practice.

**P2-d3-S90** Fat Metabolism and Obesity 4

**Differences between prepubertal obese children with and without fatty liver using two ultrasonographic methods**

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**Aims:** We aimed to determine clinical, metabolic and anthropometric differences between obese prepubertal children with and without fatty liver (FL) using hepatic vein Doppler ultrasonography (USG) and B-mode USG. Additionally, our aim is to investigate the gender differences in prepubertal obese children between two groups using two methods.

**Subject and methods:** Ninety seven prepubertal obese children aged between 7-11 years were included in this study. Hepatic vein Doppler USG and B-mode USG were performed to all children to identify FL.

**Results:** When evaluating all children, among all parameters, only triglyceride levels were significantly higher in obese with FL identifying Doppler USG than those in obese without FL (p=0.009). In girls, Body Mass Index (BMI) SDS, triglyceride levels and homeostasis model assessment of insulin resistance (HOMA-IR) were found significantly difference between two groups (p=0.028, 0.013, 0.025, respectively). In boys, no significant difference was found (p>0.05). In all children, Alanine aminotransferase (ALT), triglyceride levels and BMI SDS circumference were significantly higher in obese with FL identifying B-mode USG than those in obese without FL (p=0.05, 0.13, 0.05, respectively). In girls, waist hip ratio was significantly higher in obese with FL than those in other groups (p<0.04). In boys, no significant difference was found between in obese with and without FL identifying B-mode USG (p>0.05).

**Conclusions:** In obese children, FL can be identified by two ultrasonographic methods even prepubertal period. Although there are some markers suggesting the presence of FL in prepubertal obese girls, no markers were found in prepubertal obese boys.

**P2-d3-S91** Fat Metabolism and Obesity 4

**The metabolic parameters of insulin sensitivity relative to Body Mass Index (BMI) in Prader-Willi patients in Russian population**

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**Background:** Prader-Willi syndrome (PWS) is the most frequent cause of syndromic obesity and occurs in 1 in 15,000-25,000 live births. The syndrome is characterized by hyperphagia and weight gain between the ages of 1 and 6 years, leading most PWS subjects to develop morbid obesity and therefore premature mortality from its complications. Obesity plays an important role in the development of insulin resistance and hyperinsulinemia, that is why the metabolic profile investigation in such patients can be useful for achieving possible clinical benefits. Objective: Evaluate metabolic parameters in children with Prader-Willi syndrome (PWS)

**Methods:** We studied 25 patients with PWS nontreated with GH and 20 subjects with age, sex and BMI-matched non-PWS controls. Anthropometric measurements consisted of weight, BMI, waist and hip circumferences. Biochemical measurements included serum glucose, insulin, C-reactive protein (CRP), leptin, ALT, AST. The standard oral glucose tolerance test (OGTT) was performed using 1,75 mg/kg (maximum 75 g) oral glucose. Data are reported as mean values with standard deviations; Kolmogorov-Smirnov test was used for between-group comparisons.

**Results:** There were no significant differences in AST, ALT, lepton, CRP lev-
el. Waist circumference, fasting glucose, insulin levels (fasting and 30, 60 min response to an oral glucose), HOMA-IR, Matsuda, Kario in PWS subjects were lower (p<0.05) than in obese children (OC). Significantly different (p<0.05) clinical and metabolic characteristics of two groups are shown in Table 1. Our results are similar to those of other researchers who found a lower degree of insulin resistance and higher insulin sensitivity in PWS children than in equally obese children.

### Conclusions:

Glucometabolic disorders are common in obese PWS versus non-PWS subjects. This could suggest a different role of insulin in the pathogenesis of metabolic alterations in PWS as compared to simple obesity and further long-term studies are needed.

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### P2-d3-592 Fat Metabolism and Obesity 4

**Are patients born small for gestational age at additional risk of developing metabolic syndrome?**

**Pamela Stroescu**1, Ioana Micle1; Monica Manazan1; Teofana Bizeran2

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**Background:** Approximately 3.5% of all infants are born SGA (small for gestational age). SGA and rapid increase in weight during early childhood and infancy has been strongly linked with metabolic syndrome. However, it is unknown whether it is obesity or being born SGA that leads to metabolic syndrome in these children.

**Objective and hypotheses:** We set out to investigate whether SGA constitutes an additional risk factor in the development of metabolic syndrome.

**Methods:** A retrospective study was carried out on long-term metabolic complications in children born SGA, which were admitted to our hospital over a 5 year period from 2006 to 2010. A number of 187 subjects (mean age 12 years ±6, aged between 6-18 years) were divided in two study groups, following the statistical processing of data sheets, as follows: 150 obese patients that were born AGA appropriate for gestational age (80,21% of the total) and 37 obese patients that were born SGA (19,78% of the total). Blood pressure, lipid, glucose and insulin levels of the patients were measured. Oral glucose tolerance tests (oGTT) were performed on all patients.

**Results:** The metabolic syndrome prevalence (according to the IDF definition) was more than double in obese patients born SGA (8 patients, account- ing for 21,62%) compared to obese patients born AGA (9,33%, representing 14 subjects). The remaining subjects of the SGA group had all developed one of the components of metabolic syndrome, besides obesity (dyslipidemia, hypertension or impaired glucose tolerance).

**Conclusions:** Increased prevalence of metabolic syndrome in patients born SGA compared to obese patients born AGA indicates that being born SGA appears to be an additional risk factor in the development of metabolic syn- drome. Monitoring, periodic evaluation and appropriate dietary therapy in the case of obese children born SGA is crucial in preventing or reversing meta- bolic syndrome. Phylprophylactic treatment of obesity in patients born SGA is of paramount importance.

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### P2-d3-593 Fat Metabolism and Obesity 4

**Correlation between segmental body fat and anthropometric parameters**

**Nihal Hatipoglu**1; Mustafa Mumtaz Mazicioglu1; Ahmet Ozturk2; Betul Cicek1; Demet Unalan1; Demet Unalan1; Vesile Senof1; Meral Bayat2; Ferhan Elmat2; Selim Kurtoglu2; Hasan Basri Ustunbas3

1Erciyes University, Medical Faculty, Pediatric Endocrinology, Kayseri, Turkey; 2Erciyes University, Medical Faculty, Family Medicine, Kayseri, Turkey; 3Erciyes University, Medical Faculty, Biostatistics, Kayseri, Turkey; 4Erciyes University, Ataturk Health School, Nutrition and Dietetics, Kayseri, Turkey; 5Erciyes University, Halil Bayraktar Health Services Vocational College, Public Health, Kayseri, Turkey; 6Erciyes University, Faculty of Health Science, Pediatric Nursing Department, Kayseri, Turkey

**Background:** It is now known that fat distribution is important than total body fat. Bioelectric impedance analysis (BIA) is well-known method for body composition analysis. Anthropometric measurements are also used to determine the distribution of the body fat. Objective and hypotheses: Aim of this study is to determine the relationship between anthropometric measurements (AM) and regional body composition by using BIA.

**Methods:** A total of 4,151 (2,927 girls, 1,854 boys) children and adolescents aged 6-17 years were recruited for this study. Regional body fat percent (BF%), fat mass (FM) and fat free mass (FFM) distribution were evaluated using BIA. The measurements were made from total body, upper limbs, trunk, and lower limbs. We examined the growth patterns of these parameters according to gender and age. Body mass index (BMI), waist circumference (WC), mid-upper arm circumference (MUAC), waist-to-height ratio (WHR) were used as anthropometric parameters.

**Results:** Among all the anthropometric parameters, BMI showed best correlation with total and regional BF% and FM. The other anthropometric pa- rameters showed also strong correlation with both BF% and FM. The leg fat percent showed the best correlation with total BF%, while arm fat percent showed the best correlation with trunk fat percent.

**Conclusions:** BMI is the best indicator of both total and regional fat percent and fat mass. WC, WHR and triceps skin fold well show correlation with especially total trunk, and leg fat percent and FM.

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### Table 1: Partial correlation between segmental body fat and anthropometric parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fat mass (kg)</th>
<th>FM (kg)</th>
<th>Trunk fat mass (kg)</th>
<th>Trunk fat percent (%)</th>
<th>Trunk fat mass (kg)</th>
<th>Arm fat mass (kg)</th>
<th>Arm fat percent (%)</th>
<th>Leg fat mass (kg)</th>
<th>Leg fat percent (%)</th>
<th>Leg fat mass (kg)</th>
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<tbody>
<tr>
<td>BMI</td>
<td>0.854</td>
<td>0.773</td>
<td>0.813</td>
<td>0.840</td>
<td>0.580</td>
<td>0.687</td>
<td>0.797</td>
<td>0.576</td>
<td>0.846</td>
<td>0.850</td>
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<tr>
<td>WC</td>
<td>0.784</td>
<td>0.732</td>
<td>0.643</td>
<td>0.789</td>
<td>0.584</td>
<td>0.660</td>
<td>0.765</td>
<td>0.533</td>
<td>0.775</td>
<td>0.635</td>
</tr>
<tr>
<td>MUAC</td>
<td>0.685</td>
<td>0.660</td>
<td>0.501</td>
<td>0.647</td>
<td>0.521</td>
<td>0.560</td>
<td>0.655</td>
<td>0.497</td>
<td>0.791</td>
<td>0.688</td>
</tr>
<tr>
<td>Triceps</td>
<td>0.803</td>
<td>0.686</td>
<td>0.634</td>
<td>0.785</td>
<td>0.741</td>
<td>0.523</td>
<td>0.724</td>
<td>0.706</td>
<td>0.740</td>
<td>0.556</td>
</tr>
<tr>
<td>Muac</td>
<td>0.917</td>
<td>0.678</td>
<td>0.388</td>
<td>0.784</td>
<td>0.751</td>
<td>0.532</td>
<td>0.664</td>
<td>0.510</td>
<td>0.501</td>
<td>0.387</td>
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<td>WHR</td>
<td>0.777</td>
<td>0.729</td>
<td>0.980</td>
<td>0.878</td>
<td>0.300</td>
<td>0.916</td>
<td>0.800</td>
<td>0.215</td>
<td>0.939</td>
<td>0.615</td>
</tr>
<tr>
<td>BMI</td>
<td>0.777</td>
<td>0.729</td>
<td>0.980</td>
<td>0.878</td>
<td>0.300</td>
<td>0.916</td>
<td>0.800</td>
<td>0.215</td>
<td>0.939</td>
<td>0.615</td>
</tr>
<tr>
<td>WC</td>
<td>0.644</td>
<td>0.709</td>
<td>0.343</td>
<td>0.678</td>
<td>0.735</td>
<td>0.384</td>
<td>0.677</td>
<td>0.472</td>
<td>0.396</td>
<td>0.858</td>
</tr>
<tr>
<td>MUAC</td>
<td>0.585</td>
<td>0.760</td>
<td>0.202</td>
<td>0.887</td>
<td>0.010</td>
<td>0.908</td>
<td>0.865</td>
<td>0.356</td>
<td>0.899</td>
<td>0.586</td>
</tr>
<tr>
<td>Triceps</td>
<td>0.906</td>
<td>0.760</td>
<td>0.302</td>
<td>0.887</td>
<td>0.272</td>
<td>0.912</td>
<td>0.778</td>
<td>0.185</td>
<td>0.875</td>
<td>0.584</td>
</tr>
<tr>
<td>Muac</td>
<td>0.878</td>
<td>0.788</td>
<td>0.480</td>
<td>0.897</td>
<td>0.438</td>
<td>0.776</td>
<td>0.803</td>
<td>0.381</td>
<td>0.712</td>
<td>0.484</td>
</tr>
<tr>
<td>BMI</td>
<td>0.830</td>
<td>0.433</td>
<td>0.902</td>
<td>0.727</td>
<td>0.438</td>
<td>0.141</td>
<td>0.447</td>
<td>0.853</td>
<td>0.759</td>
<td>0.836</td>
</tr>
<tr>
<td>WC</td>
<td>0.903</td>
<td>0.168</td>
<td>0.912</td>
<td>0.776</td>
<td>0.141</td>
<td>0.776</td>
<td>0.737</td>
<td>0.267</td>
<td>0.605</td>
<td>0.317</td>
</tr>
<tr>
<td>MUAC</td>
<td>0.816</td>
<td>0.677</td>
<td>0.584</td>
<td>0.712</td>
<td>0.759</td>
<td>0.468</td>
<td>0.725</td>
<td>0.787</td>
<td>0.605</td>
<td>0.883</td>
</tr>
<tr>
<td>Triceps</td>
<td>0.324</td>
<td>0.472</td>
<td>0.956</td>
<td>0.308</td>
<td>0.484</td>
<td>0.836</td>
<td>0.169</td>
<td>0.936</td>
<td>0.317</td>
<td>0.883</td>
</tr>
<tr>
<td>Muac</td>
<td>0.001</td>
<td>1.000</td>
<td>0.000</td>
<td>1.000</td>
<td>0.000</td>
<td>1.000</td>
<td>0.000</td>
<td>1.000</td>
<td>0.000</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Note: All correlations are significant at p<0.001.
Changes in NC were best correlated with BMI. Changes in total cholesterol (r = 0.223, p<0.027) and related with changes in BMI. The changes of MUAC were correlated with total cholesterol (r = 0.215, p<0.021), changes in TG (r = 0.349, p<0.001), changes to systolic blood pressure (r = 0.359, p<0.001) and changes in HOMA-index (r = 0.275, p<0.003). The changes of WC were only correlated with changes in BMI. The changes of MUAC were correlated with changes in BMI and NC, changes in total cholesterol (r = 0.223, p<0.027) and changes in TG (r = 0.201, p<0.047).

Conclusions: Changes in NC were best correlated with BMI. Changes in WC didn’t show good correlation with changes in anthropometric and metabolic risk factor as expected.

P2-d3-596 GH and IGF Physiology 2

Insulin like growth factor-I (IGF-I) levels and metabolic parameters in a population of obese children and adolescents

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1Division of Pediatrics, Department of Health Medicine, University of Piemonte Orientale, Novara, Italy; 2Endocrinology, Dept of Translational Medicine, University of Piemonte Orientale, Novara, Italy

Introduction: The risk association between the insulin like growth factor-I (IGF-I) and cardiovascular risk is inconclusive in adults and under-explored in the pediatric population. We aimed to investigate the associations between serum concentrations of IGF-I and cardiovascular risk factors in obese children and adolescents.

Methods: Cross-sectional study. Clinical and metabolic evaluations including an oral glucose tolerance test (OGTT) were performed at fasting in 594 overweight obese children and adolescents (295 males and 299 females). IGF-I levels were measured by Immulite and IGF-SDS for each age and gender subgroup was calculated and, then, divided into quartiles.

Results: 239 subjects were in Tanner 1, 206 in Tanner 2 or 3, 149 in Tanner 4 or 5 stages, respectively. Subjects in the lowest quartile of IGF-I SDS were older (p<0.01) and with higher BMI (p<0.03) respect to the highest quartile. After correction for age, gender and pubertal stages, subjects in the highest quartile presented higher insulin levels at fasting (p<0.01), post-OGTT (p<0.03) and higher HOMA-index (p<0.01). No significance was detected for glucose, lipids or pressure with exception of higher triglycerides in the lowest quartiles of IGF-SDS in the crude (p<0.03) but not in the corrected models. Continuous IGF-I levels maintained the same associations observed for IGF SDS. Acanthosis index did not correlate with IGF-I levels.

Conclusions: IGF-I levels were directly associated with insulin levels and insulin resistance in obese children and adolescent irrespective of gender and puberty. The association with other cardiovascular risk factor observed in adults could be modulated by age.
concentration of total ghrelin and the maximal secretion of GH in stimulation tests in the GHD group.

Conclusions: These results may suggest that there is a negative feedback loop between GH and ghrelin. Ghrelin concentrations were associated with the metabolic state of the body and were related with the nutritional status. Whether high levels of ghrelin (a potent stimulator of appetite and energy balance) in hypopituitarism compensates the metabolic effects of GHD needs further clinical and biochemical prospective analysis.

P2-d3-598 GH and IGF Physiology 2
Clonidine and glucagon provocative tests for growth hormone deficiency: can we reliably perform them with fewer samples?

Methods: Two hundred and forty-five tests (158 clonidine and 87 glucagon) were performed in a total of 188 children and adolescents (104 boys and 84 girls) with a mean age of 9.93 ± 2.88 years in a single center during the last five years. Results: Ninety-one out of 158 (57.59%) clonidine tests and 47/87 (54.02%) glucagon tests had at least one sample above 10 mg/ml and were characterized negative for GH sufficient. For clonidine tests, not measuring GH at 30 minutes would have missed only one sufficient case (0.63% false positive results). For glucagon tests, more than half of the tests peaked at 120 minutes (56.32%). Skipping sampling at 0 and 180 minutes provided a false positive rate of 5.75%.

Conclusions: We can perform provocation tests for GH secretion with fewer samples analyzed (60, 90’ and 120’ for clonidine and 90’, 120’ and 150’ for glucagon) without compromising the diagnostic specificity.

P2-d3-599 GH and IGF Physiology 2
Diagnosis of growth hormone deficiency in the transition period

Methods: We present preliminary data of 69 subjects (30F, 39M) recruited from a multicenter cross-sectional study, in whom anthropometrics, ITT (n=53), GHRH-arginine (n=67), IGF-1 evaluations were undertaken at a mean age of 17.3±1.8yrs. Thirty-three subjects had idiopathic GHD (IGHD), 36 secondary GHD (SGHD); 45 isolated GHD (IGHD; n=29 iGHD, n=16 SGHD) and 23 MPH (n=4 iGHD, n=19 SGHD). Peak GH values >6µg/L for ITT and >19µg/L for GHRH-arginine were considered normal.

Results: Peak GH responses to ITT (P=0.002) and GHRH-arginine (P=0.0003) were lower in SGHD (5.2±6.0 and 14.2±12.9µg/L, respectively) compared to iGHD subjects (13.0±11.6 and 19.8±14.4µg/L, respectively); there were no differences in mean IGF-1 values. Peak responses to ITT and to GHRH-arginine were lower in SGHD whit IGHD compared to IGHD with IGHD (P=0.0039 and P=0.03, respectively), while patients with MPH did not display any differences after both tests. Patients with SGHD and IGHD showed higher GH responses after GHRH-arginine compared to MPH (P<0.005). In IGHD IGF-1 values were significantly lower in MPH compared to IGHD (P=0.02), while there was no significant differences in SGHD subjects either they had IGHD or MPH. A GH peak <6µg/L for ITT was found in 28/53 of whom 22 SGHD and 6 iGHD; a GH peak <19µg/L after GHRH-arginine was obtained in 35/67 of whom 26 SGHD and 9 IGHD. Mean BMI SDS was higher in patients with SGHD compared to iGHD (P=0.01). A negative correlation was found between BMI SDS and GH peak to ITT (P=0.01 for GH; P=0.07 for SGHD) or GH peak to GHRH-arginine (P=0.0008 for GH; P=0.01 for SGHD).

Conclusions: Patients with childhood onset SGHD are at higher risk of permanent GHD compared to iGHD. ITT confirms to be reliable in the identification of patients who may need rhGH treatment in adult life. BMI affects more profoundly GH response after GHRH-arginine.

P2-d3-600 GH and IGF Physiology 2
Effects of GH treatment on oxygen-transporting properties of the erythrocytes and blood antioxidant system in GHD children

Methods: Two hundred and forty-five tests (158 clonidine and 87 glucagon) were performed in a total of 188 children and adolescents (104 boys and 84 girls) with a mean age of 9.93 ± 2.88 years in a single center during the last five years. Results: Ninety-one out of 158 (57.59%) clonidine tests and 47/87 (54.02%) glucagon tests had at least one sample above 10 mg/ml and were characterized negative for GH sufficient. For clonidine tests, not measuring GH at 30 minutes would have missed only one sufficient case (0.63% false positive results), whereas not measuring both at 0 and 30 minutes would have missed only one sufficient case (0.63% false positive results). For glucagon tests, more than half of the tests peaked at 120 minutes (56.32%). Skipping sampling at 0 and 180 minutes provided a false positive rate of 5.75%.

Conclusions: We can perform provocation tests for GH secretion with fewer samples analyzed (60, 90’ and 120’ for clonidine and 90’, 120’ and 150’ for glucagon) without compromising the diagnostic specificity.

Background: The diagnosis of Growth Hormone Deficiency (GHD) in children is based on a number of tests that determine GH response to provocative agents during standardized protocols requiring serial serum GH analyses.

Objective and hypotheses: Our objective was to evaluate the possibility to reduce the number of GH analyses during clonidine and glucagon GH provocation test without compromising the diagnostic specificity.

Methods: Two hundred and forty-five tests (158 clonidine and 87 glucagon) were performed in a total of 188 children and adolescents (104 boys and 84 girls) with a mean age of 9.93 ± 2.88 years in a single center during the last five years.

Results: Ninety-one out of 158 (57.59%) clonidine tests and 47/87 (54.02%) glucagon tests had at least one sample above 10 mg/ml and were characterized negative for GH sufficient. For clonidine tests, not measuring GH at 30 minutes would have missed only one sufficient case (0.63% false positive results), whereas not measuring both at 0 and 30 minutes would increase the false positive percentage to 2.53%. Ending the clonidine test at 90 minutes would result in 7 GH-sufficient cases missed (4.43% false positive results). For glucagon tests, more than half of the tests peaked at 120 minutes (56.32%). Skipping sampling at 0 and 180 minutes provided a false positive rate of 5.75%.

Conclusions: We can perform provocation tests for GH secretion with fewer samples analyzed (60, 90’ and 120’ for clonidine and 90’, 120’ and 150’ for glucagon test) without sacrificing the validity of the method but significantly reducing the cost.

Objective and hypotheses: To reassess GH status in young adults with childhood-onset GHD.

Methods: We present preliminary data of 69 subjects (30F, 39M) recruited from a multicenter cross-sectional study, in whom anthropometrics, ITT (n=53), GHRH-arginine (n=67), IGF-1 evaluations were undertaken at a mean age of 17.3±1.8yrs. Thirty-three subjects had idiopathic GHD (IGHD), 36 secondary GHD (SGHD); 45 isolated GHD (IGHD; n=29 iGHD, n=16 SGHD) and 23 MPH (n=4 iGHD, n=19 SGHD). Peak GH values >6µg/L for ITT and >19µg/L for GHRH-arginine were considered normal.

Results: Peak GH responses to ITT (P=0.002) and GHRH-arginine (P=0.0003) were lower in SGHD (5.2±6.0 and 14.2±12.9µg/L, respectively) compared to iGHD subjects (13.0±11.6 and 19.8±14.4µg/L, respectively); there were no differences in mean IGF-1 values. Peak responses to ITT and to GHRH-arginine were lower in SGHD whit IGHD compared to IGHD with IGHD (P=0.0039 and P=0.03, respectively), while patients with MPH did not display any differences after both tests. Patients with SGHD and IGHD showed higher GH responses after GHRH-arginine compared to MPH (P<0.005). In IGHD IGF-1 values were significantly lower in MPH compared to IGHD (P=0.02), while there was no significant differences in SGHD subjects either they had IGHD or MPH. A GH peak <6µg/L for ITT was found in 28/53 of whom 22 SGHD and 6 iGHD; a GH peak <19µg/L after GHRH-arginine was obtained in 35/67 of whom 26 SGHD and 9 IGHD. Mean BMI SDS was higher in patients with SGHD compared to iGHD (P=0.01). A negative correlation was found between BMI SDS and GH peak to ITT (P=0.01 for GH; P=0.07 for SGHD) or GH peak to GHRH-arginine (P=0.0008 for GH; P=0.01 for SGHD).

Conclusions: Patients with childhood onset SGHD are at higher risk of permanent GHD compared to iGHD. ITT confirms to be reliable in the identification of patients who may need rhGH treatment in adult life. BMI affects more profoundly GH response after GHRH-arginine.
Background: GH replacement therapy during the childhood-adult transition period is important for somatic maturation.

Objective and hypotheses: The aim of the study was to explore the factors influencing IGF-I responses to GH during transition.

Methods: From the KIMS (Pfizer International Metabolic Study) UK database, 99 patients with childhood-onset GH deficiency (GHD), who had been transitioned to an adult GH dose (at age 15-26 years) were identified. IGF-I standard deviation scores (SDS) were calculated using age and gender-specific references. 'IGF-I response' was calculated from IGF-I levels while off therapy, and mean IGF-I levels and GH dose after dose titration, using the formula: D IGF-I SDS/ GH dose (mg/surface area).

Results: IGF-I SDS (±SD) increased from -2.90±1.96 to 0.05±1.79 during 12.1±3.5 months of GH therapy. However, on-treatment IGF-I levels were suboptimal (>0 SDS) in 43 patients (44%) despite dose titration. Compared with men, women had lower baseline IGF-I levels (p=0.006), required higher GH doses (p=0.001) and had lower IGF-I responses (p=0.025).

IGF-I responses were also positively associated with age (r=0.29, p=0.003). Among women, oral oestrogen therapy (mean dose 0.66 and 0.54 mg/d). Other data for each group at each visit are available for all patients. For the adult follow-up, parameters of the metabolic, bone and cardiovascular status were recorded at several hospitalisations: the first one (V0) and at 1 (V1), 3 (V3) and 5 (V5) years after transition. Three groups of patients were studied: treated and untreated persistent GHD and resolute GHG.

Results: We present a cohort of 113 patients with a median age at transition of 19.5 years. Aetiologies of GHD were acquired in 54%, congenital in 34% and idiopathic in 12% of cases. GHD was complete in 72% of patients (mostly congenital GHD) and otherwise partial (mostly idiopathic GHD). Other pituitary deficits were often associated in congenital (70%) or acquired GHD (78%), but idiopathic GHD were generally isolated (64%). In childhood, GH was started at a mean dose of 34.6 mg/kg/d and a mean age of 9.9 years. Mean difference between final and target heights was 0.45 SD. At transition, 14% of patients had a normal GH axis. Forty eight patients completed V1, among whom 30 were under GH (mean dose 0.62 mg/d). At V3 and V5, 32 and 22 patients were studied respectively, 18 and 5 respectively being under GH (mean doses 0.66 and 0.54 mg/d). Other data for each group at each visit are under current investigation.

Conclusion: This is the largest cohort CO-GHD patients followed until adulthood. It allows us to evaluate our medical practices, in a time when GH supplementation in adults remains a matter of debate.
P2-d1-604 GH and IGF Treatment 2
Impaired energy expenditure and growth hormone deficiency activity in children affected by GH deficiency measured by SenseWear Armband: preliminary results
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Background: Influence of growth hormone on energy expenditure and physical performance is clearly known.

Objective and hypotheses: The aim of our study is to evaluate the energy expenditure (EE) during physical (PA) and sedentary activities (SA), in a group of children/adolescents affected by growth hormone deficiency (GHD) compared to healthy subjects, using an objective measure as SenseWear Armband (SWA-BodyMedia).

Patients, methods and results: These preliminary data included 13 untreated, consecutive GHD children and adolescents (6 males) (GH peak <10 ng/ml; IGF1 SDS -2.0±0.3) and 10 controls (6 males), age and sex matched. As expected, the GHD group showed statistically lower height (-2.7±0.9 vs 0±0.5 SDS), weight (-1.5±1.2 vs 1±0.6 SDS) and Body Mass Index (BMI) (-0.1±1.2 vs 0±0.2 SDS).

The use of SWA demonstrated that the GHD children showed lower Energy expenditure, total (1007±458 vs 1337±125 cal/d;1.7±0.2 vs 1.9±0.2 Mets/d) and active (214±136 vs 435±88 cal/d;7.3±13±4 kcal/kg/d) and spent statistically less time in physical activity (3 Mets) (1.5±0.8 vs 2.5±1.1 h/d), especially moderate (3-6 Mets) (1.4±0.8 vs 2.2±0.9 h/d), moderate (5.6±3.1 vs 2.3±0.9% of daily hours) compared with healthy subjects. A tendency to spend more time in sedentary activities was found in GHD group (16±4 vs 14±3 h/d), although not statistically significant. In multivariate regression IGF1 and BMISD resulted positive predictors of EE (daily/cal/daily) in GHD children.

Conclusions: In conclusion our preliminary results seem to confirm that children affected by growth hormone deficiency showed lower energy expenditure as calories/daily and spent less time in physical activities compared to normal children. This result seems correlate to IGF1 values indicating a possible role of GH in physical performance. Further evaluations on greater number of patients, before and after GH therapy, are ongoing to confirm our findings.

P2-d1-605 GH and IGF Treatment 2
A puzzling case of growth hormone deficiency in the neonatal period
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Background: Hypoglycemia may be caused by neonatal GHD and/or ACTH deficiency.

Objective and hypotheses: To report a puzzling case of neonatal GHD.

Method and results: A twin preterm infant, born appropriate for gestation age presented with recurrent hypoglycaemia (blood glucose <45 mg/dl). Diagnostic work-up during hypoglycaemia revealed GHD (glucose 40 mg/dl; kGH 2.7 µg/l, cortisol 22 µg/dl, insulin <2 µU/ml, C-peptide 0.2 mmol/l, free fatty acids 0.21 mmol/l, beta-hydroxybutyrat 0.03 mmol/l, IGF-1 <25 µg/l, IGF-BP3 0.5 mg/l). There was no evidence for TSH deficiency or other metabolic diseases. Cerebral MRI showed a normally located and structured pituitary gland. GH therapy was started at a conventional dose (25-30 µg/kg/d) and blood sugars rose slightly, but intermittent hypoglycaemia reappeared. Simultaneously hepatopathy with elevated liver transaminases and hypogammaglobulinemia occurred (GOT 123 U/l, GPT 86 U/l, GGT 345 U/l, AP 640 U/l, IgG <40 mg/dl). The coincidence of GHD and hypogammaglobulinemia led to the diagnosis of suspicion of X-chromosomal recessive isolated GHD type 3, but no mutation was found in the ELF4 and BTK gene. Searching for an X-inactivation because of the X-chromosomal recessive inheritance, surprisingly Turner’s Syndrome (TS) was diagnosed with a karyotype 45,X[75]/46,X,t(Xq)(21)47,X,t(Xq)(24). GH dose was therefore further increased (50-55 µg/kg/d) and subsequently blood sugars completely normalized. Clinically no signs of TS were present in the patient. Initially FSH was not significantly elevated (LH 0.6 U/l, FSH 2.5 U/l) but rose to 80 U/l at the age of three months. Within three months the hepatopathy resolved and increase of immunoglobulins was observed. During follow-up, thyroid and adrenal function remained normal so far.

Conclusions: If GHD induced hypoglycaemia does not respond to GH treatment as expected, GH resistant states should be considered. The pathophysiology of the associated hepatopathy in the absence of cortisol deficiency is poorly understood so far.

P2-d1-606 GH and IGF Treatment 2
Insulin sensitivity and glucose tolerance in a large cohort of GHD children: results from a 4-years prospective study
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Background: The effects of Growth Hormone (GH) replacement therapy on insulin sensitivity and glucose metabolism in GH deficient (GHD) subjects are still debated. Only a few studies investigated glucose homeostasis in children with GHD before and after GH treatment.

Objective and hypotheses: To evaluate the effects of GHD and GH treatment on glucose metabolism in a large cohort of GHD children before and after GH replacement therapy.

Methods: Fasting glucose, insulin, HbA1c, and HOMA were assessed in 60 GHD children, aged 9±0.3 years, before and after 1, 2 and 4 years of GH replacement treatment. 60 healthy, age-, sex- and BMI-matched healthy controls were enrolled.

Results: In GHD children at baseline, fasting glucose (77.8±1 vs 77.9±1.2, mg/dl), insulin (4.7±0.4 vs 4.6±0.4 µU/ml), HOMA (1.13±0.2 vs 1.12±0.1) and HbA1c (5.29±0.1 vs 5.29±0.0% levels were comparable to healthy controls. One year of GH therapy (33µg/kg/d) was associated with significant increase in insulin (7.69±0.6, p<0.0001) and HOMA (1.64±0.15, p<0.005) without significant changes in fasting glucose and HbA1c levels. Insulin and HOMA levels did not further increase after 2 (7.56±0.6 and 1.85±0.2, respectively) and 4 years (7.65±0.7 and 1.5±0.1, respectively) of treatment, remaining significantly elevated compared to pre-treatment levels. Fasting glucose and HbA1c did not change after 2 and 4 years of GH therapy.

Conclusions: In our cohort of GH deficient children, untreated GHD was not associated with significant alterations of insulin sensitivity and glucose homeostasis. A slight impairment in insulin sensitivity occurred after one year of GH treatment but then remained stable during long-term replacement therapy. Neither GHD nor GH treatment were associated with impaired glucose tolerance.

P2-d1-607 GH and IGF Treatment 2
Initiation of growth hormone therapy in idiopathic short stature: do gender differences exist?
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Background: Growth hormone (GH) registries indicate that boys receive preferential GH treatment for idiopathic short stature (ISS). However, data comparing the clinical characteristics of boys and girls at initiation of treatment remain scarce.

Objective and hypotheses: To determine whether age, auxological parameters, pubertal status and target height differ between genders at initiation of GH therapy for ISS.

Methods: Review of the computerized files of the endocrine department in a tertiary pediatric medical center identified 184 patients who started GH therapy for ISS in 2003-2011. Data on auxological parameters, predicted height, and parental height were collected and compared between boys and girls.
Results: Boys accounted for a significantly higher percentage of the study group (n=121, 65.8%) than girls (n=75; p<0.001). At onset of GH therapy, there were no significant differences between boys and girls in age (10.2±3.1 vs. 9.9±2.4 years) and had a poor AH prediction ability were able to gain height in first year of therapy: -2.9±0.5 vs. -2.7±0.5, p=0.0071), body mass index-SDS (-0.65±1.01 vs. -0.60±1.33, p=0.349), or pubertal status (66% vs. 63.5% prepubertal, p=0.917). Predicted height-SDS was significantly higher among boys than girls (-1.48±1.01 vs. -2.22±0.75, p=0.001). Target height SDS (-1.10±0.77 vs. -1.01±0.08, p=0.482) as well as paternal (169.5±7.7 vs. 169.7±7.8 cm; p=0.889) and maternal (155.4±6.3 vs. 156.9±6.2 cm, p=0.112) stature were also similar in boys and girls.

Conclusions: Despite the male predominance among patients treated with GH for ISS, there appear to be no gender differences in auxological characteristics at initiation of therapy. The present study shows that male and female patients with ISS start therapy at the same age, with a similar height deficit, pubertal status, and target height.

P2-d1-609 GH and IGF Treatment 2

**Effect of short term growth hormone (GH) replacement on whole body bone mineral measures of children with GH deficiency**

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Introduction: GH has a well recognized role in bone elongation and skeletal maturation. However a direct role of GH for bone mineral accrual and bone density is controversial.

Objective: The objective of this study was to assess effect of one year GH replacement on whole body (WB) bone measures corrected for size in children suffering from GHD.

Methods: Whole body bone mineral content (WB BMC), WB Bone area (BA), and lean body mass (LBM) were measured in 35 GHD children (aged 5-12 years) and 80 controls (aged 4-12 years) by using dual energy X-ray absorptiometry (DXA). Multiple linear regression model used calculate size corrected (Sc) WB BSAC and WB BMCsc using control population. Muscle and bone relationship was studied by first assessing LBM for height (LBMMH) and then determining WB BMC for LBM (WB BMCLbm). All values were converted to Z score and compared with control at baseline as well as one year after GH replacement. Z- Score value -2 SD was chosen to represent the cut-off between normal and abnormal. Out of total, 20 (M=11, F=9) could complete one year of replacement with GH (dose= 0.02-0.03 mg/Kg/d).

Results: At diagnosis Z-score for size corrected WB BMC was not significantly different from control whereas WB BSAC (-0.55±1.15, p<.02), and LBMMH (-0.57±1.75, p<.04) was significantly reduced compared to control. The mean increase in height SDS (1.25, p<.001), weight SDS (1.06, p<.0001), WB BASc (0.7, p<.02), LBMMH (1.68, p<.0001), and WB BMCLbm SDS (0.98, p<.05) after one year GH replacement was significantly different from control at baseline as well as one year after GH replacement.

Conclusion: One year GH replacement did not significantly increase WB BMsc of GHD children. However bone area and muscle mass was significantly increased. Short term growth hormone therapy has primarily beneficial effect on bone area, bone size, geometry, and muscle mass rather than mass of the bone.

P2-d1-610 GH and IGF Treatment 2

**Influence of cytosine-adenine (CA) repeat polymorphism of the IGF-1 promotor gene on growth hormone effect in children with growth hormone deficiency**

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Objective and hypothesis: The objectives of the present study was to investigate the effect of polymorphic cytosine-adenine (CA) repeat of the IGF-1 promotor gene in children with idiopathic growth hormone deficiency (IGHD) during first 1 year GH therapy.

Population and method: 70 iGHD patient (43 boys 27 girls), aged 3-15 year, were involved in this study. The diagnosis of iGHD was based on the short stature, low annual growth rate (< 4 cm/yr), and failure to show serum GH levels > 10ng/mL after at least 2 provocation test. 53 GHĐ (32 boys and 21 girls), aged 5-12 year, who remained in prepubertal status after 1 year GH therapy were finally analyzed for the evaluation of the effect of 1 yr GH therapy on growth. The mean dose of GH was 0.28±0.08 (0.25-0.30) mg/kg/wk.

Results: Deletion of 2 bp(G,A) following 3 end of CA repeat were observed in all Korean children. The CA repeat sequences ranged from 16 to 22, and 19CA were the most common with an allele frequency of 28.6%. Considering genotype, homozygote for 19 CA repeat was 5.7%, heterozygote for 19 CA repeat was 45.7%, and 19 CA non carrier was 48.6%. Height standard deviation score(SDSD) revealed -2.39±0.65 in 19 CA carrier and -2.29±0.66 in 19CA non carrier (P<0.05). Serum IGF-I levels showed 180.42±107.65 ng/mL in 19CA repeat and 170.08±88.12 ng/mL in 19 CA non-carrier (P>0.05). The mean height velocity during first 1 yr GH therapy in iGHD patient was...
P2-d1-611 GH and IGF Treatment 2

Intra-uterine and early life events in short children born small for gestational age (SGA): relationship to first year response to recombinant human growth hormone (rhGH)

Gianluca Torinese1; Leena Patel2; Indi Banerjee1; Raja Padidela2; Sarah Ethisham2; Mars Skae3; Julie Jones2; Elaine O'Shea2; Peter E. Clayton1; Sarah Ehtisham2; Raja Padidela2
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Background: rhGH can be an effective treatment for the short stature associated with SGA children without catch-up. There is however significant variability in first year growth response, of which 52% can be explained by baseline auxology and GH dose used.

Objective and hypotheses: To assess whether intra-uterine and early life events experienced by SGA patients influenced first year response to rhGH treatment.

Methods: Retrospective review of clinical data in 61 SGA children receiving rhGH for SGA indication from one tertiary centre. Variables were tested for their effects on birth size and first year growth response.

Results: Data are reported in the Table.

<table>
<thead>
<tr>
<th>CAUSE OF SGA</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known</td>
<td>44</td>
<td>72.1</td>
</tr>
<tr>
<td>-1 cause</td>
<td>30</td>
<td>49.2</td>
</tr>
<tr>
<td>-2 causes</td>
<td>14</td>
<td>23.0</td>
</tr>
<tr>
<td>Unknown</td>
<td>17</td>
<td>27.9</td>
</tr>
</tbody>
</table>

MATERIAL FACTORS (maternal age, use of drugs, problems in pregnancy, medications)

| No | 37 | 60.7 |
| Yes | 24 | 39.3 |

PLACENTAL FACTORS (placental age, use of drugs, problems in pregnancy, medications)

| No | 52 | 85.2 |
| Yes | 9 | 14.8 |

FETAL FACTORS (including identified genetic/malformation conditions)

| No | 40 | 67.2 |
| Yes | 21 | 32.8 |

PERINATAL PROBLEMS

| No | 37 | 60.7 |
| Neonatal care | 15 | 24.6 |
| Intensive neonatal care | 9 | 14.7 |

FEEDING DIFFICULTIES

| No | 33 | 54.1 |
| Some minor | 17 | 27.9 |
| Major | 11 | 18.0 |

FETAL GROWTH

| No IUGR | 12 | 19.7 |
| IUGR | 38 | 62.3 |

Severe IUGR

| 11 | 18.0 |

CONSANGUINITY

| No | 52 | 85.2 |
| Yes | 9 | 14.8 |

DYSMORPHIC FEATURES

| No | 10 | 16.4 |
| Minor | 21 | 34.4 |
| Major | 30 | 49.2 |

GENETIC OPINION SOUGHT

| No | 19 | 31.1 |
| Yes | 42 | 68.9 |

DEVELOPMENTAL DELAY

| No | 34 | 55.7 |
| Yes | 27 | 44.3 |

FAMILY SHORT STATURE

| No | 39 | 63.9 |
| Yes | 22 | 36.1 |

The presence of developmental delay was the only variable inversely correlated with the degree of SGA (birth weight SDS) (Spearman’s rho=–0.25, p=0.05) and with the first year response to rhGH (annualized Δ height SDS) (r=–0.31, p=0.01). A stepwise multivariate analysis confirmed developmental delay as the only significant variable related to first year response to rhGH (ANCOVA, p=0.01, adjusted R² 0.10). Developmental delay was correlated with the presence of dysmorphic features (r=0.30, p=0.02) and inversely correlated with familial short stature.

Conclusions: SGA children receiving rhGH treatment have a high incidence of co-morbidity, including 40% with developmental delay and 83% with dysmorphic features. Searching for genetic aetiologies should be an important part of the management plan. Intra-uterine and early life events do not however have a major impact on first year response to rhGH, although those with developmental delay do have a better response to rhGH.

P2-d1-612 GH and IGF Treatment 2

Simultaneous assessment of nocturnal GH secretion and IGF-I concentration as a screening test in diagnosing GHD in children

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Background: In diagnosing growth hormone (GH) deficiency (GHD) in children, the procedures, allowing to avoid unnecessary GH stimulating tests (GHT) are of great importance. It has been proposed that combination of low height velocity (HV) and IGF-I SDS < -1.0 suggests GHD, while normal results of these tests exclude GHD. In Poland, the assessment of GH peak after falling asleep is currently a screening test in diagnosing GHD.

Objective and hypotheses: The aim of the study was to compare the accuracy of the above-mentioned screening procedures either separately or in combination (with normal results of both tests required to exclude GHD).

Methods: Analysis comprised 500 children (324 boys, 176 girls), age 11.1±3.4 years (mean±SD), with height SDS < -2.0 and HV SDS < -1.0 for (with excluded concomitant diseases). In all of them, basal IGF-I concentration was expressed as IGF-I SDS, and GH secretion was assessed every 30 minutes during 2 hours after falling asleep and in 2 GHT (with clonidine and with glucagon), with the cut-off value of 10.0 ng/ml. The following indices of accuracy of screening tests were calculated: sensitivity, specificity, positive (PPV) and negative (NPV) predictive value.

Results: The sensitivity of both the procedures, analysed separately, was too low with respect to the recommendations for screening tests. However, only 6 patients with decreased GH peak in GHT presented with the combination of nocturnal GH peak >10.0 ng/ml and IGF-I SDS < -1.0 (only 2 of them had IGF-I SDS >0). Even so, the specificity of any variant of screening test was poor. The detailed data are presented in the Table.

Conclusions: Normal GH peak after falling asleep together with normal IGF-I SDS seem to exclude GHD with no need for performing GHT in such patients. However, all the analysed variants of screening tests present with unsatisfactory specificity.
Background: In the majority of the patients with childhood-onset isolated, non-acquired growth hormone (GH deficiency) (GDH) a normalization of GH secretion at the attainment of final height (FH) is observed.

Objective and hypotheses: The aim of the study was to find out the prognostic factors of persistent and transient GH in the patients with isolated, non-acquired childhood-onset GDH, available at therapy onset.

Methods: Analysis comprised 100 patients (74 boys, age 17.9±0.9 years and 26 girls, age 15.7±0.9 years) with isolated, non-acquired childhood-onset GDH (diagnosed on the basis of GH peak <10 ng/ml in 2 stimulating tests: with clonidine and with glucagon), who attained near-FH (height velocity < 2 cm/year, bone age >16 years in boys and >14 years in girls) and completed GH therapy. In all the patients 2 GH stimulating tests (with insulin and with clonidine) were performed with the cut-off level of 6 ng/ml for transient and persistent GH.

Results: Before treatment, there was no significant difference in both patients’ height SDS (HoSDS) and GH peak in stimulating tests, while IGF-I SDS for GH therapy. In all the patients 2 GH stimulating tests (with insulin and with clonidine) were performed with the cut-off level of 6 ng/ml for transient and persistent GH.

Conclusions: It seems that in children with isolated, non-acquired GDH, only the severe IGF-I deficiency is associated with persistent GDH, while normal IGF-I secretion before therapy onset may be a prognostic factor of transient GH.

<table>
<thead>
<tr>
<th>data before treatment</th>
<th>persistent GDH</th>
<th>transient GDH</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>age [years]</td>
<td>12.1±1.8</td>
<td>12.5±2.4</td>
<td>0.46</td>
</tr>
<tr>
<td>HoSDS</td>
<td>-2.0±0.34</td>
<td>-2.15±0.62</td>
<td>0.41</td>
</tr>
<tr>
<td>GH peak [ng/ml]</td>
<td>6.4±3.9</td>
<td>7.8±5.1</td>
<td>0.92</td>
</tr>
<tr>
<td>IGF-I SDS</td>
<td>3.3±2.21</td>
<td>-0.85±1.66</td>
<td>0.04</td>
</tr>
</tbody>
</table>

P2-d1-614 GH and IGF Treatment 2

Are there any predictive parameters for successful response to growth hormone therapy in patients born small for gestational age?

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Background: Most children who were born small for gestational age (SGA) have adequate catch-up growth without pharmacologic intervention. However, for a minority, growth hormone can augment growth parameters.

Objectives: 1-Describe SGA children in treatment with GH in our region. 2-Evaluate treatment response according to different variables.

Methods: Retrospective review of SGA children in treatment with GH in our Community, using as data sources the GH Committee Register. Description of categorical (%) and continuous (mean±SD) variables. Comparative study of different parameters and growth rate (GR) (Kruskal-Wallis non-parametric test).

Results: 87 SGA patients (43M, 44F). Birth height (BH) 42.9±4.3cm (-2.8±1.2SD) and birth weight (BW) 2067.96±38g (-2.1±0.7). No one had phe-notypic anomalies, 5 (5.74%) had psychomotor retardation and 27 (31%) were premature. Target height in girls was 154.7±7.4cm (-1.5±0.8SD) and in boys 170.8±4.5cm (-0.9±0.8SD). 14 patients (16%) had family history of delayed puberty. Evolution is shown on table.

We established 3 groups depending on the growth rate in the first year of treatment: <1SD: n=17; 1.1-2SD: n=14; >2.15SD: n=56. Comparative study between the 3 groups showed no statistical association with paternal and maternal size, BH and BW, gestational age (preterm / term), initial parameters (size, CA and BA, GR) or the dose of GH, similar in the 3 groups (34.5/35/31.3/36 µg/kg/d). Familial short stature individuals (28%) had lower height at baseline (-3.3±0.6 versus -3.0±0.5) (p 0.04). Conclusion: 1-Treatment response to GH was favorable with a height gain of 0.5 and 1.2 SD after 1 and 4 years, respectively. 2-We have not found any predictive parameters for successful response to GH therapy.

P2-d1-615 GH and IGF Treatment 2

A dose-dependent effect of growth hormone on growth velocity in Chinese children with idiopathic short stature

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Background: What dose of growth hormone is more effective on height for idiopathic short stature continue(ISS) to puzzle endocrine doctor. Objective: To assess the dose-dependent effect of recombinant human growth hormone(rhGH) in Chinese children with ISS.

Methods: A total 106 ISS patients(52 males and 54 females)are enrolled from endocrine clinic of two centers. 75 cases are Tanner stage I and 31 stage II. They are divided into 3 dose groups according to GH doses: low-dose group (0.26mg/kg.w), the middle-dose group (0.35 mg /kg.w) and high-dose group (0.41 mg / kg.w) with 39, 23 and 44 patients, respectively. They were given rhGH 7 days per week for 1-2 years.Observed the changes of Ht, GV, HoSDS, bone age, PAH and side effects.

Results: (1) GV of 3 groups after 1 year treatment were enhanced to 8.22 plus/minus1.93cm , 9.97 plus/minus1.95cm and 11.48 plus/minus1.63cm comparison to 4.59 plus/minus1.45cm, 3.65 plus/minus1.81cm and 4.5 plus/ minus 0.67cm of basic GV, respectively, P <0.01. High dose group gained better growth than middle dose group, P=0.01. GV of the 3 groups after 2 years, were 7.33 plus/minus3.18cm, 7.73 plus/minus1.11cm and 8.39 plus/ minus 1.48cm,no difference in three groups,P= 0.05. (2)Bone age progress of three groups after one and two year treatment were 1.31 plus/minus0.81,1.07 plus/minus0.41,1.16 plus/minus0.49 and1.43 plus/minus0.69,1.27 plus/minus0.26,1.31 plus/minus0.37 respectively P=0.05. (3) 2 cases of high-dose group had mild high fasting blood glucose after 3 months of treatment with 5.7, 6, 5.89, 6.62, 6.05mmol/L,.respectively, but came back to normal after short period stoped GH and kept normal during continuing treatment. Knee pain occurred in occasional individual, no bone and biochemical abnormalities.

Conclusion: A more obvious dose-response relationship for the effect of GH treatment on GV appeared during catch-up growth period of first year. There were no significant differences among the three dose groups in the rate of bone age progression.Only occasional side effects happened in high-doses group.
Background: Growth hormone (GH) and sex hormone are cooperated in the pubertal growth of children.

Objective and hypotheses: To evaluate the influence of sexual gonadal function on the final adult height (FAH) in GH-treated growth hormone deficiency (GHD) children.

Methods: 134 children with GHD who reached final adult height (FAH) after receiving recombinant human growth hormone (rGH) treatment were included in this study. They were divided into two groups, spontaneous puberty development group (n=18, 10 boys and 8 girls) and induced puberty group (n=12, 6 boys and 6 girls). All cases of induced puberty group had gonadotropin deficiency.

Results: Standard deviation score (SDS) of FAH were (-1.13±0.54) in spontaneous group and (-1.00±0.47) in induced puberty group. A total of 77.8% (14/18) of spontaneous puberty development group and all induced puberty group achieved final adult height which was comparable to or above their target height. There was no statistic significant difference of FAH-SDS and TH-SDS between two groups (FAH-SDS by age at puberty of spontaneous puberty development group were (12.98±0.59) years old for boys and (10.75±0.84) years old for girls, and the pubertal age in induced puberty group were (21.92±5.81) years old for boys and (19.44±6.08) years old for girls. Puberty height gain of spontaneous puberty development group were (24.38±1.86) cm for boys and (22.47±2.65) cm for girls, which accounted for (14.91±1.15) % and (15.21±1.43)% of final adult height, respectively. Puberty height gain of induced puberty group were (3.07±2.64) cm for boys and (3.63±2.18) cm for girls, which accounted for (1.86±1.61)% and (2.35±1.40)% respectively.

Conclusion: GH could improve FAH in GHD children. Delayed induction of puberty can prevent FAH in GHD children with gonadal deficiency who start rGH treatment late and height significantly behind normal children at the beginning of the therapy.

P2-d1-619 GH and IGF Treatment 2

Growth hormone deficiency associated with pituitary abnormalities in 14q microdeletion syndrome. A new phenotype-genotype correlation.

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Background: 14q Microdeletion syndrome is a rare congenital disease characterized by dysmorphic features, developmental delay, mild-to-moderate mental retardation, and variable degree of postnatal growth retardation.

Objective and hypotheses: Growth hormone deficiency (GHD) has not been reported as cause of growth impairment in 14q microdeletion syndrome. To date, no candidate gene for short stature has been hypothesized to map in region 14q32.31q32.33.

Case presentation: A 12 2/12 year old boy was referred to us because of short stature. The child was born at term from two unrelated and healthy parents. The boy was 136.5 cm tall (-2.5 SDS) and his face was characterized by micrognathia, hypertelorism, blefarophimosis, epicantal folds, long broad philtrum. The pubertal stage was Tanner I. Due to his dysmorphic features, developmental delay and growth retardation, he was investigated cytogetically.

Results: Karyotype was normal, but array-CGH showed a de novo 14q32.31q32.33 microdeletion. Thyroid function and screening for celiac disease were normal. IGF-I was 146 ng/ml (-1.86 SDS). The highest GH peak in two different provocative tests was 3.16 ng/ml. Brain MRI showed hypoplasia of corpus callosum, hypoplasia of anterior pituitary and ectopic posterior pituitary. The other pituitary hormones were in the normal range. Patient was started on rGH therapy at the dose of 27 µg/kg/day with an improvement of growth velocity after 6 months. To date, no candidate gene associated with pituitary alterations has been mapped in the microdeleted region.

Conclusions: Here we first describe a child with GHD and pituitary abnormalities associated with 14q microdeletion syndrome. This case illustrates the importance to assess pituitary function in short patients with this syndrome in order to start replacement therapy. Furthermore, this case suggests the presence in 14q32.31q32.33 locus of gene(s) potentially involved in pituitary development.
idopathic growth hormone deficiency (iGHD).

Methods: Height data at start and after one year of GH therapy were retrieved from the Belgian Registry for growth and pubertal disorders on 358 (240 male and 118 female) children with iGHD, who were prepubertal (age between 1.2 and 14 years) at start and remained prepubertal during the first year of GH therapy (20-35 µg/kg bodyweight/day). One year growth velocity percentile and SD curves were constructed with the LMS method.

Results: The growth velocities were log-normal distributed by age and decreased significantly (p<0.001) with age: median growth velocity decreased from 12.0 cm/y at 2 years to 8.2 cm/y at 12 years. The mean growth velocity SDS was not different between boys (0.01 ± 0.98) and girls (-0.08 ± 1.31) (p = 0.5). Children with isolated GHD (n=274) showed a significantly lower mean response than those with multiple pituitary hormone deficiencies (GV SDS -0.13 ± 0.95 vs. 0.44 ± 1.04; p = 0.001). Children with severe GH deficit (peak GH value < 3 µg/L; n=102) had a higher mean response than those with a less severe form (GV SDS 0.64 ± 0.93 vs -0.25 ± 0.92; p < 0.001).

Conclusions: Disease (type and severity of the GHD) specific charts were developed to evaluate the first-year growth response to GH treatment in prepubertal children with iGHD in Belgium. They have the advantage to be easy to use in daily clinical practice, enabling the rapid identification of poor responders to GH treatment.

P2-d1-620 GH and IGF Treatment 2

Predictors of height gain in children born small for gestational age under treatment with recombinant human growth hormone

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Background: Small for gestational age (SGA) children whose height did not attain the percentile related to the genetic growth potential until 24-36 months of age may benefit from treatment with rhGH.

Objective and hypotheses: To identify in SGA children the predictors associated to growth response after two years of treatment with rhGH.

Methods: We evaluated 25 SGA children (16 boys) with short stature treated with rhGH. The criterion for SGA was birth weight-SDS for gestational age. The IGF1 generation test showed an increase in 1,25 v -0,67±0,58). In all 38 SGA children HOMA increased from 0,8± 0,4 to 1,48 ± 0,76 (p=0,05) after one year of treatment. No significant differences between HOMA in SGA-GHN and in SGA-GHD group (0,77 ± 0,39 v 0,84 ±0,42) and after one year (1,57 ±0,78 v 1,27 ± 0,67) were observed. HbA1c levels did not change significantly.

Conclusions: After 1 year of GH treatment SGA children experienced significant height increase; SGA-GHN and SGA-GHD group showed comparable height. Insulin sensitivity decreases in SGA children after GH treatment irrespective of the GH secretory status.

P2-d1-622 GH and IGF Treatment 2

Positive outcome of GH therapy in a patient carrying a mutation in the CHD7 gene (CHARGE Syndrome)

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Background: CHARGE syndrome (Coloboma, Heart defects, choanal Atresia, Retarded growth and development, Genital and/or urinary abnormalities, Ear abnormalities) is a genetic disorder characterized by a specific pattern of anomalies. De novo mutations in the gene encoding chromodomain helicase DNA binding protein 7 (CHD7) are the major cause of this syndrome. Genetic hypoplasia, delayed puberty, and retarded growth are common, but GH deficiency have been documented in rare cases in literature.

Objective and hypotheses: The aim of this study is to report the clinical outcome of GH therapy in a child affected by CHARGE syndrome.

Methods: We describe a child presented a severe phenotype of the CHARGE syndrome. All the major criteria of the syndrome were present, moreover, bilateral surgery for cryptorchidism was performed and a severe scoliosis of the thoracic and lumbar spinal region was present. We performed the molecular analysis of the CHD7 gene that revealed a novel de novo heterozygous mutation in intron 32 (c.6936+1 G>A), with a splicing effect. At the age of 4 he showed a severe delayed growth with height at -3 SDS and weight at -2.5 SDS. The secretion study of the growth hormone (GH) showed an insufficient response to two subsequent stimulation tests. IGF1 and IGFBP3 levels were below the normal limits for age. The IGF1 generation test showed an increase of GH secretion more than 15 ng/ml. At the age of 5 years he started therapy with recombinant somatropin at the dose of 0.033 mg/Kg/die.

Poster Presentations
Results: After 2 years of therapy he showed an height gain of +1 SDS (12 cm) and a weight gain of +0.5 SDS. A significant improvement of the muscle mass was also evident while the parameters of the spinal defects were stable.

Conclusion: Our clinical report confirmed that GH deficiency can be present in patients affected by CHARGE syndrome. In this observation the GH treatment showed a significative increase of growth velocity after 2 years of therapy without adverse effects, in particular on the severe scoliosis of the child.

Background: Prepubertal growth hormone (GH) deficiency is characterized by cardiac atrophy with a significant reduction in left ventricular mass that can lead to the development of dilated cardiomyopathy (DCM) and ultimately to heart failure.

Objective and hypotheses: Presentation of a case of pituitary dwarfism with restrictive cardiomyopathy (RCM) developed during the growth hormone replacement treatment. Hypothesis - the restrictive cardiomyopathy is a consequence of the treatment with recombinant growth hormone (rGH).

Methods: Clinical evaluation, assessment of the GH reserve, cardiological exam.

Results: Male patient, 11 years old, without a documented history of cardiovascular pathology, diagnosed with GH deficiency at the age of 6 years. Treatment with rGH was initiated with gradually increasing doses from 0.6 mg/day to 1 mg/day, with positive response. Since January 2011, the patient presents fatigue, dyspnea with medium effort, palpitations with a sudden onset. The cardiological exam confirmed the presence of restrictive cardiomyopathy, with the characteristic “dp and plateau” pressure type during catheterization. rGH therapy was stopped. The reassessment of the GH reserve proved the complete GH deficiency – ITT (hGH: 2.57-2.99-2.45-3.27 ng/ml, with a basal level of 2.22 ng/ml).

Conclusion: GH therapy is beneficial for improving cardiac contractility and hemodynamic, but may be associated with transient side effects such as induction of left ventricular hypertrophy with worsening diastolic function. Restrictive cardiomyopathy hasn’t been described so far as a side effect of somatropin treatment. We may conclude that the association found in our case is just a coincidence. Nevertheless, rGH therapy wasn’t restarted.

P2-d1-623 GH and IGF Treatment 2

Restrictive cardiomyopathy during rhGH treatment – coincidence or consequence?

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Background: Prepubertal growth hormone (GH) deficiency is characterized by cardiac atrophy with a significant reduction in left ventricular mass that can lead to the development of dilated cardiomyopathy (DCM) and ultimately to heart failure.

Objective and hypotheses: Presentation of a case of pituitary dwarfism with restrictive cardiomyopathy (RCM) developed during the growth hormone replacement treatment. Hypothesis - the restrictive cardiomyopathy is a consequence of the treatment with recombinant growth hormone (rGH).

Methods: Clinical evaluation, assessment of the GH reserve, cardiological exam.

Results: Male patient, 11 years old, without a documented history of cardiovascular pathology, diagnosed with GH deficiency at the age of 6 years. Treatment with rGH was initiated with gradually increasing doses from 0.6 mg/day to 1 mg/day, with positive response. Since January 2011, the patient presents fatigue, dyspnea with medium effort, palpitations with a sudden onset. The cardiological exam confirmed the presence of restrictive cardiomyopathy, with the characteristic “dp and plateau” pressure type during catheterization. rGH therapy was stopped. The reassessment of the GH reserve proved the complete GH deficiency – ITT (hGH: 2.57-2.99-2.45-3.27 ng/ml, with a basal level of 2.22 ng/ml).

Conclusion: GH therapy is beneficial for improving cardiac contractility and hemodynamic, but may be associated with transient side effects such as induction of left ventricular hypertrophy with worsening diastolic function. Restrictive cardiomyopathy hasn’t been described so far as a side effect of somatropin treatment. We may conclude that the association found in our case is just a coincidence. Nevertheless, rGH therapy wasn’t restarted.

P2-d1-625 GH and IGF Treatment 2

Patient perspectives on a new injection pen for growth hormone: results of a multinational clinical study in children and adults

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Background: To achieve optimal therapeutic results with growth hormone therapy, continuous, long-term adherence is essential. To enhance treatment compliance it is important that the device used for drug administration is convenient and acceptable to the subject. In this study [NC101112865], the ease of use and preference for a new injection pen versus an existing pen were evaluated in a population of treatment naïve children and adults in seven European countries.

Objective and hypotheses: The study was designed to assess the ease of use/convenience characteristics of two injection pens individually and comparatively. Patient preference based on self-report and observed behavior, when possible, was also assessed at the conclusion of the study.

Methods: Treatment naïve subjects primarily with a diagnosis of growth hormone deficiency or short for gestational age [and their caregivers in the case of children] were included in the study. Three study groups were identified: 1) self-treating adults; 2) children between the ages of 8 and 18 and their caregiver (dads); and 3) caregivers of patients ages 4 to 7 years. The study was an open-label randomized crossover design and the endpoint was measured using the Injection Pen Assessment Questionnaire (IPAQ), a validated self-report measure of ease of use and preference.

Results: Overall, 67.2% (95% CI - 59% – 76%) and 64.2% (95% CI - 56% – 73%) reported the new pen as easy or easier to use and equal or preferred, respectively.

Conclusion: Both pens were considered easy to use with the majority finding the new pen easier or easier to use than the current pen. Among those expressing a preference, the majority preferred the new pen. Adult participants selected the new pen more often than child/parent dyads as did participants from the Eastern as opposed to Western parts of Europe.
Hallerman-Streiff Syndrome with growth hormone (GH) deficiency: is GH therapy beneficial?  
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2Hospital Universitario Central Asturias, Genetics, Oviedo, Spain  

**Background:** Hallerman-Streiff syndrome (HSS) is a rare genetic disorder which involves multiple congenital abnormalities affecting head and face: malformations of craniofacial region (bird face) and ocular abnormalities. Short stature is a common feature. All cases are sporadic with an unknown pattern of inheritance.  

**Objective:** To report a patient with HSS and growth hormone (GH) deficiency with very low levels of IGF-1.  

**Methods:** Case report and evolution.  

**Results:** A 22 months old girl diagnosed of HSS was referred to our center because extreme growth failure (height -6.6 SD). She was the second child of healthy non-consanguineous parents. Family history was unremarkable. Pregnancy was uncomplicated and delivery at term (38 weeks) with normal birth weight (2800 g) and length (48 cm). Physical examination showed brachycephaly with a prominent forehead, a thin tapering nose, maxillary and mandibular hypoplasia, sparse hair, hypodontia, and hypoplastic thorax with protuding abdomen. She was operated for bilateral congenital cataract. It was not possible to implant intraocular lens due to microphthalmia. She suffered multiple respiratory infections. Intellect is normal. Repeated IGF-1 blood determinations disclosed levels under 25 ng/mL and IGFBP3 also very low (1.64 mcg/mL). The GH response to pharmacological stimuli reached maximal levels of 1.52 ng/mL after glucagon stimulus and 8.7 mg/mL after clonidine stimulus. Other laboratory tests, including extensive metabolic studies and karyotype were normal. Nutrition status was good with an intake over 175 kcal/kg/day. Growth velocity was very low (-3.95 SD). Bone age was retarded two years. She initiated GH therapy at 0.028 mg/kg/day (off label indication) with initial good auxological answer, remarkable general improvement, and no adverse effects. IGF-1 has raised soon to 79 ng/mL.  

**Conclusions:** GH therapy seems to benefit this patient. Further investigation is needed in view of the possibility of realizing a therapeutic clinical trial in this rare syndrome.

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Effects of recombinant human growth hormone treatment on myocardial geometry and functions in children with growth hormone deficiency  
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1Ankara Child Health and Hematology Oncology Hospital, Pediatric Endocrinology, Ankara, Turkey;  
2Ankara Child Health and Hematology Oncology Hospital, Pediatric Cardiology, Ankara, Turkey  

**Aim:** This study was designed to investigate the effects of recombinant human growth hormone (rGH) treatment on myocardial geometry and functions in children with idiopathic isolated growth hormone deficiency (IGHD) by conventional echocardiography and tissue Doppler imaging.  

**Patients and method:** Thirty patients (19 boys and 11 girls) who were diagnosed as having idiopathic isolated GH Deficiency between December 2010 and July 2011 in our hospital were followed for 6 months. The mean age of patients was 11.0±2.6 (6.3 - 15.5) years. At baseline, 3rd and 6th month of treatment, the structure of left ventricle (LV) was assessed by conventional echocardiography and tissue Doppler imaging. By using these data; LV mass indexes (LVMI) by two different methods (LVM1: g/m² and LVM2: g/m².7), relative wall thickness indexes (RWTI) and myocardial performance indexes (MPI) for LV, IVS and RV were calculated. Patients who have co-morbidities and who have taken any other medication were excluded.  

**Results:** There were no significant differences for LVM1 (59.5±13.3 and 64.0±13.9), LVM2 (31.3±5.7 and 32.4±6.8) and RWTI (0.40±0.03 and 0.42±0.03) at 3rd month. However, the differences for LVM1 (68.6±17.4, p<0.05) and LVM2 (34.0±7.3, p<0.05) were significant, except for RWTI (0.43±0.03) at 6th month. There were also no significant differences for LV MPI (0.51±0.07, 0.52±0.07 and 0.51±0.07), IVS MPI (0.51±0.07, 0.50±0.05 and 0.53±0.04) and RV MPI (0.48±0.65, 0.48±0.05 and 0.49±0.04) at both 3rd and 6th months according to baseline measurements.  

**Conclusion:** The results of this study showed that the rGH treatment increases the LV mass; however it does not affect the LV geometry and also both systolic and diastolic functions of the myocardium.

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Italian survey on GH management in transitional age (the ANTARES project)  
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**Background:** There is no general consensus among endocrinologist on the management of GH deficiency during the transitional age.  

**Objective and hypotheses:** Aim of the present survey is to analyse the attitude of Italian endocrinologists in this context.  

**Methods:** A questionnaire on GHD management in the transitional age designed by the Italian Society of Paediatric Endocrinology and Diabetology (ISPED) was filled by 78/98 centres involved (paediatrics and endocrinology). The questionnaire was divided in 4 sections with 28 total questions.  

**Results:** There was no agreement on the definition of transitional age. Mean age at rGH discontinuation was 15.7 y. Retesting was performed on average 13 weeks after stopping therapy. GH secretory status was retested by measurement of IGF-I in 7.5% of the centres, and by GH stimulation tests in the remaining cases. Among them 68.8% used the GHRIH + arginine and 28.1% the ITT. 30.7% of the centres did not follow a structured follow-up program for GHD patients after rGH discontinuation, 97.1% of the centres measured patients’ height, 95.7% weight and only 49.3% of them evaluated bone metabolism and peak bone mass. However, bone mineral density and peak bone mass were considered the most relevant clinical outcome to be pursued for 61.5% of the centres.  

**Conclusions:** The present survey indicate that there are a number of differences among several Italian Paediatric and adult endocrinology centres in the management of GHD in the transitional age. This observation highlights the actual need of a consensus guideline in the diagnostic and therapeutic approach of GHD in this particular age.

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Elevation of serum creatine phosphokinase during growth hormone treatment  
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5; on behalf of Working Group on Growth Factors and Puberty, Division of Endocrinology, Diabetology and Metabolism, Torino, Italy;  
6; Department University-Hospital, Endocrinology, Diabetology and Metabolism, University of Turin;  
7; Ihsan Esen;1 Iker Cetir;2 Fatma Demirel;3 Filiz Eko;2**  
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2Ankara Child Health and Hematology Oncology Hospital, Pediatric Cardiology, Ankara, Turkey  

**Background:** Repeated intramuscular or subcutaneous (s.c) injections of recombinant human growth hormone (rGH) in GH deficient patients have been believed to be safe for muscle tissues. However we recently observed an elevation of serum creatine phosphokinase (CPK) during GH therapy in some patients with GH deficiency so we evaluated the CPK levels of GH deficiency patients receiving rGH.  

**Patients and methods:** 47 patients (26 female, 21 male) receiving rGH in the last 2 years were taken into the study. CPK levels were measured every 3 months during subcutaneous rGH treatment. If CPK elevated, GH treatment was stopped for ten or fifteen days, later CPK level was reappraised.  

**Results:** Mean age of patients at diagnosis was 11.8±2.9 (7-16) years. Four patients had multiple pituitary hormone deficiency with complete GH, TSH and gonadotropin deficiency. The others were isolated GH deficiency. Mean
duration of treatment was 12.11± 5.3 (6-24) months. In eight patients CPK level increased to over 200 U/L. We stopped rhGH treatment until CPK levels decreased to normal values. Mean duration was 16±4.9 (10-30) days. In one patient CPK level was increased up to 2000 U/L after three months of therapy who had multiple pituitary hormone deficiency after brain trauma. CPK levels are shown on the table 1: CPK levels were compared with initial values.

**Discussion:** CPK levels showed a gradual and significant increase during treatment in spite of all patients administered rhGH subcutaneously not intra-muscularly. Although mechanism is not clear, we recommend the measurement of CPK levels closely.

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<tr>
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<th>CPK</th>
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<tr>
<td>Initial</td>
<td>92.5 ±21.8 U/L (48-153)</td>
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<tr>
<td>At 6 months of therapy</td>
<td>122 ±31.9 U/L (72-197)</td>
<td>p&lt;0.001</td>
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<tr>
<td>At one year of therapy</td>
<td>154.7±54.3 U/L (108-239)</td>
<td>p&lt;0.001</td>
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<tr>
<td>At two years of therapy</td>
<td>163±43.8 U/L (113-258)</td>
<td>p&lt;0.001</td>
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**P2-d1-630** GH and IGF Treatment 2

**Adherence to growth hormone treatment before and during puberty assessed with an electronic injection recording device**

Kevin Hartmann, René Rasmussen

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**Background:** The safety and efficacy of recombinant human growth hormone (rhGH) has been demonstrated. However, accurate data about the adherence to GH are lacking. easypod™ is the only electronic injection device for growth hormone (Saizen®) which accurately records dose and injection time.

**Objective and hypotheses:** To evaluate adherence to rhGH treatment under everyday conditions through the use of easypod™.

**Methods:** This is a prospective, observational, open-label, non-controlled, multicentre study. Patients with growth hormone deficiency (GHD), small for gestational age (SGA), Turner Syndrome (TS) and chronic renal insufficiency (CRI) were included. Differentiation between pre-pubertal and pubertal children was performed by collecting clinical signs of puberty. Results of the first interim analysis are reported here.

**Results:** Data from 75 patients (46 male, 29 female), mean age 12.5 ± 3.5 years, treated with GH over a mean period of 343 (±21) days were analyzed. Overall male and female children showed a similar mean adherence of 90.5 % and 92.2 % respectively, pubertal children had a lower mean adherence (89.2 %) in comparison to pre-pubertal children (96.5 %).

**Conclusion:** The first results of this study demonstrate that especially pubertal children face difficulties in sticking to rhGH treatment properly which may lead to suboptimal growth. Appropriate measures such as personalized trainings should be taken envisaged in order to foster the child’s adherence to the treatment regimen.

**P2-d1-631** GH and IGF Treatment 2

**A comparison of factors that influence choice of growth hormone device in those children commencing and already established on growth hormone**

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**Background:** Several devices are available for administration of recombinant growth hormone (GH). A prospective study was undertaken to look at those attributes of GH delivery device most important to patients when choosing a device.

**Objective and hypotheses:**

- To understand which features of a GH delivery device are considered most important to patients when choosing a device.
- Comparison of the patient device preferences at start of GH treatment and after two years of treatment.
- Correlation of these factors to the actual GH device chosen after demonstration of device.

**Methods:** Children attending a large tertiary paediatric endocrine centre were enrolled in the study. Ethical approval was obtained. The parent/child preference for various device characteristics was evaluated through two questionnaires including a pictorial chart. The eight delivery devices currently available were then demonstrated. Children were divided into two groups:

- Treatment-naive (Group I)
- Treatment-established (Group II).

**Results:** There were 33 children (aged 1-16 years) in Group I and 27 children (aged 4-17 years) in Group II. The option of prefilled cartridges was ranked as the top most desirable characteristic in both groups (85% in Group I, 44% in Group II). The Easypod™ device was the most commonly chosen device in both groups (42% in Group I, 37% in Group II). 36% of Group I and 70% of Group II picked the device identified as their top preference. 79% of Group I and 96% of Group II picked a device among their top three choices. In Group II, 70% of subjects chose the same device they are currently using.

**Conclusions:** The patient device preference was similar at the start of treatment and after two years of treatment, but 30% of those established on treatment would consider choosing an alternative device. These questionnaires can be used to streamline the devices shown to patients.

**P2-d1-632** GH and IGF Treatment 2

**Successful growth hormone replacement therapy in Costello syndrome**

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**Background:** Costello syndrome (CS) is considered an overgrowth disorder given the macrosomia that is present at birth in 89% of the cases. However, shortly after birth the weight drops dramatically and the patients are usually referred for failure to thrive. Subsequently, affected patients develop the distinctive coarse facial appearance and are at risk for cardiac anomalies and solid tumor malignancies. Various endocrine disorders, although not very often, have been reported in patients with CS, including growth hormone deficiency, hypoglycemia, ACTH deficiency, cryptorchidism and hypothyroidism.

**Objective and hypotheses:** We report a case of Costello syndrome and growth hormone deficiency and we evaluate the long-term safety and efficacy of growth hormone replacement therapy.

**Methods:** The index patient is a male born macroscopic at 35 weeks’ gestational age by phenotypically healthy, non-consanguineous parents. Shortly after birth he was diagnosed with congenital hypothyroidism due to thyroid hypoplasia and put on thyroxine. At the age of 3.5 years he was diagnosed with Costello syndrome based on clinical presentation and the diagnosis was confirmed with sequencing analysis of DNA sample indentified a heterozygous mutation, c.34G>A (p.Gly12Ser), in exon 2 of HRAS. Both weight and height were 5 SD below the mean and he found to have cryptorchidism on the right. Serial two-dimensional echocardiograms showed very mild thickening of the intraventricular septum. He was diagnosed with growth hormone deficiency and put on growth hormone replacement therapy.

**Results:** On follow-up the patient’s height gradually improved without any signs of worsening cardiomyopathy or malignancies. He is currently 14-year-old and his height is at 10th percentile.

**Conclusions:** Given the limited literature on growth hormone deficiency in patients with CS the current case adds useful information on this field. Since patients with CS are at increased risk for cardiac myopathy and tumor development they deserve close monitoring during treatment.

**P2-d1-633** GH and IGF Treatment 2

**Treatment with GH is more effective than IGF-I to improve growth in normal female rats**

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**Background:** The growth-promoting effect of rhIGF-I is well established in GH-deficient hypothyroidism treated rats. However, in normal rats the effects of rhIGF-I or rhIGF-I+rhGH are poorly documented.
Objective and hypotheses: The objective was to compare the growth promoting effects between rhIGF-I and rhGH and also evaluate the combination of rhIGF-I-rhGH in normal female rats.

Methods: Female, prepubertal Sprague-Dawley rats (23 days of age) were treated with vehicle, rhIGF-I (2.2 or 4.4 mg/kg/d; using Alzet osmotic mini-pumps) and/or rhGH (5 mg/kg/d; daily subcutaneous injections) for 4 weeks. Longitudinal bone growth was monitored by weekly X-ray. Blood samples were obtained weekly. Serum IGF-I levels were determined by radioimmunoassay detecting both rat and human IGF-I.

Results:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Vehicle</th>
<th>rhIGF-I (2.2 mg/kg/day)</th>
<th>rhIGF-I (4.4 mg/kg/day)</th>
<th>rhGH (5 mg/kg/day)</th>
<th>rhGH (5 mg/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta body weight</td>
<td>129.1±4.9</td>
<td>144.0±4.0</td>
<td>174.0±4.2</td>
<td>213.7±5.8</td>
<td>230.3±6.8</td>
</tr>
<tr>
<td>Delta nose-anus length</td>
<td>7.3±0.2</td>
<td>7.6±0.1</td>
<td>8.3±0.2</td>
<td>9.2±0.2</td>
<td>9.5±0.2</td>
</tr>
<tr>
<td>Serum IGF-I (ng/ml)</td>
<td>521</td>
<td>(447-721)</td>
<td>(522-829)</td>
<td>1625</td>
<td>(1024-1670)</td>
</tr>
</tbody>
</table>

Conclusions: Therapy with rhGH is more effective than rhIGF-I to increase body weight, nose-anus length, and tibia length. Nose-anus length and tibia length were similar in rats treated with rhGH alone compared to those receiving rhIGF-I+rhGH in combination.

Background: Apoptosis is a selective process for deletion of cells in various biological systems. Enzyme systems including the aspartate-specific cysteinyll proteases or caspases play role in the apoptosis pathway. A member of this family, caspase-3 has been identified as being a key mediator of apoptosis of mammalian cells.

Objective and hypotheses: We aimed to evaluate the caspase-3 activity in the descended and undescended rat testes after human chorionic gonadotropin (hCG) treatment.

Methods: 30 Sprague-Dawley rats weighing 300 to 350 g were allocated randomly into 6 groups consisting of 6 animals each and evaluated at 7 groups: A; Sham operated (control), B and D; Unilateral undescended testis-1500 U/m2 hCG treatment descended and undescended one, C and E; Unilateral undescended testis-5000 U/m2 hCG treatment descended and undescended one, F; Bilateral undescended testis-1500 U/m2 hCG treatment, G; Bilateral undescended testis-5000 U/m2 hCG treatment. hCG treatment were performed subcutaneously once daily for 5 days. At the end of the treatment rats in each group were sacrificed and their testes removed. The testes were immunohistochemically examined to evaluate the caspase 3 activity.

Results: Immunohistochemical stainings with caspase-3 antibody were performed to all collected tissues. H scores were calculated for each tissue according to density and percentage of the staining in the tissues. Caspase-3 activity was higher in high doses, bilateral and unilateral-undescended one when compared with low doses, unilateral and unilateral-descended one, respectively (Kruskal-Wallis test, p=0.0001).

Conclusions: This study indicates that HCG treatment lead higher caspase-3 activity depending on dose, laterality and severity of cryptorchidism.

Background: Plant Growth Regulators are generally used in greenhouses to obtain maximum yield. 4-Chlorophenoxy acetic acid being the most widely used one. Plant Growth Regulators remnants may lead to adverse effects at inappropriate or high doses. Hepatocellular necrosis and/or increased apoptosis in genital organs have been reported in rats exposed to this substance.

Methods: We aimed to investigate the possible role of oxidative mechanisms in rat testis exposed to 4-chlorophenoxy acetic acid.

Objective and hypotheses: The study was implemented on 20 day-old Wistar albino rats. Forty rats were randomized into five groups (a control group, a saline group and three 4-Chlorophenoxy acetic acid groups that received 25-50-100 mg/kg/day until 50 days of age respectively).

Results: There was no statistical significant difference between saline and control group in terms of in terms of oxidative stress markers (MDA, GSH and NOx levels) whereas there was a significant difference between 4-Chlorophenoxy acetic acid received group and control group in terms of MDA and NOx levels.

Conclusions: 4-Chlorophenoxy acetic acid may have an impact on rat testis at tissue level by oxidative stress and may eventually lead to infertility.

Background: Bilateral macroorchidism has been described with no testicular hyponfunction in Fragile X syndrome, adrenal rest tumors or infiltrative disorders, and with testicular hyperfunction, due to increased gonadotropin signaling activity, in gonadotropin-secreting adenomas, McCune-Albright syndrome, aromatase deficiency and severe hypothyroidism. Testis size is mainly dependent on Sertoli cell number, whose proliferation is regulated by testosterone and other factors.
**P2-d3-637** Gonads and Gynaecology 2  
**Primary clear cell adenocarcinoma of the uterine cervix in a 8-year-old: a transgenerational effect of DES?**  
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**Background:** Primary clear cell adenocarcinoma (CCAC) of the uterine cervix and vagina are tumors occurring in adolescent girls and young women prenatally exposed to diethylstilbestrol (DES). Conversely, before the clinical use of DES, CCAC was rare and affected exclusively post-menopausal women. Based on the wide range of reproductive adverse health outcomes in human female and male offspring, DES has been considered as a prototype of endocrine-disruptor chemicals and is thus used experimentally. Prenatal DES-exposed mice have raised the suspicion of a transgenerational effect on reproductive health outcomes in offspring and some human reports have shown an increased risk of hypospadias in sons of DES daughters. We report here for the first time a case of CCAC of the uterine cervix in an 8-year-old girl whose grandmother received DES therapy.

**Case report:** A 8-year-old girl was admitted to the pediatric emergency department after 2 days of severe vaginal bleeding, with no sign of abuse or pre-cocious puberty, and no pain or mass at abdominal palpation. Vaginal bleeding continued to occur frequently. Pelvic ultrasonography was unremarkable. A vaginoscopy was performed and showed a friable burgeoning cervix mass. Pathology examination of tissue samples raised the hypothesis of CCAC. Abdominal and pelvic MRI evidenced no abnormality. She underwent surgery and staging that revealed CCAC confined to the uterine cervix. Medical records established unequivocally that her grandmother had received DES therapy before becoming pregnant with the patient’s mother, that the patient’s mother underwent surgical removal of left ovary for a rapidly increasing cyst early in life, and that the patient’s brother presented severe microcephaly.

**Conclusions:** Despite no molecular demonstration of direct relationship, this case raises for the first time the hypothesis of transgenerational effects of DES in girls also. It strongly suggests the need to follow the grandchildren of DES-treated women.

**P2-d3-638** Gonads and Gynaecology 2  
**Gonadal failure in children with acute lymphoblastic leukaemia treated by bone marrow transplantation: prevalence and risk factors**  
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**Background:** Gonadal failure is a well-recognised long-term complication of bone marrow transplantation (BMT) in children with acute lymphoblastic leukaemia (ALL). Identifying key risk factors is helpful in planning and counselling for hormone replacement therapy (HRT) and in targeting future research.

**Objective and hypotheses:** To determine the prevalence and risk factors for primary gonadal failure (PGF) in childhood ALL treated with BMT in a single centre.

**Methods:** Retrospective study of 108 patients treated from 1989-2009. Of 54 survivors, 40 (25 males and 15 females) aged 22.6 (range 11-32) years were assessed with the Female Sexual Function Index and Female Sexual Distress Scale.

**Results:** 14% of the women had vaginal sensitivity lowest when stimulating the clitoris and sides of the clitoris. For vaginal sensitivity, scores for sexual pleasure, discomfort, orgasm intensity and effort increased with increasing vaginal depth. 14% of the women had experienced orgasm, as the latter appears to be closely related to genital sensitivity.

**Conclusion:** Despite no molecular demonstration of direct relationship, this case raises for the first time the hypothesis of transgenerational effects of DES in girls also. It strongly suggests the need to follow the grandchildren of DES-treated women.

**P2-d3-639** Gonads and Gynaecology 2  
**Relationship between self-reported genital sensitivity and female sexual function**  
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**Background:** Perceived genital sensitivity represents a potentially important component of sexual well-being.

**Objective and hypotheses:** Clarify the implications of self-perceived genital sensitivity of the clitoris and vagina for women’s sexuality, and particularly the experience of orgasm, as the latter appears to be closely related to genital sensation.

**Methods:** 302 genitally unoperated, sexually active women (18-67 yrs, median 22 yrs) rated the sexual pleasure, discomfort, orgasm intensity and effort to attain orgasm in specified areas around the clitoris and within the vagina through an online survey (validated Dutch translation of the Self-Assessment of Genital Anatomy and Sexual Function). Psychosexual functioning was assessed with the Female Sexual Function Index and Female Sexual Distress Scale.

**Results:** Sexual pleasure and orgasm intensity was strongest and effort and discomfort lowest when stimulating the clitoris and sides of the clitoris. For vaginal sensitivity, scores for sexual pleasure, discomfort, orgasm intensity and effort increased with increasing vaginal depth. 14% of the women had a sexual dysfunction and experienced difficulty in achieving orgasm. Women with a sexual dysfunction also reported to be most genitally sensitive on and around the clitoris and within the deep vagina, but experienced significantly less sexual pleasure and orgasm intensity and more effort and discomfort in these same areas as compared to women without a sexual dysfunction(r<0.001).

**Conclusions:** Our findings suggest that self-perceived genital sensitivity and sexual well-being are interrelated. Further elucidation of the causal relationship is necessary. Although some genital cosmetic surgeries are sought to improve women’s genital functionality, most are undertaken in order to address perceived flaws in appearance or enhance psychosexual well-being; however, our results do not suggest that these procedures would alleviate this distress. Genital surgery risks disruption of nerves, which may impair sensation to the genital area and affect future capacity for sexual pleasure.

**P2-d3-640** Gonads and Gynaecology 2  
**Diminished ovarian reserve in young survivors of childhood cancer after treatment with alkylating agents**  
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**Background:** A few studies have demonstrated partial loss of the ovarian reserve in survivors with various combination therapy. The aim of this study was to evaluate ovarian reserve in survivors of childhood cancer who received...
alkylating agents without pelvic radiation therapy in order to assess the proper role of these agents on ovarian damage.

Methods: Ovarian function was evaluated in 115 survivors aged 18 to 40 years old (median: 25 yrs). 57 patients were investigated on days 2-5 of a menstrual cycle and 58 on day 7 of the combined oral contraceptive (OC) pill-free interval. Ovarian volume and total number of antral follicles (AFC) were evaluated with transvaginal ultrasonography. Serum levels of FSH, LH, Oestradiol, inhibin B and AMH were measured.

Results: Young survivors had a reduced ovarian reserve compared to normal values, even if only 12 of them (10%) had FSH levels higher than 15 UI/L. Survivors of Hodgkin disease had the smallest mean ovarian volume (2.1 ml, median age 24.3 yrs), median total AFC (9) and median AMH level (3.6 pmol/l). Ovarian reserve was better in survivors who received only alkylating agents than in those who received alkylating agents and subdiaphramatic radiation therapy or high-dose chemotherapy before bone marrow transplantation (Table 1). A multiple linear regression analysis adjusted on age at evaluation and OC taking showed a reduced ovarian reserve with exposure to higher Procarbazine doses, high-dose chemotherapy before bone marrow transplantation, chemotherapy received after onset of puberty and subdiaphramatic radiation therapy.

Conclusions: Young women, who have been treated with alkylating agents during childhood, have evidence of diminished ovarian reserve, especially after treatment for Hodgkin’s disease or high-dose chemotherapy before bone marrow transplantation and should be advised not to postpone childbearing after the age of 30-35 years.

### P2-d3-641 Gonads and Gynaecology 2

**Genetic analysis of atypical cases of polycystic ovary syndrome**

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Background: Although polycystic ovary syndrome (PCOS) is a very common endocrinopathy the pathogenesis is not yet entirely understood. In most cases women with high testosterone levels show a high grade of virilization. We report two groups of patients in which testosterone levels are either unexpectedly high despite low grade of virilization or low despite a high grade of virilization.

**Objectives and hypotheses:** Several mutations have been described that lead to more severe PCOS, e.g. changes in the poly-(CAG)-region in the androgen receptor coding sequence. In this study, the androgen receptor of six patients with untypical PCOS was examined for alterations that could potentially explain unexpected androgen action. When possible we also included in our analyses the parents of the affected patients.

**Methods:** In a first step, GTG banding of the metaphase chromosomes were analyzed for aberrations, in a second step we screened for altered length of the poly-(CAG)-region of the androgen receptor gene and in a third step, the entire androgen receptor gene of the patients was sequenced.

**Results:** No changes of the androgen receptor gene sequence were detected. To our knowledge this is the first report of combining the chromosomal analysis of PCOS patients with full sequencing of the entire human androgen receptor gene.

**Conclusions:** We postulate that other causes for untypical PCOS exist beyond mutation of the androgen receptor gene. Further examinations including e.g. expression analysis and epigenetic changes are required to reveal the mechanism of altered androgen receptor activity.

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### P2-d3-642 Gonads and Gynaecology 2

**Bilateral macroorchidism with extremely high AMH and inhibin B secretion: which underlying defect?**

*Patricia Bretonnet*; *Michel David*; *Daniela Gorduza*; *Sndrine Glisard d’Estaing*; *Ingrid Pirotton*; *Juan-Pablo Llano*; *Delphine Mallet*; *Jean-Pierre Pracros*; *Marie-Pierre Courdi*; *Vincent Jacard*; *Claire-Lise Gay*; *Bénédicte Laurent-Attalain*; *Pierre Chatelain*; *Pierre Mouriquand*; *Yves Moret*; *Marc Nicolino*

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Background: Bilateral macroorchidism is a rare condition described in fragile X syndrome, hypothryoidism, amyloidosis, adrenal rest tumors, McCune-Albright syndrome (MAS), activating mutation of FSH-receptor and FSH-secreting pituitary adenomas. We report a puzzling case in whom both Sertoli cell secretion and FSH are increased.

**Case report:** A healthy boy referred for bilateral embarrassing macroorchidism at the age of 12. There is no gonad pathology in the family. He is the only male from non-consanguineous Algerian parents. Macroorchidism was noticed at the age of 6 and increased dramatically with puberty. The clinical exam confirmed bilateral enlarged 9x5 cm smooth testis and puberty A2P3G3. No organomegaly, dimorphic features or mental retardation were retained. Growth is normal. Testicular ultrasonography (US) confirmed high volume (Table) and revealed homogeneous tissue and few microlithiasis. Hormone assays showed high FSH, AMH and inhibine B but normal LH and testosterone for the pubertal stage (Table). Thyroid hormones, prolactin and tumoral markers are normal. Karyotype is 46, XY. DNA-analysis for Fragile X syndrome and MAS R201H mutation are negative. No adenoa was seen in consecutive pituitary MRI (interval of 2 years).

**Methods:** 1) GnRH-agonist treatment was initiated: triptorelin 3 mg intramuscular every 4 weeks. 2) Surgical testicular biopsies were realized 2 months after Rx break.

**Results:** 1) GnRH-agonist Rx leads to: a) testicular volume reduction, b) LH, FSH and testosterone suppression, c) but no modification in Sertoli cell secretion.

**Conclusions:** In our patient, the initial hormonal data would suggest a FSH-secreting adenoma. The response to triptorelin evidences Sertoli-cell autonomy, as macroorchidism without sexual precocity described in McCune-Albright syndrome.
The spectrum of molecular defects in the CYP21A2 gene in heterogeneous girls with premature adrenarche

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Background: Female carriers of CYP21A2 mutations are at increased risk of developing premature adrenarche (PA) during childhood which might evolve into polycystic ovary syndrome (PCOS) in adolescence.

Objective and hypotheses: The present study was designed to seek evidence on the prevalence and consequences of heterozygous CYP21A2 mutations in girls with PA.

Methods: The hormonal response to ACTH was evaluated in 81 girls with clinical signs of PA along with direct DNA sequencing and MLPA analysis for mutations in the CYP21A2 gene.

Results: Twelve girls were diagnosed with NC-CAH based on 17-OHP response and confirmed with genetic studies. Thirty five patients out of the 81 with PA were identified as carriers of CYP21A2 mutations. The most frequent mutations among the carriers were the mild p.V281L (54.3%), followed by p.Q318stop (20%), p.P482S (2.8%) and the large deletion/insertion exons 1-4 (2.8%). Higher values of stimulated 17-OHP levels were observed in the carriers of the p.V281L mutation compared with carriers of other mutations (Avg = 23.6 nmol/l ± 16.1 nmol/l; P = 0.02). Additionally, high allelic frequency of 61.8% of the p.N493S variant was observed in the group of 34 girls with PA and no mutation and which was significantly different when compared to the group of 35 heterozygous girls with PA (61.8% vs 22.8%).

Conclusions: Girls with PA are likely to bear heterozygous CYP21A2 mutations, therefore systematic evaluation of 17-OHP values in combination with the molecular testing of CYP21A2 gene is beneficial. Ii. Carriers of the mild p.V281L are at higher risk of androgen excess compared to carriers of other types of mutations and iii. Hyperandrogenic signs in the group of girls with no mutation in CYP21A2 could implicate p.N493S variant as a plausible disease causing factor.

Social abilities and gender identity recognition in adolescent girls with polycystic ovary syndrome

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Background: Polycystic ovary syndrome (PCOS) is the endocrine disorder characterized by hirsutism, acne, menstrual disturbances and hyperandrogenemia. It was postulated that these clinical aspects of PCOS can be associated with psychological distress and influence the feminine identity.

Objective and hypotheses: The aim of the study was to determine the social competence and psychological gender profile in adolescent girls with PCOS and compare it to regularly menstruating, non-hirsute peers.

Method: In 28 adolescent girls with PCOS (mean age 16.8±0.9 yrs; mean glycosylated age 51.0±18.7 mo) and in 12 healthy, regularly menstruating girls without hirsutism (mean age 16.7±1.2 yrs; mean glycosylated age 53.4±15.6 mo) androgens and gonadotropins levels were measured, social competence questionnaire (SCQ) and psychological gender test (PGT) were performed.

Results: There were no significant differences in all parts of SCQ (competence in the intimate situation (IS), competence in the social situation (SS), assertiveness (A)) between the study and control group. Also in PGT, in both feminine (FS) and masculine scales (MS), the differences between the groups were statistically insignificant. In the study group concentration of DHEAS correlated positively with SS score (r=0.49, p=0.01) as well as A score (r=0.46, p=0.02). FS score correlated positively with androstenedione concentration (r=0.4, p=0.04).

There was no significant correlation between SCQ or PGT and BMI z-score as well as degree of hirsutism.

Conclusions: It is concluded that despite the existence of biochemical features that can influence sociopsychological condition, the social abilities and gender identification seem to not be disturbed in adolescents with PCOS.
Persistant gynecomastia: hidden genetic defects

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Background: Gynecomastia is a frequent reason for consultation in pediatric endocrinology in both prepubertal and pubertal boys. It is usually idiopathic and generally regresses at the end of puberty when the testosterone (T) level increases. However, hypogonadism, hyperprolactinemia, hyperthyroidism and rare testicular or adrenal tumors must be considered, especially at prepubertal age.

Conclusions: This study underlines that persistent gynecomastia may be due to a rare genetic defect and points out the usefulness of investigating affected children to identify a specific cause and thus propose adequate management.

P2-d3-649 Gonads and Gynaecology 2
Final adult height and its impact in 102 girls with central precocious or early and fast puberty treated with gonadotropin releasing hormone analogues
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Objective: We assessed in a retrospective uncenter study the efficacy and its impact factors of treatment with Gonadotropin-releasing hormone analog (GnRHa) in central precocious puberty (CPP) or early and fast puberty (EFP) girls.

Methods: One hundred and two girls, seventy-five CPP and 27 EFP, were treated with GnRHα alone and were followed up to their final adult height (FAH). Predicted adult height (PAH) at beginning and discontinuation of treatment and FAH were compared to estimate the efficacy of GnRHα to improve FAH. The factors affecting the efficacy were analyzed.

Results: FAH was 158.0±4.8cm, significantly higher than pretreatment PAH (151.1±5.1cm) (P<0.01), and similarly with posttreatment PAH (157.3±5.2cm) (P<0.078). Compare to pretreatment PAH, FAH was increased 6.8±4.5cm, and average 2.9±2.2cm per year, by GnRHα treatment for 2.3±0.7yr. There was no significant difference between CPP (7.2±4.5cm) and EFP (5.5±4.5cm) in net height gain. Hight standard deviation score for bone age (HSDSBA) increased 0.9±0.7. Pretreatment bone age (BA)/chronological age (CA), age at start, treatment time, hight gain during treatment, pretreatment PAH SDS for target hight (TH) and hight gain after treatment were 6 independent factors influence net height gain, which stands for efficacy of GnRHα treatment. There was no significant improvement between FAH and pretreatment PAH for the patients who had menarche before treatment or growth velocity less than 4cm during the first year.

Conclusions: GnRHα treatment can improve FAH efficiently for both CPP and EFP girls. There are many factors affecting treatment effect. Those with more difference between BA and CA, more difference between pretreatment PAH and TH, younger CA to start treatment, longer treatment time, more hight gain during and after treatment, will have better treatment effect. While those who had menarche before treatment or growth velocity less than 4cm during the first year can hardly improve FAH by GnRHα treatment alone.
High diagnostic accuracy of central precocious puberty in girls using aqueous triptorelin compared with GnRH test

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Hospital de Niños Ricardo Gutiérrez, Endocrinology Division, Buenos Aires, Argentina

Background: The GnRH test is the gold standard to confirm the diagnosis of Central Precocious Puberty (CPP), however, this compound is not always readily available. Diagnostic accuracy of aqueous GnRH analogs tests compared to GnRH test has not been reported using gonadotropin ultrasensitive immunoassays.

Objective and hypotheses: To evaluate the diagnostic accuracy of Triptorelin test compared to the GnRH test in girls with suspicion of CPP.

Methods: A prospective, case-control, randomized clinical trial was performed. CPP or idiopathic precocious thelarche (IPT) was diagnosed according to maximal LH response to GnRH test and clinical characteristics during follow-up. Girls with premature breast development randomly underwent two tests: a) intravenous GnRH 100 μg blood sampling 0-30-60 min for LH, FSH and b) subcutaneous Triptorelin acetate 0.1 mg/m² with blood sampling at 0, 3 and 24 hours for LH, FSH and estradiol ascertainement. Gonadotropin levels under Triptorelin test in all patients (n=46) were measured by two assays (IFMA and ECLIA). In addition, in 31 cases, gonadotropins were measured by ICMA-IMMULITE. Estradiol was measured by ECLIA.

Results: Clinical features in CPP girls (n=33) and IPT girls (n=13) were similar. Using ROC curves, maximal LH response (LH-3h) under Triptorelin test >7 IU/L by IFMA or >8 IU/L by ECLIA confirmed the diagnosis of CPP with 100% specificity and 76% sensitivity. Considering either LH-3h or maximal estradiol response at 24h (cutoff ≥ 80 pg/mL), the test sensitivity increased to 94% and the diagnostic efficiency to 93%. In the subgroup evaluated by ICMA (21 CPP and 10 IPT) a cutoff of LH-3h was 6.7 IU/L and with a diagnostic efficacy of 90%.

Conclusions: The Triptorelin test had high accuracy for the differential diagnosis of CPP vs IPT in girls compared to GnRH test, providing a valid alternative for testing when GnRH formulation is not available. To this end, we presented the most appropriate LH cutoff values employing 3 ultrasensitive assays used worldwide for gonadotropin measurement.

A case of severe maternal virilisation in pregnancy

Claire Hughes; Girish Rayanagoudar; Les Perry; Rakesh Amin; Scott Akker;
1Barts and the London School of Medicine, Paediatric Endocrinology, London, United Kingdom; 2Barts and the London School of Medicine, Endocrinology, London, United Kingdom; 3Barts and the London School of Medicine, Clinical Biochemistry, London, United Kingdom

Background: A primigravid Nigerian lady aged 29 years presented at 35 weeks gestation following a planned, unassisted pregnancy. She reported a deepening voice, temporal hair loss and hirsuitism from 25 weeks. She had significant cliteromegaly and increased upper body musculature.

Objective and hypotheses: To ascertain the cause of maternal virilisation.

Methods: Appropriate biochemical and radiological investigations were performed.

Results: Serum testosterone was 255nmol/l (confirmed by x10 dilution and mass spectrometry) and Androstenedione (A4) 168nmol/l. DHEAS 2.6umol/l, 17-hydroxyprogesterone 26nmol/l, hCG (51318 IU/l) and oestradiol (139450pg/ml) were appropriate for gestation. MRI revealed grossly enlarged and multicystic ovaries but no mass suggestive of an ovarian tumour. Both adrenal glands were normal. A female baby born by spontaneous labour at 39 weeks had normal female internal and external genitilia with no evidence of excess androgen exposure. Cord blood analysis revealed a normal foetal androgen profile including testosterone (0.9nmol/l) and A4 (3.2nmol/l). Mother’s androgen profile normalized rapidly following delivery, at postnatal week 2 testosterone had fallen to 1.2nmol/l and A4 to 1.3nmol/l. MRI 6 weeks postnatally showed normal sized but polycystic ovaries.

Conclusions: We report a lady presenting with severe virilisation during pregnancy with extremely elevated testosterone levels. This case dramatically illustrates the efficacy of placental aromatase as the female foetus demonstrated no evidence of excess androgen exposure including normal cord blood testosterone levels. It is likely she demonstrated a severe case of hyperreactio luteinalis with hypersensitivity of ovarian tissue to hCG. This may recur in future pregnancies.
These data support T-gel use for inducing puberty in pts with KS or AN.

Conclusions: A baseline value of LH below 0.8 IU/L or a peak LH stimulated-GnRH below 3 IU/L were associated with clinically optimal control.

Background: Growth hormone has proven its efficacy in children born SGA, but with a highly variable response. It is therefore crucial to better understand the clinical and biological parameters underlying this variability.

Objectives: The main objective of data analysis was to assess the key parameters influencing growth response during the first two years of GH in children born SGA using the French cohort of the NordiNet® IOS.

Population and methods: 110 children born SGA (65/45 F/M) treated with Norditropin® entered into the French IOS database and with complete 2 year data available were included in the analysis. The effect on height gain (SDS) of gender, height SDS, age, average GH dose and IGF-1 SDS change from treatment start to 2 years follow-up were analysed using an ANCOVA model.

Results: Treatment start age was 6.9±3.3 years, height SDS was -3.10±0.74 and IGF-1 SDS was -0.6±1.5. The average GH dose during treatment was 51.14 µg/kg/d. After two years the mean height gain was 1.26±0.66 SDS and the change in IGF-1 SDS was 2.4±1.6. Among the included parameters in the model, age at treatment start (p <0.001), gender (p=0.0238), average GH dose (p=0.0038), and change in IGF-1 SDS from 0 to 2 years (p=0.0085) displayed a significant effect on height gain (SDS).

Conclusions: Based on the French IOS cohort we have shown that, an earlier treatment start and the degree of the IGF-1 response under GH might be critical in growth response optimization. Moreover, the effect of both GH dose and IGF-1 change emphasizes the added value of GH dose individualization in the growth management of children born SGA.

Table:

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<td>Mean (SD)</td>
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TT change from baseline at 6 months (ng/mL)

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<tr>
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E2 change from baseline at 6 months (pg/mL)

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SHBG change from baseline at 6 months (ng/dL)

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<tr>
<td>5</td>
<td>-0.3 (11.3)</td>
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Posters
P2-d1-656 Growth 2
Correlation of single nucleotide polymorphisms of NPR3 gene and COL11A2 gene with idiopathic short stature
Linqi Chen1, Zheng Lan Li1; Ying Wang2; Yue Chun Teng3; Wei Wang4; Sijin Li5
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Background: Idiopathic short stature (ISS) is a multi-genie disease. Its etiological pathogenesis is not yet clear, and it is a heterogeneous disease, in which genetic factors play a major role.

Objective and hypotheses: Its main clinical manifestation is pituitary growth hormone insulin-like growth factor 1 axis and bone growth plate dysfunctions. Based on the important role of the growth plate in the pathogenesis of ISS, we study single nucleotide polymorphisms of NPR3 gene and COL11A2 gene which in the growth plate to identify the correlation with the ISS.

Methods: We selected twenty sSNP of NPR3 gene and COL11A2 gene and genotyped allele frequencies of the 185 ISS cases’ DNA and 474 control cases’ DNA in Illumina GoldenGate genetic analysis platform. The results of the genotyping were checked with Hardy-Weinberg genetic equilibrium tests to determine whether the genotype frequencies have genetic equilibrium, and represented general population. It was compared that frequency distribution of the allele, genotype and the dominant or recessive model’s genotype with 2 test between the case group and control group, and the analytical results of genotype and allele were showed with the relative risk ratio (Odds ratio, OR) and 95% confidence interval (CI).

Results: SNPs of COL11A2 gene loci rs9368758, rs970901, rs277934, rs2855440, rs2855437, rs179998, rs1256336 and of NPR3 gene locus rs973079 are related to the morbidity of ISS. SNPs of COL11A2 gene loci rs2257126, rs986522, rs2855430, rs2071025 and of NPR3 gene loci rs6886068, rs696831, rs16890208, rs1177374 are uncorrelated with the morbility of ISS. 

Conclusions: ISS is a multi-genie and heterogeneous disease. As the third generation of genetic markers, SNP became one of the most powerful tools for ISS and other polygenic disease research.

P2-d1-657 Growth 2
 Noonan syndrome and related disorders: experience of a single centre
Chong Kun Cheon1; Sue Yong Kim1
Pusan National University Children’s Hospital, Pediatrics, Yangsan, Republic of Korea

Background: The RAS-MAPK (Ras/Mitogen-activated Protein Kinase) pathway is known as a key pathway in embryonic development and it is involved in the development of many congenital disorders. The RAS-MAPK pathway is activated by a variety of stimuli such as growth factors, cytokines, and hormones. This pathway regulates a wide range of cellular responses, including proliferation, differentiation, survival, and migration. In cases of Noonan syndrome and related disorders, the RAS-MAPK pathway is activated, leading to developmental anomalies. The RAS-MAPK pathway is also involved in the regulation of immune responses and the development of cancer.

Objective and hypotheses: Noonan syndrome is a genetic disorder associated with developmental anomalies, such as cardiac malformations,学习障碍, and learning disabilities. It is caused by mutations in various genes, including PTPN11, SHOC2, SOS1, and RASGRF1. The purpose of this study is to identify the frequency of mutations in these genes in a group of patients with Noonan syndrome and related disorders.

Methods: We retrospectively evaluated 12 individuals: 9 with NS, 2 with CFC syndrome, Costello syndrome, and Lepor syndrome. Learnd are heterogeneous conditions with phenotypic overlap. The aim of the study was to evaluate the diversity of clinical manifestation in patients with NS and clinically related disorders.

Methods: Twelve Korean patients were diagnosed with NS and related disorders between March 2009 and Oct 2011. All matched the diagnostic criteria for NS, as defined by van der Burgt et al. [1994]. Six genes in the RAS-MAPK pathway associated with NS and related disorders were analyzed for mutations.

Results: We retrospectively evaluated 12 individuals: 9 with NS, 2 with CFC syndrome, and 1 with LEOPARD syndrome. We found disease-causing mutations in 7 (58.3%) patients, which were located in the PTPN11 (33.3%), RAF1 (14.3%), BRAF (14.3%), and SMAD5 (4.3%) genes. In 9 patients with NS, 8 cases (88.9%) were sporadic and one case had an affected father and we identified mutations in 4 (44.4%); three (33.3%) in PTPN11 and one (11.1%) in RAF1. Mutation analysis of PTPN11 showed a total of 2 different heterozygous missense variations. One novel heterozygous mutation (F498Y in BRAF) and previously described mutation (Y130C in MEK1) in patients with CFC syndrome were identified. One known mutation (Y279C in PTPN11) in patients with LEOPARD were identified. Two patients (22.2%) with NS showed lymphatic vessel dysplasia. Short stature, webbed neck, and lymphatic vessel dysplasia are most common among the PTPN11-mutation-positive patients. Four patients (44.4%) with NS were treated with growth hormone. Treatment with GH resulted in short-term increases in growth velocity. 

Conclusions: Increased awareness by paediatricians will lead to earlier diagnosis, and provide patients and their families with accurate genetic counselling.
We report a 4 ½ year-old German girl who presented with growth retardation, short stature, dark pigmented skin and loose, easy break anagen hair. The typical mutation c.4A>G showed syndromic features that could not be attributed to a special syndrome, Noonan-like syndrome is a possible explanation. We suggest molecular analysis of SHOC2 in these patients. Extended sequence analysis should be performed in the absence of the common c.4A>G mutation in patients with typical SHOC2 phenotype. As in Noonan syndrome, patients can develop heart problems. Therefore echocardiography is recommended every two years after diagnosis.

Background: Mild prenatal growth retardation is commonly reported in patients with Prader-Willi syndrome (PWS). In this context, it has been reported that average birth weight seems to be lower in subjects with a deletion of the paternal-derived chromosome 15 (DEL15), in comparison to individuals with uniparental maternal disomy for chromosome 15 (UPD). These data, however, were not confirmed by other Authors.

Objective and hypotheses: To describe the early development of infants with PWS, and to investigate whether there are differences according to the genetic subtype.

Methods: Data from family health records concerning birth weight and gestational age were collected from 85 subjects with DEL15 (44 females) and 34 individuals with UPD (22 females), and compared against national norms and between groups. Student t-test for unpaired data and analysis of variance for parametric and nonparametric data have been employed, where appropriate.

Results: Significant findings include: an increased frequency of premature term (<37 weeks of gestation) in UPD (5/34 UPD = 14.7% vs. 8/85 DEL15 = 9.4%, p<0.04); a similar birth weight for the whole cohort of newborns with DEL15 (girls 2.71±0.06 kg, boys 2.62±0.08 kg) and UPD (girls 2.66±0.11 kg, boys 2.61±0.09 kg) (mean±SE); a similar birth weight for babies born at term (>2 weeks with DEL15 (girls 2.76±0.06 kg, boys 2.76±0.07 kg) and UPD (girls 2.75±0.1 kg, boys 2.62±0.09 kg); a high rate of small-for-gestational-age (SGA) birth weight in both subgroups (23/85 DEL15 = 27%, 9/34 UPD = 26.5%).

Conclusions: Our study did not detect any significant difference in birth weight among DEL15 and UPD, but it demonstrated an increased risk of premature term in UPD and the presence of SGA in about one fourth of patients, regardless of genetic subtype.

**P2-d1-661 Growth 2**

**Effects of biologic treatment with tocilizumab on longitudinal growth in children with juvenile idiopathic arthritis**

A. Rossetti1; Ekaterina Alekseeva2; Rina Denisova3; Tatiana Steptsovskaya2
1Scientific research center of children’s health RAMS, Endocrinology and Metabolism, Moscow, Russian Federation; 2Scientific research center of children’s health RAMS, Rheumatology, Moscow, Russian Federation

Background: Inflammation and glucocorticoid therapy are major factors in the growth retardation seen in children with severe systemic juvenile idiopathic arthritis (JIA).

Objective and hypotheses: The objective of this study was to evaluate effects of biologic treatment with recombinant humanised monoclonal antibody that acts as IL-6R antagonist (tocilizumab) on longitudinal growth.

Methods: Nineteen patients with severe systemic JIA were included into the study (8 boys and 11 girls). The mean age at first visit was 6.8 ± 2.4 years, and disease duration 4 (2.2-9) years. All patients had stage 1 of sexual development, Tanner scale and before therapy with tocilizumab had standard antirheumatic therapy. Anthropometric parameters were estimated one year before tocilizumab treatment, at the day of first infusion and in one year after tocilizumab treatment was started. Tocilizumab was administered intravenously once every 2 or 4 weeks at a dose of 8-10 mg/kg of body weight. In all patients who received corticosteroids before tocilizumab treatment dose of these drugs was reduced, but in one case it was completely abolished. Treatment efficacy was assessed according to criteria ACR pedi scale.

Results: The mean height SDS one year before treatment was -2.38 ±1.43 and height velocity SDS was -4.24 ±1.18. On the standard antirheumatic therapy during the first year of monitoring in all patients was noted deterioration in growth, and by the day of 1st tocilizumab infusion height SDS was -2.64 ±1.34 and height velocity SDS -4.55 ±0.99 (p < 0.001). After one year of treatment clinical response ACR 50 to the treatment was obtained in all patients included in this study. The mean height SDS was -2.27 ±1.85 and height velocity SDS -2.51 ±1.98 (p < 0.001).

Conclusions: An intensified biologic treatment with tocilizumab has a beneficial effect on growth in children with JIA. This effect might be related to the inhibitory effect of proinflammatory cytokines, especially II-6, on the synthesis of IGF-1 and IGF-BP-3.

**P2-d1-662 Growth 2**

**Evaluation of bone mineral density and markers of bone turnover in normal short children**

Zeynep Gokce Gayretli1; Ayşen Bideci2; Nurullah Celik1; Neslihan Bukar1; Eser Doger2; Ummügülsüm Yıldız2; Hamdi Cihan Emeksiz1; Mehmut Orhan Camurduan1; Peyami Cinaz1; Gazi University, Pediatric Endocrinology, Ankara, Turkey; 2Gazi University, Biochemistry, Ankara, Turkey

Background: A common valid consideration about bone metabolism for cases with constitutional delay of growth and puberty (CDGP) does not exist. Some authors declare increased osteoporotic risk in CDGP cases but some reports in literature did not note such a difference when CDGP cases were compared for bone metabolism and bone mineral density.

Objective and hypotheses: In this study, we aimed to investigate whether children with CDGP differs from normal prepubertal boys for biochemical parameters of bone metabolism and bone mineral density (BMD).

Population and methods: This study included 31 boys with CDGP, 30 boys with familial short stature (FSS) and 30 normal boys. All the cases participating in this study were prepubertal boys and their ages ranged between 6-11
Completing pubertal growth is complex, due to the significant delay and short duration of puberty. Significantly higher urinary pyd level in CDGP group when compared to control group suggests that bone resorption in CDGP group starts in prepubertal period which is a risk factor for osteoporosis and and bone fractures.

**P2-d1-663 Growth 2**

“Grow-up Gothenburg”: a population based survey of self-evaluated body image related to weight, height and personal characteristics in final year high school students

**Background:** Population-based studies of unbiased estimates of obesity prevalence, weight and height values are lacking in youth populations. Attitudes to body image and the personal characteristic of resilience are factors associated with obesity and psychological problems related to body size but associations between these factors have not been fully examined in a general adolescent population.

**Objective and hypotheses:** The study aim was to describe a population based sample of adolescents and test the effect of gender, height, BMI, and resilience on self-reported body image.

**Methods:** Weights and heights of students from 40 high schools in their final year (yr.12) in Gothenburg, Sweden and suburbs were measured using standard procedures (2008/9). Data were collected from school health records and a self-completion socio-demographic questionnaire which included the 8 item body image scale (BI8) and the short resilience scale (RS11).

**Results:** A representative sample was collected (n=5066, male 50%). Participation rates were for measurements 59%; questionnaire completion 63%; average age 18.5 years (SD=0.47); height of males 180cm (SD=8.3cm) and females 176cm (SD=6.4cm). The prevalence of overweight and obesity was respectively 15.3% and 3.6% in males and 11.1% and 2.3% in females. Aver.

**Correlations with age Phase of puberty**

<table>
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<tr>
<td>PPIS WeightSDS</td>
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$p<0.1$ **$p<0.01$ ***p<0.001

For 72 children with measurements in both the Pre and Completing phases, a change of more than one centile space (0.67 SDS) over time was seen in only 15% (11) for PPIS heightSDS and only 26% (17) for PPIS weightSDS.

**Conclusions:** Children entering puberty relatively late appear shorter and lighter based on the conventional UK90 chart, but not when compared to a reference that adjusts for phase of puberty. The PPIS reference shows a good fit to UK children and should allow growth though puberty to be tracked more accurately.

**P2-d1-664 Growth 2**

Can we characterize growth in puberty more accurately? validation of a new puberty phase specific (PPS) growth chart

**Introduction and aims:** Assessing pubertal growth is complex, due to the variation in age when puberty begins. We have developed a new puberty phase specific (PPS) growth reference, constructed using Dutch national cross-sectional data, recalibrated to match the UK 1990 reference. It uses Tanner staging simplified into three phases: Pre-puberty (Tanner stage 1), In-puberty (2/3) and Completing-puberty (4/5). The aim of this analysis was to validate the accuracy of the PPS reference in UK children, and the impact on the assessment of pubertal growth.

**Methods:** We used the Chard data set: longitudinal height and weight data collected on 124 healthy UK children from 1981 to 1988 for ages 8.3-16.6 years. There were 1-14 measurement occasions per child, 1,252 in total, with exact age and Tanner pubertal staging. Measures were converted into SD scores (SDS) based on the UK90 reference and the new PPS reference.

**Results:** Within each phase, the measurements fitted closely to the PPS reference (mean heightSDS by phase: Pre 0.1, In 0.1, Completing 0.3; mean weightSDS: Pre -0.1, In 0.1, Completing 0.1). PPS SDS showed little trend with age in each phase, in contrast to UK90 where the SDS fell significantly (see table).

For 72 children with measurements in both the Pre and Completing phases, a change of more than one centile space (0.67 SDS) over time was seen in only 15% (11) for PPS heightSDS and only 26% (17) for PPS weightSDS.

**Conclusions:** Children entering puberty relatively late appear shorter and lighter based on the conventional UK90 chart, but not when compared to a reference that adjusts for phase of puberty. The PPIS reference shows a good fit to UK children and should allow growth though puberty to be tracked more accurately.

**Background and aims:** Assessing growth at puberty is difficult and children with late puberty may be called abnormal. We added a lower pubertally adjusted (PA) 0.4th centile to the prototype chart for children aged 8-13 still in Pre-puberty, with shading between this and the standard 0.4th centile. We aimed to evaluate users’ understanding of this feature and its impact on clinical judgement.

**Methods:** Three evaluation workshops were performed with GP trainees (N=26) and paediatricians (N=48). In each session, explanations were given. All completed workbooks testing aspects of the new charts using plotting and
interpretation with two standardised scenarios where a height at 11 years was in the shaded area between the conventional and the PA 0.4th centile. One was a pre-pubertal girl growing steadily within the PA normal range and the other a girl in puberty with declining growth, dropping below the PA 0.4th centile. Results: The pubertal phase was reported correctly by 93% (74). Only 61% (23) viewing the pre-pubertal child recognized that she was above the PA 0.4th centile, though 79% (30) recognised she required no further investigation. Of those viewing the pubertal child 31% (11) incorrectly stated that she was above the PA 0.4th centile and only 47% (17) recognised she required further investigation. In 2/3 sessions more specific questions were asked about centile position and 88% (42/48) correctly reported the unadjusted centile position (±0.4th). Of these, only 10/18 then recognized that the pre-pubertal child was above PA 0.4th centile while 5/20 incorrectly stated that the in-puberty child was on or above the PA 0.4th centile. Unfavourable comments, describing the pubertal element as complex and confusing were made by 49% respondents.

Conclusions: The proposed shaded area was ineffective at identifying lower risk children and seemed to create false reassurance concerning children with disordered growth in puberty, so the design has now been radically modified. This study shows that formal evaluation of ‘improvements’ to growth charts is essential.

P2-d1-667 Growth 2
Assessing the quality of life of children and adolescents with short stature: development and psychometric testing of the QOLISSY instrument
Julia Quitmann1; Monika Bullinger1; Hartmut Wollmann2; Andreas Pfeil3; Anja Rohenkohl4; Mick Power5; Kendra DeBusk6; Michael Herdman7; Dolores Sanz8; Emmanuelle Mignon9; Eva Feigerlová10; John Eric Chaplin11
1University Medical Center Hamburg-Eppendorf (UKE), Department of Medical Psychology, Hamburg, Germany; 2Pfizer, Ltd, Pfizer, Walton Oaks, United Kingdom; 3Pfizer Incorporated, Pfizer, San Diego, CA, United States; 4University of Edinburgh, Clinical and Health Psychology, Edinburgh, United Kingdom; 5Insight Consulting & Research S.L., Insight Consulting & Research S.L., Barcelona, Spain; 6Hôpital des enfants, Hôpital des enfants, Toulouse, France; 7The Queen Silvia Children’s Hospital, Paediatric Growth Research Centre, Göteborg, Sweden

Background: In families with short stunted children and adolescents, behavioural & emotional problems can be experienced. When evaluating the outcomes of treatments or making treatment decisions, health related quality of life (HRoQL) should be taken into consideration.

Objectives and hypotheses: So far, no standardised HRoQL instrument for this population exists. Through consensus building in 5 countries, the objective of this study was to develop & psychometrically test a growth-related HRoQL instrument for use in clinical & epidemiologic research.

Methods: The target population consists of short stature children (height < -2 SDS) with a diagnosis of GHD / ISS, treated / untreated with GH. Children & adolescents (8-18) were included as well as their parents and parents of children between 4 -7yrs. The project followed international instrument development guidelines and a patient-centred methodology. Both qualitative & quantitative analyses were carried out.

Results: Following item generation through focus groups with a total of 196 participants, 124 items for children & 156 for parents were included in a pilot test with cognitive debriefing. Statistical analysis of the pilot test results identified the psychometric properties of the instrument. A total of 336 families participated in the field test. Of these, 162 completed the full questionnaire. Further item reduction was performed using differential item functioning & structural equation modelling.

Conclusions: The final questionnaire consists of a 3-domain core structure with 21 items, the full questionnaire being 49 items for children in 6 domains & 65 items for parents across 8 domains. The questionnaire demonstrated good criterion and construct validity. In addition the questionnaire has good face validity and has been shown to provide reliable results over time.

P2-d1-668 Growth 2
Do children with CHARGE syndrome benefit from growth hormone (GH) therapy?
Helmut G. Döer1; Margaret Boguszewski2; Jovanna Dahlgren3; David Durger4; Mitchell Geffner4; Anita Hakken-Koelega5; Anders Lindberg6; Michel Polak7; Raoul Roomans3; Hartmut Wollmann8
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Background: CHARGE is a rare genetic condition associated with coloboma, heart defects, atresia of the choanae, retardation of growth, and genital and ear abnormalities. Despite normal birth size, growth is retarded after early infancy, and ~70% of affected adolescents are short. Although GH deficiency is reported with a frequency of 15% in CHARGE syndrome, data on the effects of GH treatment are sparse.

Patients: Data from 37 children (21 M) with CHARGE and treated with Genetic testing were identified in the KIGS database. Median chronological age 206 Horm Res 2012;78(suppl 1)
To investigate the effect of prednisone use and RA disease activity during pregnancy and their effects on growth of children born from mothers with rheumatoid arthritis (RA) has been insufficiently explored. Active RA during pregnancy is associated with lower birth weight, whereas studies have shown that prednisone use during pregnancy in patients with RA reduces the gestational age. Too little is known about the longer effects of prednisone use and active RA disease activity on the growth of the child. The birth data of 6600 children were evaluated, with 122 (77 m and 45 f; 1.8%) being SGA. The mean height and weight SDS were -1.8 and -2.3 at birth and -0.6 and -0.7 at the actual evaluation; the prevalence of subjects with height SDS ≤-2, according to Italian growth charts, were referred to our Pediatric Endocrinology Clinic.

**Method**: Our data suggest that using appropriate reference and the cut-off of -2 SD, the prevalence of born SGA is around 3-5 fold lower than usually reported. The prevalence of born SGA who do not completely catch-up is around 10% as expected and mean height of this population remain < the 50th %ile. GH and/or other interventions to improve catch-up growth, especially in the first years of life, should be considered.

**Results**: Prednisone use and RA disease activity during pregnancy is associated with lower birth weight, whereas studies have shown that prednisone use during pregnancy in patients with RA reduces the gestational age. Too little is known about the longer effects of prednisone use and active RA disease activity on the growth of the child.

**Objectives and hypotheses**: To investigate the effect of prednisone use and RA disease activity during pregnancy on 2 year postnatal growth (length and weight) in children of mothers suffering from RA.

**Methods**: Growth charts were collected from children born from a prospective nationwide study on RA during pregnancy. Dependent variable: height SDS and weight SDS. Independent variable: prednisone use and RA disease activity (DAS2k; range 0-10) during pregnancy.

**Results**: 167 growth charts were collected and 161 were analyzed after excluding 3 twin pregnancies. 67 women used prednisone at some point during their pregnancy. The mean disease activity during pregnancy was significant correlated to lower birth weight. The mean disease activity during pregnancy was still a point of discussion. Active RA during pregnancy is associated with lower birth weight, whereas studies have shown that prednisone use during pregnancy in patients with RA reduces the gestational age. Too little is known about the longer effects of prednisone use and active RA disease activity on the growth of the child.

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**Conclusion**: Our data suggest that using appropriate reference and the cut-off of -2 SD, the prevalence of born SGA is around 3-5 fold lower than usually reported. The prevalence of born SGA who do not completely catch-up is around 10% as expected and mean height of this population remain < the 50th %ile. GH and/or other interventions to improve catch-up growth, especially in the first years of life, should be considered.

**Background**: Hydrocephaly is a life-threatening condition, which needs to be diagnosed at an early age to ensure normal neurological development. In children under 2 years-of-age, before fusion of the cranial sutures, hydrocephalus can be suspected by accelerated growth rate of HC before any other symptoms, even before the development of macrocephaly (HC greater than 2.0 SDS). However, the screening for hydrocephaly based on the HC growth has been insufficiently explored.

**Objective and hypotheses**: We developed a new screening method for HC in children under 2 years. We hypothesized that screening for accelerated HC growth would improve sensitivity of diagnosing hydrocephaly compared with the screening for large HC alone.

**Methods**: A new screening method for accelerated HC growth was based on mathematical modeling of HC growth in a population of 18,232 healthy children aged 0 – 2 years. Growth data and medical records of children with operated hydrocephalus aged 0 – 2 years (n = 62, boys 41, girls 21) were collected from two university clinics between 1.1.1996 and 1.6.2010. ROC (Receiver Operating Characteristic) curve was applied to evaluate the accuracy of the two screening methods.

**Results**: HC exceeding 2.0 SDS had a sensitivity of 64.5% (specificity 93.7%, 51st Annual Meeting of the ESPE
AUC 0.86 [95% CI 0.80-0.92]). The same specificity level (93.7%) had a sensitivity of 69.4% in the accelerated HC growth screening (AUC 0.85[95% CI 0.78-0.92]). After combining these two screening methods the sensitivity increased up to 85.5% at the specificity level of 93.7%. The AUC was 0.94 [95% CI 0.89-0.98] indicating an excellent accuracy for the combination of the two screening methods (HC SDS and accelerated HC growth).

Conclusions: Combined HC screening by HC SDS and accelerated HC growth should be applied to HC growth screening in children under 2 years.

The ROC curves for the two screening methods for abnormal HC growth.

**P2-d1-673 Growth 2**

**The S447X polymorphism of LPL gene and physical development in children born with low birth weight (below 2500g)**

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Background: Children, who are born with low birth weight (LBW - less 2500g) are known to have disturbances in physical development. Lipoprotein lipase (LPL) plays a regulatory role in the pathogenesis of atherosclerosis and a modulatory role in the control of inflammatory response.

Objective and hypotheses: The aim of this study was to determine whether the presence of polymorphism S447X in gene of lipoprotein lipase is associated with the disturbance of physical development and susceptibility to apoptosis.

Methods: The relation between S447X polymorphism in the gene for LPL and physical development, as well as relation with apoptosis activation were analyzed in 154 children with LBW, aged 4 -11 years, and in 39 children born with normal weight (NBW) as a comparative group.

Results: The frequencies of L162V LPL were 11.03% (17/154) in LBW children and 10.25% (4/39) in the comparative group. Correlation of genomic DNA. Functional analysis of mutated IGF1R in fibroblasts was evaluated by total IGF1R protein and its cell surface expression, AKT phosphorylation and IGF-1-stimulated DNA synthesis.

Results: We identified 1 child (4%) carrying a nucleotide substitution in heterozygous state in IGF1R. The variant leading to a substitution of arginine by tryptophan in codon 511 of the IGF1-R (p.R511W). Clinical data and the response to rhGH therapy are shown below.

**Laboratory and clinical data of the affected patient**

| Birth weight SDS | -2.2 |
| Mothers height SDS | -3.0 |
| Age (y) | 5.8 |
| Head circumference SDS | -2 |
| Height SDS | -2.3 |
| IGF-1 SDS | +1.3 |
| IGFBP-3 SDS | +1.0 |

After rhGH therapy

| Duration of rhGH therapy (y) | 4.5 |
| rhGH dose (µg/kg/day) | 50 |
| Height SDS | -1.4 |
| IGF-1 SDS | +0.8 |
| IGFBP-3 SDS | +1.0 |

* - affected parent.

Fibroblast cultures were developed from the affected patient and age-matched controls. Cell proliferation induced by IGF-1 and AKT phosphorylation were lower (55% and 40%, respectively) in fibroblasts from the affected patient in comparison to controls. Leucocytes and fibroblasts from the patient harboring p.R511W mutation presented 60% increase in IGF1R expression, also confirmed at protein level and at cell surface expression (p < 0.001).

Conclusions: A novel mutation in IGF1R gene associated with pre and postnatal growth impairment is described. Mutations in IGF1R gene emerge as a relevant cause of intraterine growth retardation.
Follow-up of a cohort of subjects born small gestational age and treated with growth hormone: interim analysis

P2-d2-675 Growth 3

Background: It is well known that estradiol play a crucial role during pubertal growth and epiphyseal closure in both sexes but detailed information about the relationship between estradiol levels and pubertal growth ending in epiphyseal closure is lacking.

Objective: To determine estradiol levels and assess their relationship to growth velocity during puberty up to Peak Height Velocity (PHV) in healthy boys admitted for short or tall stature or participating as health subjects at Queen Silvia Children’s Hospital.

Methods: 26 boys with 37 profiles of 24h serum 17β-estradiol were included in this study. Inclusion criteria: birth weight and length above -2SDS, gestational age 37-42 weeks, prepubertal length and weight within ±3SDS, normal 24h growth hormone (GH) profile and no GH treatment. A 6th grade polynomial was fitted to each child’s growth data and growth velocity and age of PHV was calculated. Serum 17β-estradiol was determined after extraction of sera using a modified assay (Spectria E2, ORION Diagnostica, Finland) with a detection limit of 4 pmol/L.

Results: There was a positive correlation between morning 17β-estradiol and increased growth velocity (r=0.55). In the 50% of increase in growth velocity from prepubertal growth to PHV was observed at a morning estradiol level of 6.6 pmol/L (4.2-10.5 95% CI), EC50 value. All boys with less than 4 % left of their growth up to PHV had 17β-estradiol above 9 pmol/L (n=7). The morning estradiol median of the 6 boys who were investigated at PHV ±3 months was 14.2 pmol/L (9.5-24.8).

Conclusions: 1) Low levels of estradiol, 6.6 pmol/L (4.2-10.5) are associated with a 50% of increase in growth velocity from prepubertal growth to PHV in healthy boys. 2) Morning estradiol levels above 9 pmol/L are seen close to PHV.

Follow-up of a cohort of subjects born small gestational age and treated with growth hormone: interim analysis

The differences in referral age and height standard deviation score among boys and girls receiving growth hormone therapy: analysis of data from the ANSWER Program

P2-d2-676 Growth 3

Background: The American Norditropin Studies: Web-Enabled Research (ANSWER) Program®, a US-based registry, has collected data on pediatric patients treated with Norditropin® (somatropin rDNA origin, Novo Nordisk A/S).

Objective and hypotheses: To assess trends in registry enrollment age (designated as referral age) and severity of short stature, by gender and diagnostic indication in GH-naïve children enrolled in the ANSWER Program.

Methods: Data from patients with growth hormone deficiency (GHD; n=5024), multiple pituitary hormone deficiency (MPHD; n=436), idiopathic short stature (ISS; n=1096), small for gestational age (SGA; n=647), Turner syndrome (TS; n=472), and Noonan syndrome (NS; n=120) were analyzed.

Results: Referral age (y) showed a slight upward trend from 2004 (10.3±3.7) to 2011 (10.9±3.8) for the overall population (trend p=0.0001), which was mostly contributed by males (10.8±3.6 for 2004, 11.4±3.9 for 2011, trend p=0.0004). Referral age was younger for patients with MPHD (7.3±5.4), NS (9.2±3.8), SGA (8.3±3.9), and TS (8.6±4.1) compared with GHD (10±3.5), whereas ISS patients were enrolled at a later age (11.2±3.1). Females were referred earlier than males for GHD and ISS, and mean HSDS at referral was lower for females for GHD, ISS, and NS (p<0.05, Table 1). Those patients with HSDS between -5 and -4 were referred earliest (9.0±3.7), whereas those with HSDS between -2 and -1 were referred later (11.2±3.3).

Conclusions: No trend toward decreasing referral age was observed for any indications in the ANSWER Program®. This is counter to the known fact that younger starting age is an important factor for good response to GHT, and reveals that more effort in education is needed with regard to an earlier and appropriate referral for children with short stature. Females were younger with more severe short stature than males, consistent with a referral bias that requires females to be much shorter than males to be treated with GH.
Results: In genotype analyses, the frequency of A/A genotype at the Cdx-2 binding site locus (rs11568820) upstream of exon 1 of VDR was decreased (OR 0.098, P<0.05), but the one of G/G genotype at rs827421 of intron 1 of ESR1 was increased (OR 19.147, P<0.05) in ISS patients, significantly.

Conclusions: The genetic variations at the Cdx-2 binding site of VDR promoter and ESR1 intron 1 region can be contributing factors of the growth of height.

P2-d2-679 Growth 3
Prevalence of radiological features of SHOX haploinsufficiency in a group of Italian children with short stature
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Background: Heterozygous SHOX mutations (80% deletions) (SHOX-D) are detected in 2–15% of individuals with idiopathic short stature (ISS). The search for subtle radiographic signs is an important key to the diagnosis which has to be confirmed by genetic analysis.

Aim: We evaluated the prevalence of radiological signs of SHOX-D in short Italian children showing a scoring system for identifying SHOX-D lower than 7.

Methods: We enrolled 146 children (61 M, mean age 12.52 ± 3.87 years) affected by different types of short stature: 60 growth hormone deficiency (GHD) (41%), 10 ISS (6.8%), 11 small for gestational age (SGA) (7.5%), 25 costitutional growth retardation (17%), 3 precocious puberty (2%), 37 familial short stature (25.3%). Left-hand radiographs of all patients were analyzed by an experienced radiologist to search for the main characteristics of SHOX-D (triangularization of the distal radial epiphysis, pyramidalization of the distal carpal row, and lucency of the distal ulnar border of the radius).

Results: Thirty out of the 146 (20.5%) analyzed subjects (3 SGA, 14 GHD, 10 ISS, 3 familial short stature) had at least one of the radiological signs of SHOX-D: 18 (60%) had triangularization of the distal radial epiphysis, 7 (23.3%) had lucency of the distal ulnar border of the radius, and 5 (16.6%) had both former signs.

Conclusions: Radiological signs of SHOX haploinsufficiency can be found in children with different kinds of short stature. The clinical reassessment of patients to identify mild clinical signs of SHOX-D and the genetic analysis of SHOX gene are in progress in order to evaluate the relevance of the radiological signs of SHOX-D in short children not showing the classical clinical signs of SHOX-D.

P2-d2-678 Growth 3
Association of polymorphisms in the VDR promoter and ESR1 intron 1 region with idiopathic short stature
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Background: The genetic alterations of vitamin D receptor (VDR) or estrogen receptor (ESR) are related with the growth of long bone, in other word, height. There were a lot of reports regarding the association of polymorphisms in the VDR promoter and ESR1 intron 1 region with many disorders.

Objective and hypotheses: We investigated the association of them with idiopathic short stature (ISS).

Methods: A total of 50 subjects, including 29 ISS patients and 21 healthy controls with their heights within the normal range were recruited. We selected two single nucleotide polymorphisms (SNPs) from VDR promoter (rs4516035 and rs11568820) and three from intron 1 of ESR1 (rs3779609, rs12665044 and rs827421) as candidates, respectively. The SNaPshot assay was performed according to the instruction (ABI PRISM SNaPShot Multiplex kit). Analysis was carried out using Genemapper ver. 4.0. The frequencies of allelle and genotype, and the departures of the genotype distribution from Hardy-Weinberg equilibrium for each SNP were analyzed using the chi-square test or Fisher exact test.

Conclusions: SW children show a lower glucose (P<0.05), VLDL-C (P<0.01), triglycerides (P<0.05), IS (P<0.03) and body composition in pediatric kidney transplantation recipients does not allow improving longitudinal growth post-Tx.

Objective: To determine the effect of early (6d) steroid withdrawal (SW) in longitudinal growth, growth factors, insulin sensitivity (IS) and body composition.

Methods: Prospective, randomized, multicenter study in first pediatric kidney transplant (Tx) recipients does not improve longitudinal growth post-Tx. Objective: To determine the effect of early (6d) steroid withdrawal (SW) in longitudinal growth, growth factors, insulin sensitivity (IS) and body composition.

Results: In genotype analyses, the frequency of A/A genotype at the Cdx-2 binding site locus (rs11568820) upstream of exon 1 of VDR was decreased (OR 0.098, P<0.05), but the one of G/G genotype at rs827421 of intron 1 of ESR1 was increased (OR 19.147, P<0.05) in ISS patients, significantly.

Conclusions: The genetic variations at the Cdx-2 binding site of VDR promoter and ESR1 intron 1 region can be contributing factors of the growth of height.

P2-d2-680 Growth 3
Early start of growth hormone (GH) treatment leads to significantly better long-term growth outcome in GH deficient children
Isabelle Oliver-Petit1; Michael Schlumpf2; Birgitte Tannes Pedersen3; Lars Sävendahl4
1Hôpital des Enfants, Department of Paediatric Endocrinology, Toulouse, France; 2Novo Nordisk Health Care AG, Global Medical Affairs, Zurich, Switzerland; 3Novo Nordisk A/S, Biostatistics & Epidemiology, Søborg, Denmark; 4Karolinska Institutet, Division of Paediatric Endocrinology, Department of Women’s and Children’s Health, Stockholm, Sweden

Background: Improving adult height is the major goal of growth hormone treatment (GHT) in short children with growth hormone deficiency (GHD). Limited data are available on the impact of age at treatment start on adult height.

Objective: To investigate the influence of age at treatment start on adult height in short GHD children.

Methods: From the NordiNet® International Outcome Study (IOS) database, GHD children treated with Norditropin® were identified. Only patients who had reached near adult height (NAH) were included. NAH was defined as height at last visit when:

- age ≥18 years or
- boys were ≥16 years and height velocity (HV) <2cm/year or
- girls were ≥15 years and HV <2cm/year
Included patients were divided into two groups based on age at treatment start:
- Group A: Early start of GHT: girls: age <8 years; boys: age <9 years
- Group B: Late start of GHT: girls: age ≥8 years; boys: age ≥9 years

Statistical analysis was performed by descriptive statistics, simple t-test and an ANCOVA model. Results are presented as mean ± SD.

**Results:** In total 256 children were included, 59 in group A and 197 in group B. Mean age at treatment start was for group A 5.9±2.1 years (45.8% girls) and for group B 11.6±1.8 years (34.5% girls). Height SDS at treatment start was lower in group A than in group B (-3.4±1.2 SDS vs. -2.9±1.1 SDS; p<0.01) and the duration of GHT was longer in group A than in group B (10.4±2.2 vs. 5.7±1.3 years; p=0.0001). No differences between groups A and B were found for average relative GH dose (31.7±7.2 vs. 30.2±7.1 µg/kg/day) and midparental height SDS (-0.45±0.98 vs. -0.72±0.99 SDS). Patients in group A had a significantly better growth outcome as determined by height SDS increment from treatment start to NAH (2.0±0.30 vs. 1.5±1.16 SDS; p<0.0001) and height SDS at NAH (-0.83±1.23 vs. -1.35±1.37 SDS; p=0.010).

**Conclusions:** Early start of GHT leads to significantly better long-term growth outcome in GHD children. Children with an early GHT start were taller at near adult height even though they had been smaller before treatment than children who started treatment late.

**P2-d2-681 Growth 3**

**Progression of bone age maturation during GH treatment - Is there an effect of initial GH dosing?**

Ruth Gausche1; Mandy Vogel2; Eberhard Keller3; Klaus Mohr4; Wieland Kess5; Roland Pfaeffle6

1CrescNet gGmbH, University of Leipzig, CrescNet, Leipzig, Germany; 2University Hospital Magdeburg, Pediatric Endocrinology, Leipzig, Germany; 3University Hospital Leipzig, Dept. of Women and Child Health, Leipzig, Germany

**Background:** Until now it has been discussed controversially to which extent Growth Hormone (GH) therapy influences bone age maturation and thereby final height. Auxological data of children treated with rhGH were collected by multiple treatment centers (n=13) as an independent quality assurance initiative using an established structured online database (CrescNet).

**Objective and hypotheses:** We ask whether or not the initial GH-dose has an effect on maturation of bone age in children treated with GH under different indications.

**Methods:** Effect of growth hormone dosage on the progress of skeletal maturation was analyzed in three diagnosis groups: GH deficiency (GHD), Turner Syndrome (TS) and patients born small for gestational age without catch-up growth (SGA). Bone age was assessed using the Greulich and Pyle method. For the entire group (n=2296) a positive correlation was established between placebo and bone age (R=0.63; p<0.001).

**Results:** For the entire group (n=2296) a positive correlation was established between placebo and bone age (R=0.63; p<0.001).

**Conclusions:** Recombinant growth hormone therapy leads to acceleration of growth rate and weight gain. Moreover, it improves the memory and thinking process and elevates the intelligence level.

**P2-d2-683 Growth 3**

**Evaluation of puberty phases, a new system for rating puberty in general paediatric practice**

Gary Butler1; Tim Cole2; Victoria Dablon3; Charlotte Wright4

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**Background and aims:** Estimation of pubertal status using Tanner stages is usually performed unconfidently by general paediatricians and also requires a physical examination. Self-assessment methods have been shown not to be reliable. As assessment of growth on the new UK growth charts necessitates establishing pubertal status, we have designed and evaluated a simpler non-invasive approach.

**Methods:** The new system has 3 Phases– Pre-Puberty (Tanner stage I), In-Puberty (stages 2/3) and Completing-Puberty (stages 4/5).

<table>
<thead>
<tr>
<th>Phase</th>
<th>Pre-puberty (P)</th>
<th>In Puberty (I)</th>
<th>Completing Puberty (C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girls</td>
<td>No signs of areolar (nipple) or breast development No pubic hair</td>
<td>Any breast enlargement so long as nipples also enlarged Any pubic or axillary (armpit) hair growth</td>
<td>Started periods (menarche) Adult areolar (nipple) enlargement Adult pubic and axillary hair pattern</td>
</tr>
<tr>
<td>Boys</td>
<td>No growth of testes or penis No pubic hair High voice</td>
<td>Reddening of the scrotum Any testicular or penile enlargement Any pubic or axillary hair growth Deepening of the voice</td>
<td>Moustache and/or early facial hair growth Voice broken (deepened) Adult penile and testicular size Adult pubic and axillary hair pattern</td>
</tr>
</tbody>
</table>

The Phase system was tested on 3 separate occasions amongst 28 specialist nurses, 87 general paediatric trainees and 11 consultant general paediatricians after basic training was given. They each evaluated puberty phase and Tanner stage on 10 standardised line drawings.

**Results:** Recognising pubertal development was performed more accurately.
and all in each group were able to participate fully when using Puberty Phases. Most rating errors arose due to a failure to recognise the start of puberty. The accuracy of Tanner stage estimation was poor.

<table>
<thead>
<tr>
<th>Mean (range)</th>
<th>Correct % Tanner stage</th>
<th>Correct % Phases</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Consultants</td>
<td>43 (0-90)</td>
<td>79 (50-100)</td>
</tr>
<tr>
<td>General Trainees</td>
<td>48 (0-90)</td>
<td>78 (30-100)</td>
</tr>
<tr>
<td>Specialist Nurses</td>
<td>54 (30-80)</td>
<td>79 (50-100)</td>
</tr>
</tbody>
</table>

Conclusions: The new simpler Puberty Phase approach was well accepted and allowed to clear even more accurate rating of pubertal development, which is a new requirement for the correct interpretation of the UK growth charts. User education is still required, however.

P2-d2-684 Growth 3
Peculiarities of the growth hormone and insulin-like growth factor secretion in genetically determined types of short stature
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Background: Study of the growth hormone (GH) and insulin-like growth factor (IGF-1, IGFBP-3) secretion in genetically determined types of short stature (GDSS)

Objective and hypotheses: To study the growth hormone (GH) and insulin-like growth factor (IGF-1, IGFBP-3) secretion in genetically determined types of short stature (GDSS) in Uzbek population.

Materials and methods: We examined 92 patients with GDSS (11 patients with Russell-Silver syndrome (RSS), 16 patients with Noonan syndrome (NS), 10 patients with Skekkel syndrome (SS), 9 patients with Prader-Willi syndrome (PWS), 8 patients with Cornelian de Lange syndrome (CLS), 38 girls with TS) at the age of 7 to 18. A level of GH, IGF-1, IGFBP-3, anthropometry (SDS) was studied.

Results: According to the past history, 45.6% of patients examined had parents who were married to close relatives. Stunting of various degrees of expression was observed in all patients with GDSS but it was most expressed in patients with RSS (-5.16±1.18 SDS), SS (-4.18± 1.12 SDS) and CLS (-6.10± 1.14 SDS). A reliably low level of GH vs. the control was found in patients with CLS (0.6±0.05 ng/ml, p<0.05), RSS (0.7± 0.04 ng/ml, p<0.05), SS (1.02±0.07 ng/ml, p<0.05) on the background of a low level of IGF-1 and IGFBP-3. Patients with NS, TS and PWS had a level of GH within the lower limit norm, 12 girls with TS had a GH level which was reliably low (0.40±0.05 ng/ml, p<0.05) but IGF-1 and IGFBP-3 rates corresponded to the lower limit of the age norm.

Conclusions: In Uzbek patients with GDSS pronounced stunting was found in patients with RSS, SS and CLS which is associated with disturbances of a direct and reverse relation in the GH-IGF-IGFBP-3 system. A low GH level and relative deficiency of IGF-1 and IGFBP-3 in girls with TS was related with disturbances in the pituitary-ovarian system.

P2-d2-685 Growth 3
Short stature of MELAS in cohort study in Japan
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Background: MELAS (mitochondrial myopathy, encephalopathy, lactic acidois, and stroke-like episodes) is the most common mitochondrial disease. Eighty percent of MELAS patients have an A3243G mutation on mitochondrial DNA (mtDNA), which mutation is seen in 2% of diabetes mellitus in Japan. This mutation may be one of the most common genetic mutation in human. Details of the mechanism concerning MELAS complications such as short stature and diabetes mellitus are still unknown.

Objective and hypotheses: Clarify prevalence of short stature in MELAS patients in Japan.

Methods: Questionnaires were mailed to hospitals that have over 50 beds throughout Japan in 2001 and 2008. Short stature was defined as under -2.0SD (Japan height scale).

Results: Fifty-three out of 96 Japanese MELAS patients had short stature (55.2%).

Conclusions: We hypothesize that complicating factors are following; 1) growth hormone deficiency, 2) ischemia in hypothalamus-pituitary axis due to endochondral dysfunction, 3) dysfunction of hormone productive cells and secretory cells due to mitochondrial dysfunction, 4) decreased secretion of growth hormone due to low serum arginine and hyperglycemia. MELAS should be ruled out as a cause of short stature because MELAS has a highly complication of short stature. Moreover, carriers who have asymptomatic-like mitochondrial mutation are also important. Since MELAS has a high likelihood of short stature, physicians should be more aware against asymptomatic carriers who have the mitochondrial mutation when clarifying the diagnosis for short stature. Caution is especially warranted when there is a maternal inheritance of short stature, diabetes mellitus, deafness and migraine, since there is a higher probability of an A3243G mutation on mitochondrial DNA.

P2-d2-686 Growth 3
One-year data from a long-term phase IV study of omnitrope® (rhGH) in 269 short children born small for gestational age (SGA)
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Background: Children born SGA may be at increased risk of developing type 2 diabetes mellitus (DM) through a predisposition for metabolic abnormalities. As growth hormone (GH) therapy affects carbohydrate metabolism, there are concerns over the diabetogenic potential of such treatment in these children.

Objective and hypotheses: We present 1-year interim data from an ongoing study assessing safety and efficacy of long-term Omnitrope® treatment in short children born SGA, with particular reference to development of diabetes and response to GH treatment.

Methods: Short children (≤4 years) born SGA will be treated with Omnitrope® 0.035 mg/kg/day s.c. until final height is reached. Oral glucose tolerance tests were performed at baseline and annually thereafter.

Results: 277 children were included in the study and 269 children have completed their first year of treatment. Consent was withdrawn for 6 children, while one child discontinued due to an unrelated adverse event (AE) and another due to other reasons. None of these children developed DM within a year of treatment. In 192 (69.3%) children, 649 AEs occurred although most were mild-to-moderate in intensity (98.7%) and unrelated to treatment (96.5%). Two children (0.7%) developed anti-rhGH antibodies. Overall, treatment was effective as seen by derived height parameters (table). Only 14 (5%) children did not respond adequately after the first year (HV SDS <1) and had to stop treatment.

<table>
<thead>
<tr>
<th>Parameter Mean (SD)</th>
<th>Timepoint</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>H SDS</td>
<td>Baseline</td>
<td>-3.38 (0.77)</td>
<td>-3.40 (0.78)</td>
<td>-3.39 (0.76)</td>
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<tr>
<td></td>
<td>1 year</td>
<td>-2.59 (0.75)</td>
<td>-2.55 (0.80)</td>
<td>-2.57 (0.77)</td>
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<tr>
<td>HV (cm/year)</td>
<td>Baseline</td>
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<td>4.44 (1.28)</td>
<td>4.25 (1.30)</td>
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<tr>
<td></td>
<td>1 year</td>
<td>8.79 (1.43)</td>
<td>9.22 (1.77)</td>
<td>8.99 (1.60)</td>
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<tr>
<td>HV SDS</td>
<td>Baseline</td>
<td>-2.59 (1.88)</td>
<td>-1.54 (1.45)</td>
<td>-2.13 (1.70)</td>
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<td>(Peak-centered)</td>
<td>Baseline</td>
<td>4.21 (2.26)</td>
<td>4.10 (2.27)</td>
<td>4.16 (2.27)</td>
</tr>
</tbody>
</table>

Conclusions: Derived height parameters improved substantially within one year of Omnitrope® treatment. No child developed diabetes during this period.
P2-d2-687 Growth 3
Acродистофия с гормоном роста: новый случай с мутацией PRKAR1A
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Background: Acrodysostosis is a rare skeletal dysplasia characterised by severe brachydactyly, facial abnormalities with maxillary and nasal hypoplasia, short stature, advanced bone age, and decreased vertebral interpedicular distance. Hormone resistance has also been described.

Objective and hypotheses: The skeletal dysplasia in acrodysostosis resembles Albright’s hereditary osteodystrophy seen in patients with pseudohypoparathyroidism type 1a, but GNAS mutations have not been found in acrodysostosis. Recently a mutation in the gene encoding PRKAR1A has been described in 3 patients (NEJM 2012). Mutations in PRKAR1A, the cAMP-dependent regulatory subunit of protein kinase A, may explain the hormone resistance and the similarities in the skeletal abnormalities of the two conditions.

Methods: Born at term, small for gestational age, our patient presented normal timing of developmental milestones, regular growth in her first years of life, followed by a progressive delay in growth resulting in a height < 3rd centile by the age of 3 years. She was referred to us at age 11 yrs: height -3.13 SDS. Clinical evaluation revealed a peculiar face with a small broad upturned nose with flat nasal bridge, antverted nostrils, short columella, maxillary hypoplasia, a small broad hands and feet. Radiological features included shortened and broadened metacarpals and phalanges, cone-shaped epiphyses of the proximal middle phalanges, exostosis in the tibial region, hip osteonecrosis. High blood levels of TSH and PTH were evidenced repeatedly during the follow up with normal FT4, calcium, phosphate and calcitonin levels. Karyotype was normal.

Results: Molecular analysis of the PRKAR1A gene evidenced the c.1101C>T (p.Arg368stop) mutation resulting in the truncation of the last 14 aminoacids of the protein.

Conclusion: Our case presents a typical recognizable phenotype and we might confirm that peripheral resistance, particularly for TSH and PTH, is a characteristic of this syndrome.

P2-d2-688 Growth 3
An observational, retrospective, multicentre survey measuring patient adherence to recombinant human growth hormone (r-hGH) injections using the easypod™ auto-injector
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Background: Adherence to r-hGH therapy is important for optimal treatment outcome; children with low adherence (>2 missed injections/wk) demonstrated reduced growth velocity.

Objective and hypotheses: To evaluate adherence to r-hGH in patients using the auto-injector.

Methods: This was a retrospective, multicentre survey of children receiving r-hGH and using the auto-injector for ≥3 mths in the UK and in Ireland. Data were collected on baseline demographics, duration of both auto-injector use and overall r-hGH therapy, and other factors (e.g. age group) that may influence adherence to therapy. Adherence number of days prescribed injections were administered over a 3-mth period) was calculated from electronically recorded injection history in each auto-injector. Ad hoc summaries were: percentage adherence by age group; average number of missed injections/wk.

Results: Final data are presented for 73 patients (mean age 10.6 [SD 4.13; range 3-17] yrs; 55% [40/73] were male). Mean duration of auto-injector use was 18.7 (SD 7.45; range 6-32) mths. The auto-injector was the first device used for 52 patients (71%); 21 patients (29%) transitioned from another device. Mean duration of r-hGH use was 31.1 (SD 24.81; range 6-146) mths. r-hGH was administered by a parent/carer for 38 patients (52%) and was self-administered by 35 patients (48%). Median overall adherence with the auto-injector was 90%. Overall, the mean number of missed injections/wk was 1.22 (SD 1.46; range of means for treatment centres 0.88-1.88). 19% of patients (14/73) missed >2 injections/wk. Median percentage adherence was similar in the age groups 2-11 yrs (91.2; n=39) and 12-15 yrs (90.1; n=23), but lower in the 16-18 yrs (70.3; n=11) age group.

Conclusions: Patients aged 16-18 yrs had lower adherence vs younger age groups. Overall, 19% of patients using the easypod™ auto-injector missed >2 injections/wk. This is the first UK study of patient adherence to r-hGH therapy using accurate and reliable data recorded by the auto-injector.

P2-d2-689 Growth 3
Growth in prepubertal Nigerian children is highly socio-economy dependent
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Background: Growth is an integrated marker of child health. It is important to assess growth of children to detect disorders in individual children and to highlight the socio-economic level of the society.

Objective and hypotheses: Growth in prepubertal children is related to socio-economy status.

Methods: Cross-sectional study in 2009-10 of height, weight and body mass (BMI) of children age 5-10 yrs through random sampling in 8 public (n=975) and 8 private schools (n=588), in Sagamu Local Government Area, Nigeria. A total of 1563 children were analysed (776 boys & 787 girls). References: WHO of 5-19 yr born in 30ies and the Swedish of 19 yr born in 70ies, the latter with 0.3-0.7 SDS higher values.

Results: (WHOref) Children in private schools were significantly taller -0.4±1.16 and heavier -0.6±1.03 than those in public schools -0.1±1.15 and -1.2±0.97 (height, weight SDS, respectively), p<0.001, but with similar BMI SDS. Growth parameters increased with parental socio-economy. Children from families with the highest status had normal height SDS (-0.1±1.22), weight SDS (0.1±1.16), BMI SDS (-0.1±1.29) compared to children from the lowest status: height SDS -1.3±0.89, weight SDS -1.3±0.89, BMI SDS -0.9±0.91 (p<0.001). The prevalence of short stature based on Sf, 27%, was almost twice the WHOref 14%. For the lowest status 14% (girls and boys 14%), for the highest status 3% (girls 0%, boys 6%). The height and weight (WHOref SDS) decreased from age 5 to 10 years in both sexes; in boys height from -0.8±1.23 to -1.0±1.10 and weight from 0.9±0.97 to -1.0±1.06 and in girls height from -0.5±1.40 to -1.4±0.88, p=0.024 (Sf) and weight from -1.1±1.13 to -1.3±0.85, p<0.001 (WHOref).

Conclusions: Children in Sagamu are shorter and lighter than international standards and short stature is prevalent. Lack of significant & consistent differences in BMI would suggest factors other than pure caloric differences are involved. Disparities in parental socioeconomic conditions are constraints to optimal child growth.

P2-d2-690 Growth 3
Coexistence of holoprosencephaly 5 (HPE5) and chromosome 22q13.3 deletion syndrome in a boy with growth retardation
Iva Stoeva1; Savina Agova-Hadjidekov1; Radoslava Grosadanov1; Ananta Kata Kostova1; Ani Aroyo2; Dragi Toncheva2; 1University Pediatric Hospital, Medical University Sofia, Screening and Functional Endocrine Diagnostics, Sofia, Bulgaria; 2Medical University, Medical Genetics, Sofia, Bulgaria

Background: HPE is the most common structural anomaly of the human brain and is one of the anomalies seen in patients with deletions and duplications chromosome 13. The terminal 22q11.23 deletion syndrome is characterized by neonatal hypotonia, global development delay, normal to accelerate...
ated growth, absent to severely delayed speech, autistic behavior and minor dysmorphic features.

**Objective and hypotheses:** Description of the phenotype and chromosomal aberrations in a boy with progressing growth delay, disproportionate short stature and skeletal abnormalities.

**Methods:** SGA boy, delivered after 42 gestational weeks, with cerebral edema, BL 47 cm (3 centile), BW 3010g (50 centile), head circumference 50 percentile; Key feature: early and slowly progressing disproportionate short stature, TH 25 percentile, accompanied by delayed bone maturation, skeletal deformities (insufficient development Th12-L1), thoracolumbar kyphoscoliosis, normal mental development, isolated partial GHD, eutopic neurohypophysis, hypoplastic infundibulum and adenohypophysis. No limited neck rotation.

**Results:** Introduction of rhGH therapy after low stimulated GH (arginin test, max. 9.6 mIU/l) and pituitary hypoplasia (MRI); catch up growth (90-75 centile) during the first two yrs of rhGH treatment. Sharp decrease in growth velocity during the following yr. The unusual phenotype forced to perform comparative genomic hybridization on microarrays, covering the whole genome at a mean density of 1 BAC clone/0.8 Mb for finely mapping the aberration in the patient and direct linking to gene sequence data base. Thus we refined the manifested deletions to the regions 22q13.33 (9,824 kb, omim 606232: 22q13.3 deletion syndrome) and 13q32.3 (1,539 kb, omim 609637: holoprosencephaly 5).

**Conclusions:** The index patient represents a rare combination of two different syndromes diagnosed by microarray analysis and unique phenotype described earlier as isolated GHD and spondylo-coastal dysplasia. Grant 57/2001 Medical University Sofia.

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**P2-d2-6691 Growth 3**

**Indicators for detecting syndromic short stature**

**Elena Sukarova-Angelovska; Mirjana Kocova**

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**Introduction:** Syndromic short stature accounted for more than 25 percent of all children with delayed growth. Short stature is only one of the features of a specific syndrome, often associated with mental retardation, a set of major and minor anomalies. There are more than 900 syndromes with short stature described in the dysmorphology databases. The reasons for short stature in syndromes are different - abnormal regulation and secretion of Gh or IGF1, placental insufficiency in chromosomal abnormalities, mutations in SHOX genes, etc. Establishing the diagnosis sometimes could be difficult and demands comprehensive examination.

**Materials and methods:** We present a cohort of 185 children with syndromic short stature including children with chromosomal disorders, microdeletion syndromes, skeletal dysplasias, Noonan syndrome, Silver-Rusel syndrome, etc. All children were more than 2.5 SD below the mean, with major deviation in children with skeletal dysplasia. The pattern of minor anomalies was evaluated in each group and was highly specific. The most common features in the whole group were ear anomalies, wide nasal root, brachycephaly and abnormal palpebral slanting. In most of the children there were more than 4 minor malformations except short stature.

**Discussion:** Dysmorphic syndromes include non-random combination of major and minor malformations, and is often state of the art of clinical determination. Minor malformations, although insignificant for a child’s health, have remarkable importance for syndrome detection. Delineation of a specific syndrome in children with short stature is prerequisite for further investigation, as well as multisystematic therapeutic approach and genetic counseling.

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**P2-d2-693 Growth 3**

**Novel heterozygous IGF1 receptor variant in two siblings with short stature**

**Julia Geising; Sebastian Burkhardt; Jürgen Klammt; Marina Schlöcke; Antje Körner; Wieland Kiess; Roland Pfäffle**

University Hospital Leipzig, Hospital for children and adolescents, Leipzig, Germany

**Background:** Two brothers presented for evaluation of severe short stature at 4 and 6 years of age (-3.74 and -3.26 height SDS, respectively). Both were born small for gestational age. They achieved developmental milestones adequately, except for retardation of verbal development. Growth rate was low (-3.39 SDS and -0.93 SDS respectively). Deviation from target height was evident in both siblings, though parents’ heights were small (mother: 148 cm, father: 162 cm). The siblings showed no catch-up growth till presentation.

**Objective and hypotheses:** Our aim was to investigate the IGF1 receptor for variants as a potential underlying cause of short stature.

**Results:** Routine diagnostics ruled out chronic illness and classic endocrine disorders. However molecular genetic analyses of the IGF1 receptor revealed a novel heterozygous mutation in exon 21 causing an amino acid substitution (p.Cys1248Tyr) in both siblings as well as their father. In the mother no mutation in the IGF1 receptor could be detected. Basal IGF1 and IGFBP3 levels were high (2.02 and 2.42 SDS in the younger and 1.55 and 2.12 SDS in the older brother). Oral glucose tolerance testing (oGTT) showed high normal test results in both brothers. The father manifested with Diabetes mellitus in his twenties. HbA1c is now controlled by diet and active lifestyle. Both patients showed an increase of growth velocity after one year of hGH treatment (from 4.2 to 6.6 cm/year in the younger and 5.4 to 7.6 cm/year in the older brother).

**Conclusions:** A novel mutation within the kinase domain of the IGF1 receptor was established as a cause of short stature and intrauterine growth retardation. Other previously associated features such as mental retardation and mild dysmorphic stigmata were not found in our patients. The siblings improved their growth velocity by more than 2 cm/year after 1 year of IGH treatment.
P2-d1-694 Hypoglycaemia 2
Review of 18 patients with hyperinsulinism studied with 18-f-dopa pet-ct
Cristina Azcona1; Carlos Caicedo2; Lorena García; Ana Herranz2; Ines Domínguez2; Javier Aubitz2
1Clinica Universidad de Navarra, Pediatrics, Pamplona, Spain; 2Clinica Universidad de Navarra, Nuclear Medicine, Pamplona, Spain

Background: Congenital hyperinsulinism is the most frequent cause of refractory hypoglycaemia with subsequent irreversible neurological damage. The differential diagnosis between diffuse and focal hyperinsulinism is very important not only in the management.

Objective: To review 18 patients with hyperinsulinism and evaluated with 18-FluorDopa PET-CT.

Material and methods: Eighteen patients diagnosed with congenital hyperinsulinism who underwent 18-FluorDopa PET-CT.

Results: Fifty-nine percent were female, delivery was normal in 68.8%, median gestational age 38±3 weeks, mean percentile at birth was 85. Median age at clinical presentation was before the first moth of age (1 week-3 months) and median age at diagnosis: one month (15 days-3 months). Symptoms at onset: convulsion (41.2%), cyanosis (29.4%), hypotonia (29.4%), tremor (23.5%), sweating (11.8%), feeding difficulties (5.9%). Mean glucose value at onset: 23.7 mg/dL, mean insulin in hypoglycaemia: 42.12 μU/mL y peptide-C: 5 ng/mL. To control glucose levels 82.4% needed diazoxide (mean dose 11.3 mg/kg/day), 64.7% hydroclorotyrazide (mean dose 2.7 mg/kg/day), 35.3% octreotide (median dose 15.4 mcg/kg/day) and 52.9% intravenous glucose (mean requirement 4.7 mg/kg/min). Two patients needed glucagon continuous infusion. More than half of patients followed a strict dietetic control. Nine patients had enteral nutrition. Median age at PET-TAC performance was 6 months (3-14 months). Five cases were multifocal, 7 focal and 6 diffuse. All patients with focal hyperinsulinism are asymptomatic, without medication and they do not need nutritional care after surgery. One patient with diffuse pattern died after surgery due to sepsis. And another one died before surgery also due to sepsis. Patients with diffuse hyperinsulinism keep on diazoxide and nutritional measurements.

Conclusions: We have observed three different patterns at PET-TAC: focal, multifocal and diffuse. 18-FluorDopa PET-CT is a very sensitive test to identify the focal form and it should be performed as soon as possible in order to guide management and surgery procedures.

P2-d1-695 Hypoglycaemia 2
A new disease? Persistent isolated beta-hydroxybutyrate ketoacidosis and mild congenital hyperinsulinism
Henrik Thybo Christesen1; Klaus Brusgaard2; Lilija Dittkovskaya3; Maria Madsen1
1Odense University Hospital, H.C. Andersen Children's Hospital, Odense C, Denmark; 2Odense University Hospital, Clinical Genetics, Odense, Denmark; 3State Pediatric Medical Academy, Clinical Pediatrics, St. Petersburg, Russian Federation; 4Endocrinology Research Center, Pediatrics, Moscow, Russian Federation

Background: Congenital hyperinsulinism (CHI) does is usually non-ketotic. Ketolysis defects cause high levels of all ketone bodies. 

Objective and hypotheses: To explore the cause of hypoglycaemia in a patient with mild CHI and ketosis.

Methods: Routine blood and urine analyses, 18F* DOPA PET-CT scan, genetic sequencing and MLPA.

Results: A 1½ y-old boy of non-consanguineous parents had repeat hypoglycaemia from age 4 months. CHI was found (p-insulin 23 μU/L at glucose 2.4 mmol/L). Genetic testing showed no mutations in the genes ABCC8, KCNJ11, GCK, GLUD1 and HADH. Ocreotide up to 10.2 μg/kg/day did not prevent hypoglycaemia down to 1.7 mM; HbA1c 4.1% (4.3-6.3%). On i.v. glucose only, glucose demand was 5.5 to 11 kg/min. At blood glucose 3.0 mM, p-insulin was 48 (12-77 pmol/L), p-C-peptide 617 (130-760 pmol/L). P-glucagon was normal. A protein load excluded protein-sensitive hypoglycaemia. PET-CT scan excluded focal CHI. The patient had daily nausea, vomiting and metabolic acidosis with normal lactate. Urine ketone body sticks (measuring acetoacetate and acetone only) were low, 0 to +1, but bedside blood ketones (measuring hydroxybutyrate only) were markedly elevated. Repeated measurements (n=40) showed persistent blood ketosis (0.1 to 5.2 mmol/L), lowest at high glucose levels. Sequencing of the butyrate dehydrogenase gene BDH1

P2-d1-696 Hypoglycaemia 2
Congenital hyperinsulinism of Infancy: peculiar characteristics of patients in the Italian registry
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1University of Catania, Scienze Mediche e Pediatriche, Catania, Italy; 2University of INSUBRIA Varese-Como, Clinical and Biological Sciences, Varese, Italy; 3University Vita-salute San Raffaele, Istituto Scientifico San Raffaele, Centro di Endocrinologia dell’Infanzia e dell’Adolescenza, Milano, Italy; 4University of Milano, Scienze e Tecnologie Biomediche, Milano, Italy; 5Istituto Scientifico San Raffaele, Laboratorio di Endocrinologia Pediatrica - Divisione di Scienze Metaboliche e Cardiovascolari, Milano, Italy; 6AOU Policlinico - Vittorio Emanuele Catania, SIS, Catania, Italy; 7University Federico II Napoli, Pediatrics, Napoli, Italy; 8University of INSUBRIA Varese-Como, Dipartimento di Scienze Cliniche e Biologiche, Varese, Italy

Background: Congenital Hyperinsulinism of Infancy (CHI) is the most common cause of persistent hypoglycaemia in infancy. It is a heterogeneous entity for clinical presentation, histology, genetic and molecular bases. Hypoglycaemia is often difficult to be managed and failure to promptly recognize and treat it results in irreversible brain damage. Despite major advances CHI is still a clinical challenge for the pediatric endocrinologist.

Objective and hypotheses: The Italian National Registry for CHI has been set up in 2007-2008. Aims of this study was to describe the peculiar characteristics of a large cohort of Italian CHI patients.

Methods: We analyzed data of 54 patients enrolled in the Registry regarding: birth, consanguinity, family history, age and symptoms at diagnosis, diagnostic criteria, treatment, genetics, outcome.

Results: Birth data, age and symptoms at diagnosis, diagnostic criteria were in accordance to published data. ABCC8/KCNJ11 mutation found in 46% of patients analyzed. 74% of patients was responsive to medical treatment (88% of ABCC8/KCNJ11 non mutated and 53% of ABCC8/KCNJ11 mutated patients). Diffuse forms were 81%, focal forms 19%. Pancreatectomy was performed in 26%. Outcome: on medical treatment 55.5%, spontaneous remission 18.5%, cured after pancreatectomy 26%. Neurological complications, most minor ones, were present in 28%.

Conclusion: To date, the population evaluated seems to show some differences compared to published series; complete genetic characterization and analysis of the role of different clinical management protocol are needed to clarify these data.

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P2-d1-697 Hypoglycaemia 2
Measuring blood glucose in the newborn: how accurately is hypoglycaemia detected by two routinely used methods?
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Background: Neonatal hypoglycaemia with seizures is associated with neurodevelopmental abnormalities. Hemocue glucose analyser and Siemens Rapidlab 1265 blood gas analyser (BGA) are both used for near-patient testing. A value of below 2.6 mmol/L is generally accepted as hypoglycaemia.

Aims: To quantify the accuracy of Hemocue and BGA measurements and to establish the values that can be used to screen for hypoglycaemia.

Methods: All neonates requiring blood glucose measurements on the first day at a regional neonatal unit had measurements of blood glucose, using Hemocue, BGA and the laboratory using heel prick blood from the same sample.

Results: 253 babies (143 males) were recruited. Laboratory measurements paired with Hemocue (242) and with BGA (234) were available for analysis. The values for median (25-75 interquartile range) were as follows: birth weight 2625 grams (2316 – 3015), gestation 37 weeks (35 weeks and 5 days to 38 weeks and 5 days), age at measurement 7 hours (4 – 10) and laboratory plasma glucose 2.4 mmol/l (1.9 – 3).

Hemocue overestimated blood glucose by a mean of 0.72mmol/L, 95% limits of agreement (lab-Hemocue) were -1.92 to +0.48 mmol/L. Hemocue of <2.9mmol/L had 90% positive predictive value (PPV) for detecting hypoglycaemia and negative predictive value (NPV) of 66%. Hemocue >3.8mmol/L had PPV for normoglycaemia of 90% and NPV of 67%.

BGA also overestimated blood glucose by a mean of 0.51mmol/L, 95% limits of agreement (lab-BGA) were -1.55 to +0.53 mmol/L. BGA value of <2.9 mmol/L had PPV for detecting hypoglycaemia of 90%, and NPV of 66%.

BGA >3.3mmol/L had PPV for normoglycaemia of 91.5% and NPV of 87%.

Conclusion: Routinely used bedside methods for blood glucose measurement in the newborn have inherent inaccuracies and may fail to detect true hypoglycaemia. This has implications for practise and is of potential medico-legal significance.

Table 1. Genotype-phenotype correlation in patients with mutations detected in the newborn

<table>
<thead>
<tr>
<th>ABCCS</th>
<th>KCNJ11</th>
<th>GCK</th>
<th>GLUD1</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Number of patients</td>
<td>9</td>
<td>3</td>
</tr>
</tbody>
</table>

Mutations found in medically responsive cases
- **Y344X**
- **Y336R**
- **I511T**
- **A86T**
- **Y357H**
- **I1511T**
- **R1352H**
- **homoz**
- **V91L**

Mutations found in medically resistant cases
- **R98X**
- **Q44H**
- **Q44H**
- **R136AFsX5**
- **R841P**
- **Y214C**
- **S498L**

** *** - same patient; homoz - homozygous

We compared main clinical and biochemical features of children with found mutations in ABCCS and KCNJ11 genes (group A) and patients with wild type genes (group B)

P2-d1-698 Hypoglycaemia 2
Resolution of severe recurrent hypoglycaemia in an infant with Beckwith-Wiedemann syndrome after a single dose of lanreotide
Sebastian Rümmer; Alena Braun; Jan Marquardt; Markus Vogel; Burak Salgin; Erzhan Maystopek; Thomas Meisner; University Hospital Düsseldorf, Department of General Pediatrics and Neonatology, Düsseldorf, Germany

Background: Recurrent episodes of hypoglycaemia occur in about 50% of patients with Beckwith-Wiedemann syndrome (BWS). Some cases are associated with dysregulated insulin secretion unresponsive to diazoxide. Few patients require continuous glucose feeding, whilst partial pancreatectomy is rarely indicated.

Objective and hypotheses: Octreotide has been shown to be effective in single patients who required prolonged treatment with a continuous subcutaneous infusion or several subcutaneous injections per day. We used lanreotide depot in a 7 week old boy who suffered from recurrent episodes of hypoglycaemia despite diazoxide treatment and frequent feeding.

Methods: After surgical treatment of a congenital biliary cyst, the patient was referred to our hospital because of recurrent hypoglycaemic episodes still requiring 14mg/kg/min glucose at 5 weeks of age. Diagnostic workup confirmed diagnosis of BWS, excluded inborn errors of metabolism, hormone deficiencies and revealed hyperinsulinism (2.9 mmol/L) at the time of hypoglycaemia (plasma glucose 2.2mmol/L). Treatment with up to 12mg/kg/diaxoxide for 14 days did not lead to significant glucose stabilization.

Results: Immediately after the first s.c. application of the somatostatin analogue lanreotide autogel 30mg, normoglycaemia was achieved with a regular feeding regimen. We observed a short period of hyperglycaemia (maximal glucose 12.3mmol/L one hour after injection). However, neither hypoglycaemia occurred on subsequent days. No further side effect was observed. Discharge was possible 5 days after injection and a second application of lanreotide was not necessary. No further hypoglycaemia occurred up to the actual age of 12 months.

Conclusions: In addition to patients with congenital hyperinsulinism also patients with BWS and severe hyperinsulinism may benefit from lanreotide. We propose that lanreotide may be an useful alternative to bridge the time until remission in diazoxide-unresponsive patients.

P2-d1-699 Hypoglycaemia 2
Genotype-phenotype associations in children with congenital hyperinsulinism
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Background: Congenital hyperinsulinism (CHI) is a heterogeneous disease in terms of clinical presentation, genetics and histology. Mutations in eight genes are known to be a cause of CHI, of which ABCC8, KCNJ11, GCK and GLUD1 are among the most common.

Objective: We investigated genotype-phenotype associations in a cohort of Russian patients with CHI by clinical characterization and bidirectional direct sequencing of the ABC8, KCNJ11, GCK and GLUD1 genes.

Results: 46 children were identified, of which 28 (60.8%) responded to the medical therapy (diazoxide and/or somatostatin) and 18 (39.1%) were resistant and underwent subtotal or partial pancreatectomy. Histological examination of the removed pancreatic tissue revealed 9 (50%) diffuse, 8 (44.4%) focal, and 1 (6%) atypical form of CHI. Among medically responsive, 4 children (14%) spontaneously recovered during 1 year after the diagnosis. Mutations were found in 15/42 patients (36%); 6/26 (23%) of the medically responsive, and resistant, respectively. There were no mutation carriers among children with spontaneously recovery. Follow up studies showed high prevalence of severe mental delay in CHI patients. All but one A96T mutations were heterozygous.
Conclusion: In conclusion, a genetic cause was detected in 23%, and 56%, of children with mild, and severe CHI, respectively, in Russia. Mutations in ABC28 and KCN21 were found to be the most common cause and associated with severe course of the disease and poor neurologic outcome.

P2-d1-700 Hypoglycaemia 2

Hyperinsulinemic hypoglycaemia

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Background: In hypoglycaemia, verification of specific diagnosis is important for the treatment and future prognosis.

Objective and hypotheses: We aimed to investigate different causes of persistent/recurrent hypoglycaemia in children and evaluate clinical characteristics and neurologic features during follow-up.

Methods: We included 91 patients aged 1 day-16 years diagnosed the last 4 years. Standard evaluation included fasting test, insulin, C-peptide, cortisol, GH, urine ketone bodies during hypoglycaemia (<2,2 mmol/l), IGF-I, ACTH, TSH, fT4, lipid profile, lactate, Masspectrometry of aminoacids and carnitins. Glucose test, GH-stimulation test, OGTT, brain MRI, T2-weighted US/CT, cranial magnetic resonance imaging (3 patients), electroencephalogram (2 patients). Autonomic dysfunction was evaluated in 22 patients.

Results: Hyperinsulinemic hypoglycaemia (insulin level >2 mU/l during hypoglycemia) were found in 56 patients, congenital hyperinsulinism; n=46, pancreatic insulin-producing tumors; n=10. Among 35 children with low insulin levels, 31 patients had ketotic hypoglycaemia, 4 had low ketone bodies. Except in pancreatic insulomas, all patients had hypoglycaemia onset during the first 3 years of age.

Table 2.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of cases (%)</th>
<th>Age at manifestation of hypoglycaemia (mean, range)</th>
<th>Number (%) of severe cases</th>
<th>Neurologic outcome (mean follow up period 2 years)</th>
<th>Neurologic outcome (mean follow up period 2 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHI</td>
<td>46 (52.5%)</td>
<td>1 (0.03-30) months</td>
<td>29/48 (63%)</td>
<td>20/33 (61%)</td>
<td>8/33 (24%)</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>10 (11%)</td>
<td>10 years (8-16)</td>
<td>410 (40%)</td>
<td>19 (11%)</td>
<td>19 (11%)</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>9 (10%)</td>
<td>31 (9-35) months</td>
<td>219 (22.2%)</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Glycogen storage disease</td>
<td>4 (4.5%)</td>
<td>1.25 (0.5-3) months</td>
<td>4/4 (100%)</td>
<td>1/3</td>
<td>1/3</td>
</tr>
<tr>
<td>Idiopathic ketotic hypoglycaemia</td>
<td>17 (18.5%)</td>
<td>18 (1-36) months</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Defects of fatty acids beta-oxidation</td>
<td>1 (1.1%)</td>
<td>0.5 months</td>
<td>none</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>POMC deficiency</td>
<td>1 (1.1%)</td>
<td>12 months</td>
<td>none</td>
<td>1</td>
<td>none</td>
</tr>
<tr>
<td>Cases with unverified etiology</td>
<td>3 (3.3%)</td>
<td>24 (8-49) months</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
</tbody>
</table>

Conclusions: CHI was the most common cause of persistent severe hypoglycaemia and had the worst neurologic outcome. In 3.3% of cases with non-ketotic hypoglycaemia, specific diagnosis was not verified.

P2-d1-701 Hypoglycaemia 2

Hyperinsulinemic hypoglycaemia: experience with 18 cases

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Background: Patients with hyperinsulinemic hypoglycaemia (HIH) present neonatally, infancy or childhood period and show transient, prolonged and persistent characteristics.

Objective and hypotheses: To analyzed the clinical and biochemical characteristics and treatment and neurodevelopmental outcomes in HIH patients.

Methods: We evaluated 18 children with HIH during 14 year period.

Results: Patients presented neonatally (11), during infancy (6) and childhood (1). The age at time of presentation ranged from the first day of life to 7 years. Consanguinity was reported in 11 cases (61%). None of the mothers had gestational diabetes. Mean birth weight and gestational age were 3335 ± 38 weeks, respectively. Hypoglycemic seizure was the most common presenting symptoms (13 patients). Poor feeding (4) and asymptomatic hypoglycaemia (1) were seen at diagnosis. Insulin and C-peptide levels at the time of hypoglycemia ranged from 3.9-88 mU/ml, 1.3-12 ng/ml, respectively. The ammonia level was found to be elevated in two patients, one of whom also had high alanin aminotransferase level and was diagnosed Wilson disease together with HIH. All patients received intravenous glucose infusions (9.2 ± kg/min) and were started diazoxide at diagnosis. Diazoxide treatment was ceased in nine patients (transient HIH) and 7 of them had diagnosed neonatal period. Medical treatment was failed to maintain normoglycemia in two patients. Diazoxide unresponsive one patient underwent near total pancreatectomy and hypoglycemic episodes continued after surgery and this episodes was controlled by diazoxide, octreotide and hydrocortisoid. The other patient refused surgery and continued medical treatment and severe motor mental retardation was developed at the follow-up. Visual evoked response (2 patients), cranial magnetic resonance imaging (3 patients), electroencephalogram (2 patients) were abnormal in all group.

Conclusions: The natural history of HIH is not well understood. The long term careful monitoring is needed to avoid complications.

P2-d1-702 Hypoglycaemia 2

Hypoglycaemia as a complication of the metabolic disease aromatic L-amino acid decarboxylase deficiency

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Background: Aromatic L-amino acid decarboxylase (AADC) is an essential enzyme in the biosynthesis of the monoamine neurotransmitters serotonin and dopamine. AADC-deficiency is a rare autosomal recessive inborn error of metabolism characterized by severe developmental delay, prominent motor abnormalities, oculogyric crises and autonomic features. Prognosis is poor.

Objective and hypotheses: We describe a five year old boy with AADC-deficiency with low neurotransmitters level in CSF (low HVA and 5-HIAA and elevated 3-O-Methyltyrosine) confirmed by deficient AADC plasma enzymatic activity (0.7 mU/L) and mutation analysis (compound heterozygote A91V/A275T). He showed a severe neurologic clinical picture and no improvement was found under several dopamine agonists (DA-agonists), high dosis of vitamin B6 and an atropine agonist (see table 2). Severe, unpredictable, episodes of hypoglycaemia were documented when he was switched from bromocriptine to pramipexol, a more potent dopamine agonist, in order to try to improve his motoric disabilities. Episodes of hypoglycaemia are documented in other patients with this metabolic disease although they were mostly misdiagnosed as having epilepsy. The pathogenesis of hypoglycaemia in these patients is unknown: they are thought to reflect the relative lack of catecholamines as having epilepsy. The pathogenesis of hypoglycaemia in these patients is unknown: they are thought to reflect the relative lack of catecholamines as anti-inulinergic hormones. I hypothesize that the potent dopamine agonists in
these patients can give rise to hypoglycaemia based on inhibition of growth hormone secretion through activation of dopamine D2 receptors and/or by the autonomic dysfunction in these patients with virtually no sympathetic activity left.

Methods: During episodes of hypoglycaemia, serum growth hormone, serum insulin and serum cortisol and urinary free cortisol and catecholamines were measured.

Results: No overt hormonal abnormalities (growth hormone, insulin, cortisol) were found. The episodes of hypoglycaemia disappeared, and other severe side effects, e.g. arterial hypotension improved when the patient was switched back to bromocriptine.

P2-d1-703 Perinatal and Neonatal Endocrinology 2

Correlation of early morning plasma cortisol and salivary cortisol in extremely premature infants

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3University of Manchester, Manchester Academic Health Sciences Centre, Manchester, United Kingdom;
4Alder Hey Children’s Foundation Trust, Department of Biochemistry, Liverpool, United Kingdom;
5University of Manchester, Department of Women’s and Children’s Health, Institute of Translational Medicine, Liverpool, United Kingdom

Background: Cortisol is important for survival during illness and cortisol concentrations are expected to increase during significant stress. Extreme preterm infants may develop adrenal insufficiency in the early neonatal period. Cortisol is 90% bound to cortisol binding globulins (CBG) in the circulation, therefore measurements of plasma cortisol can be compromised by conditions that alter CBG levels. Measurement of free cortisol is the best indicator of adrenal glucocorticoid secretion and can be determined in the saliva. Several studies have been reported on salivary cortisol determination in neonates and particularly, premature infants.

Objective and hypotheses: The aim of the study was to determine the correlation of early morning plasma cortisol and salivary cortisol in extremely premature infants.

Methods: We prospectively obtained early morning plasma and salivary cortisol sampling at Day 1 of life, Day 14, Day 28 and at 36 weeks corrected gestational age (CGA). Saliva was obtained using 4 standard universal swabs by placing one swab at a time in the infant’s mouth for 1-2 minutes. No salivary stimulants were used. Salivary cortisol was measured by competitive ELISA using a commercially available kit SLV-2930 (DRG, Germany) according to the manufacturer’s instructions. Plasma cortisol was measured using DPC tri multic2000 using a solid phase 2 site chemiluminescent immunometric assay.

Results: There were 65 infants (36 males) included in the study. Mean gestation was 25.3±1.3 weeks. Mean plasma cortisol levels were 400nmol/L ± 42.8 SEM, and mean salivary cortisol levels were 127.5 nmol/L ± 66.5 SEM. Plasma cortisol was positively correlated with salivary cortisol levels (r=0.44, p<0.001).

Conclusions: The study showed a good correlation between salivary and plasma cortisol concentrations obtained early in the morning in extremely premature infants.

P2-d1-704 Perinatal and Neonatal Endocrinology 2

Ultrasound measurements of thyroid gland volume in extreme preterm infants at 36 weeks corrected gestational age in a UK population

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Background: Neonatal thyroid ultrasonography has an important role in assessing thyroid anatomy in newborns with thyroid dysfunction. Hypothyroxinaemia of prematurity is commonly reported in premature neonates.

Objective and hypotheses: We aimed to determine the mean thyroid volume in infants with extreme prematurity at 36 weeks corrected gestational age (CGA) in a UK population compared to normative data reported in term infants in the literature.

Methods: We prospectively examined babies born below 28 weeks’ gestation. The thyroid gland was measured using a linear array transducer by a single observer. Thyroid volume of each lobe was calculated by the formula depth x length x width x π/6. The means and standard deviations were calculated.

Results: There were 55 babies (28 males) who had ultrasound assessment of the thyroid gland at 36 weeks’ CGA. Mean gestational age was 26.2 ± 1.0 weeks and mean birth weight was 893.8 ± 178.1 grams. Mean thyroid volume was 0.57mls ± 0.17.

Conclusions: In this study, premature infants born below 28 weeks’ gestation had their thyroid volume measurement assessed at 36 weeks’ CGA with a mean volume of 0.57 mls compared to a Scottish data of term infants reporting a mean thyroid volume of 1.6mls. In a Turkish population, the mean thyroid volume in preterm infants of gestational age 25-28 weeks was 0.4 mls and in term infants, their mean volume was 0.72 ml. Mean thyroid volumes in term infants from a Belgium population was 0.84 ml and from a German population was 1.1ml. Thyroid volume can vary from country to country due to iodine intake and may be dependent of gestational age at birth.

P2-d1-705 Perinatal and Neonatal Endocrinology 2

Infant girls have a postnatal activation of ovarian steroidogenesis associated with biological estrogen effects

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Background: An increase in testosterone levels and testicular and penile growth after the transient postnatal gonadotropin surge is well described in boys. In girls, analogous activation of ovarian steroidogenesis has not been substantiated. The timing and magnitude of the postnatal pituitary-gonadal activation differ between full term and premature infant boys.

Objective and hypotheses: To determine longitudinal changes in E2 levels during the first six months of life and biological estrogen effects by measuring simultaneous changes in E2 sensitive tissue, the mammary gland.

Methods: Urinary E2 levels were measured monthly from one week (D7) to six months of age (M1-M6) by LC-MS/MS and compared to manually measured mammary gland diameter (MGD) in 125 infants in three gestational age (GA) cohorts: full term (FT, GA>37 weeks, n=58, 29 boys), moderately premature (MPT, GA 32-36+6 weeks, n=42, boys 19) and very premature (VPT, GA<32 weeks, n=25, 14 boys).

Results: Urinary E2 levels in full term infants during the first six months of life (presented as median and quartiles, values below the detection limit of the assay are set to zero).

In girls, median E2 levels were lowest at D7, increased significantly by M2 in FT, by M1 in MPT and by M4 in VPT girls and then remained elevated until M6. Similar increase was not observed in boys and E2 levels were significantly higher in girls from M2 in FT, from M1 in MPT and by M4 in VPT girls and then remained elevated until M6. Similar increase was not observed in boys and E2 levels were significantly higher in girls from M2 in FT, from M1 in MPT and by M4 in VPT girls and then remained elevated until M6.

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Aim of this study was to evaluate the effect of PPARγ expression on placental development and thus to the maternal-fetal transfer of oxygen and nutrients that allow for prenatal growth.

Objective and hypotheses: To establish whether the placental PPARγ expression relates to placental and fetal growth.

Population, methods: Placentas (N=116) were collected at term delivery from singleton infants, who were born either small-, appropriate- or large-for-gestational-age [32 SGA, 55 AGA or 29 LGA]. Placentas and newborns were weighed at birth. Real-time PCR was used to assess placental expression of PPARγ as compared to the housekeeping gene GAPDH.

Results: PPARγ expression in placentas from AGA and LGA infants were found to be low in placentas of SGA fetuses and to associate positively to feto-placental growth. It remains to be studied whether feto-placental growth, if reduced, can be safely augmented by upregulating placental PPARγ expression.

Background: The nuclear receptor peroxisome proliferator activated receptor γ (PPARγ) contributes to placental development and thus to the maternal-fetal transfer of oxygen and nutrients that allow for prenatal growth.

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Background: Mutations in the TMEM70 gene are the most common cause of nuclear encoded ATP synthase deficiency resulting in a syndrome characterized by neonatal lactic acidosis, cardiomyopathy, and encephalomyopathy.

Objective: To present the first Turkish patient with TMEM70 mutation who presented with hypercalcemia and bilateral congenital cataract in addition to the typical previously reported features.

Patient and results: The patient is the second child of parents who are first degree cousins, born at term with a birth weight of 2230g. He had hypertrophic cardiomyopathy, bilateral cataract, inguinal hernia, cryptoorchidism and hypospadia. He also had clear facial dysmorphisms including retrognathia, high arched palate, long philtrum, flat and thin upper lip, arched eyebrows, prominent nasal bridge and upturned nares, large posteriorly rotated low set ears, flat occiput and upper gingival hypertrophy. The serum Ca levels 15 mg/dl with supressed PTH and resolved with IV fluid administration and prednisolone in 3 days. Metabolic screening revealed elevated serum lactate (6.9 mmol/L, normal range 0.9-2.2 mmol/L), and elevated serum ammonia (163.4 µmol/l normal range <86 µmol/l). Serum amino acid analysis revealed significantly elevated alanine and urinary organic acid analysis showed increased excretion of fumaric acid and methylglutaric acid. TMEM70 genetic analysis revealed the causative homozygous c.535C>T novel mutation which is predicted to result in substitution of a highly evolutionary conserved tyrosine residue into histidine (p.Y179H). Both parents were heterozygous for the mutation.

Conclusion: This is the first Turkish case of TMEM70 gene dysfunction caused by a novel c.535C>T mutation. In addition to typical features of the disease he had bilateral congenital cataract and hypercalcemia which further extends the clinical spectrum of TMEM70 gene defects. When suspected, TMEM70 genetic analysis should be performed before the traditional assessment of respiratory chain complex activities in muscle.
Methods: A total of 39 children (17 male; mean age: 9.5 years; range: 7.9-11.9 years) of normal development were recruited. All were born with a birth weight < 1000g (BW - SDS: -0.75 +/- 0.2; birth length (BL) - SDS: 0.39 +/- 0.3). All but eight (six male) were prepubertal. Clinical data were gathered retrospectively from patient files. Head circumference was measured at birth, at discharge and during regular annually visits. At the last visit at a mean age of 9.5 years, peak jump power (PJP) was quantified using a Leonardo jumping platform.

Results: 1) Main factors influencing postnatal growth of head circumference: HC was significantly associated with beginning of full enteral feeding (r=0.38; p=0.045); duration of respiratory support (r=0.58; p=0.001), and duration of catecholamine dependency (r=0.39; p=0.032). 2) Head circumference from point of discharge onwards correlates highly significantly with PJP later on.

Conclusions: Postnatal and not fetal growth of head circumference was associated with better coordinative skills at the age of 9.5 years in formerly ELBW infants. Early postnatal growth of HC was dependent on clinical condition of the infants. Beside duration of respiratory support and duration of catecholamine dependency it was the start of full enteral feeding, which was associated with better growth of HC.

<table>
<thead>
<tr>
<th>PJP - SDS</th>
<th>HC - SDS birth</th>
<th>HC - SDS discharge</th>
<th>HC - SDS 0.5 years</th>
<th>HC - SDS 2 years</th>
<th>HC - SDS 4 years</th>
<th>HC - SDS 9.5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>for age</td>
<td>r = 0.49 p = 0.005</td>
<td>r = 0.49 p = 0.005</td>
<td>r = 0.37 p = 0.003</td>
<td>r = 0.38 p = 0.001</td>
<td>r = 0.38 p = 0.019</td>
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</table>

P2-d1-710 Perinatal and Neonatal Endocrinology 2

Neonatal salt loss: not only 21-hydroxilase deficiency. Report of six patients with aldosterone deficiency or resistance

Diego Rinaldin1; Felix Riepe2; Florence Roucher1; Maria Dracopoulos2; Angelica Marsigli1; Piero Pirazzoli2; Antonio Balsamo1

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Background: Aldosterone Synthase Deficiency (ASD) and Pseudohypoaldosteronism Type 1 (PAH1) are rare causes of salt wasting in infancy.

Objective and hypotheses: characterization of 6 cases with salt loss not related to 21OHD

Methods: 6 patients analysed by means of CYP11B2, SCNN1A, B, C and NR3C2 genes.

Results: Patient 1 and 2 were girls presenting at 28 and 16 days of life, respectively, with vomiting, failure to thrive and salt loss. Normal female genitalia and cortisol production, low aldosterone levels and high PRA induced to suspect PAH1. Fludrocortisone and NaCl administration restored the electrolyte balance and weight gain. NR3C2 gene analysis revealed two novel mutations Y134X and L722X respectively. Patient 6 was a girl showing a clinical and laboratory pattern like that of the patient 4 and 5. The severer electrolyte disequilibrium and the higher Aldosterone levels than the previous two patients induced to suspect a systemic PAH1. Therapy with Parenteral saline was successful. Molecular analysis of the SCNN1A, B, C and NR3C2 genes didn’t identify mutations

Conclusions: After 21-OHD, ASD and PAH 1 have to be taken into consideration as a possible alternative causes of neonatal endocrine salt loss.

P2-d1-711 Perinatal and Neonatal Endocrinology 2

Normal values of anti mullerian hormone in boys during the first 4 years of life: evaluation of a new immunoassay (AMH GenII)

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Background: AMH is a good marker of Sertoli cell function and is very useful for evaluation patient 46,XY DSD. In 2009, we have reported the normal values of AMH using immunoassay AMH/MIS Elisa® (Immunotech-Coulter) in a cohort of 110 male neonates without abnormalities of external genitalia and detectable diseases. AMH values were determined in each neonate three times around 15thday, 3th and 9th months of life and were expressed in pmol/L as following: mean:±SD (value range): day13-20, 88±335 (286-2116); 2,8-5,1 months, 181±577 (704-3250); 8,5-9,8 months, 173±616 (639-4364).

Objective and hypotheses: The aim of this study was to continue this longitudinal study with an evaluation at 4 years of life and to compare our results with a new immunoassay AMH Gen II® Beckman Coulter.

Methods: The pre-analytical conditions regarding the collection of blood sample (serum, EDTA plasma), the storage (±4 °C or room temperature) and the time of the freezing after the collection (24h, 48h, 72h, 96h) have been evaluated using the two AMH kits. AMH values were determined in our cohort by the new AMH Gen II® Beckman Coulter kit.

Results: Whatever the conditions of blood collect, AMH value was the same with AMH/MIS Elisa®. The AMH values with the both AMH kits were identical if the blood was collected on EDTA, but decrease from about 40% with the AMH Gen II in the other conditions of collection. The measure plasma EDTA in the cohort of 110 obtained with AMH Gen II show the result in pmol/L. [mean±SD (min-max)] 3-20days: 1256±741.84 (413-2493); 2.8-5.1months : 2443.11 (811-5320), 8.5-9.8 months 2483.60±152.49 (916-6676); 3:9-4.1 years: 1459.93±613.93 (191-2826).

Conclusions: We must be careful at the preanalytic step for the measure of AMH with the kit AMH Gen II®. The normal values obtained with the immunoassay AMH Gen II® show normal value similar to the immunoassay AMH/MIS Elisa® (Immunotech-Coulter) provided that collect of blood sample with EDTA.

P2-d1-712 Perinatal and Neonatal Endocrinology 2

IGF-I levels are related to growth of preterm infants between term age and six months post-term

Monique van de Lagemaat1; Joost Rotteweel1; Harrie Laeber1; Mirjam van Weissenbruch1

1VU University Medical Center, Pediatrics, Amsterdam, Netherlands

Background: IGF-I regulates fetal growth during the third trimester as well as postnatal growth in term infants and its production is regulated by insulin and protein intake.

Objective and hypotheses: To study IGF-I in relation to growth and protein intake between term age and six months corrected age (CA). We hypothesized that IGF-I levels are related to protein intake and growth between term age and six months CA in preterm infants.

Methods: In 139 preterm infants (51% males, gestational age 30.3 ± 1.5 weeks, birth weight 1341 ± 288 gram) IGF-I levels were measured at term and at three and six months CA. Protein intake (g/kg/d) between term age and six months CA was calculated. At six months CA, infants were categorized as non-growth-restricted (weight and height ≥-2 SDS) or growth-restricted (weight and/or length <-2 SDS).

Results: Between term age and six months CA, change in IGF-I levels was associated with change in weight, length, and head circumference (weight: β=0.17, 95%CI 0.02-0.32; length: β=0.51, 95%CI 0.33-0.69; and head circumference: β=0.23, 95%CI 0.15-0.31; all p<0.001; Table 1). IGF-I levels were associated with insulin levels at term and at three months CA (term: β=0.13, 95%CI 0.07-0.18; p<0.001; three months: β=0.20, 95%CI 0.09-0.31, p=0.001), but not at six months CA. Protein intake was not associated with IGF-I levels.
Conclusions: In preterms, IGF-I plays an important role in growth regulation, independent of protein intake. The lack of association between IGF-I and insulin after three months CA suggests that growth regulation switches from nutrition/IGF-I dependent towards GH/IGF-I dependent growth.


Table 1. Bone mineral content in AGA and SGA infants between term and six months CA

<table>
<thead>
<tr>
<th></th>
<th>Term</th>
<th>six months CA</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>mean ± sd</td>
<td>N</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>139</td>
<td>315 ± 502</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>139</td>
<td>48.5 ± 2.3</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>139</td>
<td>35.8 ± 1.4</td>
</tr>
<tr>
<td>BMC (g) term age</td>
<td>139</td>
<td>46.6 ± 10.1</td>
</tr>
<tr>
<td>BMC (g) cm</td>
<td>135.4 ± 22.9</td>
<td>130.1 ± 25.7</td>
</tr>
<tr>
<td>ARMC (g) term age</td>
<td>98.2 ± 20.7</td>
<td>91.7 ± 22.8</td>
</tr>
</tbody>
</table>

Table 1. Bone mineral content in AGA and SGA infants between term and six months CA. Multivariate regression analyses with natural log transformed parameters and covariates for between-group differences; n.s.: not significant

Conclusions: The effect of low birth weight on bone mass is already present during early infancy. Tracking from infancy to adulthood may explain decreased adult bone mass in SGA preterm subjects.

P2-d1-7114 Perinatal and Neonatal Endocrinology 2

Penile and clitoral sizes of normal full term newborns in Korea

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Background: Abnormalities of genital sizes could be early signs of underlying endocrine diseases and previous reports show ethnic differences in normal length.

Objective and hypotheses: We studied to establish reference range of genital size in normal full term in Korea and compare that with other ethnicities. We present the largest study of penile and clitoral length measurements from Korea.

Methods: Normal full term males (n=440) and females (n=390) with appropriate birth weight for gestational age were included. Newborns with ambiguous genitalia, hypospadias, marked chordee, major congenital anomalies, or clinical evidence of endocrine disease were excluded. Penile length was measured with a ruler as the distance from the pubic bone to the tip of glans or stretched flaccid length. Clitoral length and width were measured with a tumorimeter in after the labia major were spread in frog-leg position. Measurements were taken 3 times by a single examiner during the first 3 days of life. The study was carried out in Gangnam medical center, CHA University over October 2011 to December 2011.

Results: The mean penile length was 2.7cm (standard deviation(SD) 0.3). The mean clitoral width and length were 6.1mm (SD 1.4) and 3.4mm (SD 0.9) respectively. All the penile length, clitoral width and length were significantly shorter than many previous reports in other ethnicities. (p< .0001)

Conclusions: This study establishes range for genital size of normal full term newborns in Korea which would help clinicians to diagnose early and treat an underlying diseases promptly.

P2-d1-715 Perinatal and Neonatal Endocrinology 2

Maternal dietary intervention prevents postnatal weight gain and impaired glucose tolerance in the offspring of obese mice

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University Hospital of Cologne, Department of Pediatrics, Cologne, Germany

Background: The global prevalence of pediatric overweight and obesity has increased substantially over the past decades, and the majority of obese children will remain obese through adulthood. One major risk factor for childhood overweight is maternal obesity.

Objective and hypotheses: However, the molecular mechanisms responsible for this phenomenon are so far ill-defined. More importantly, effective strategies for preventing this maternally transduced predisposition for childhood obesity are missing. This study aimed to investigate, whether maternal dietary intervention during pregnancy and lactation in obese dams is able to counteract the predisposition for obesity in their offspring.

Methods: Female C57BL-6N mice were rendered obese and glucose intolerant by high fat diet feeding from 3 to 14 weeks of age. After mating, the intervention group was changed to a standard chow, rich in carbohydrates and low in fat, for the duration of pregnancy and lactation, while the control group stayed on HFD.

Results: Strikingly, offspring of the intervention group showed a higher birth weight, but exhibited massively decreased postnatal weight gain, resulting in a 22.5% reduced body weight at postnatal day (P) 21 (p<0.001). Additionally, epigonalad fat pad weight was even reduced to 19.6% (p<0.001). Moreover, offspring of the intervention group remained significantly lighter than offspring of controls until adulthood. Furthermore, blood glucose levels at P21 were significantly lower in offspring of the intervention group (p<0.001) and glucose tolerance tests at P56 revealed ameliorated glucose tolerance as a consequence of maternal dietary intervention during pregnancy and lactation.

Conclusions: Thus, we conclude that improving maternal perinatal nutrition has impact on postnatal body weight gain and glucose tolerance in the offspring. Further experiments will shed light on the underlying mechanisms mediating this effect and will thereby contribute to the development of effective strategies for the prevention of obesity and its associated co-morbidities.
P2-d1-716 Perinatal and Neonatal Endocrinology 2

**Maternal and cord blood levels of leptin, adiponectin, resistin, ghrelin, IGF-1, and insulin: relationship with fetal growth**

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1Karadeniz Technical University, School of Medicine, Pediatric Endocrinology, Trabzon, Turkey; 2Karadeniz Technical University, School of Medicine, Biochemistry, Trabzon, Turkey

**Background:** Maternal bioactive substances, such as hormones and neuropeptides, are thought to be important for fetal development. However, all of the factors that affect fetal growth and birth weight still unknown.

**Objectives:** We investigated the maternal and cord blood levels of ghrelin, some adipokines and growth factors and their effects on fetal growth.

**Population and methods:** Maternal serum and cord blood levels of ghrelin, leptin, adiponectin, resistin, insulin, IGF-1, and insulin were measured 100 healthy mothers and their offspring at delivery. Maternal body mass index (BMI) and weight were obtained before pregnancy, at first and 2nd trimesters, and at delivery. Neonatal anthropometric characteristics (birth weight [BW] and length [BL], ponderal index, head and abdominal circumferences) and placental weight were recorded.

**Results:** There was a significant positive correlation between all the neonatal and ophthalmics and mother’s weight that measured before and during the pregnancy (p<0.05). Placental weights were correlated positively with BW and BL, head and abdominal circumferences (p<0.005). The maternal serum levels of leptin, IGF-1, glucose and insulin were higher than those cord blood (p<0.001), whereas maternal adiponectin levels were lower (p<0.01). Maternal and cord blood levels of resistin and ghrelin were not found different (p>0.05). There was a positive correlation between BW and maternal and cord blood levels of leptin and IGF-1 (p<0.005). The same relation was found for BL (p<0.005).

**Conclusions:** Our data showed that fetal growth was related to maternal weight not only during pregnancy but also before pregnancy. We found that leptin was associated with fetal growth, however other adipokines and ghrelin were not related to fetal growth.

P2-d1-717 Pituitary 2

**Utility of the timed-12h urine collections during gonadotropin releasing hormone analogue stimulation testing in monitoring therapy of central precocious puberty in girls**

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1The Fourth Affiliated Hospital of Soochow University, Pediatrics, Wuxi, China

**Background:** GnRH stimulation testing is frequently uncomfortable for children. Moreover, GnRH is commercially limited.

**Objective:** To determine whether timed-12h urinary gonadotropin (UGn) during GnRH analogue (GnRHa) stimulation testing can be used for monitoring GnRHa therapy.

**Methods:** In 19 girls with central precocious puberty (CPP) who were treated with diphereline (3.75 mg, i.m., q4w), GnRHa stimulation testing were performed before the initiation of treatment as well as 3 months after the beginning of the therapy. Following injecting triptorelin (08:30 am, Decapetyl, 0.1 mg, s.c.), consecutive double timed-12h urine samples were respectively collected. Gonadotropin were assayed by immunochemiluminometric assays (ICMA).

**Results:** One in 19 cases had poor clinical efficacy. In the other 18 cases who had good efficacy, the correlation coefficient between the serum peak LH (PLH) and the content (concentration × volume) of the first urinary LH (FULH) was 0.754, and for PLH and the second urinary LH (SULH) content 0.697; for serum peak FSH (PFSh) and the first urinary FSH (FSFSh) content 0.784, and for PFSh and the second urinary FSH (SFSh) content 0.831. And in these 18 girls, the means of PLH, PFSh and UGn content be 0.831. And in these 19 girls, the means of PLH, PFSh and UGn content be 0.017 — 0.540 IU, SUFSH content 0.417 — 3.215 IU. FULH content 0.043 — 0.821 IU, FUFSH content 0.673 — 6.725 IU; SULH content 0.185 — 15.131 IU, SUFSH content 8.779 — 57.722 IU. After 0.831. And in these 18 girls, the means of PLH, PFSH and UGn content be 0.784, and for PFSH and the second urinary FSH (SUFSH) content 0.754, and for PLH and the second urinary LH (SULH) content 0.043 — 0.821 IU, FUFSH content 0.673 — 6.725 IU; SULH content 0.185 — 15.131 IU, SUFSH content 8.779 — 57.722 IU. After 0.831. And in these 18 girls, the means of PLH, PFSH and UGn content be 0.784, and for PFSH and the second urinary FSH (SUFSH) content 0.754, and for PLH and the second urinary LH (SULH) content 0.043 — 0.821 IU, FUFSH content 0.673 — 6.725 IU; SULH content 0.185 — 15.131 IU, SUFSH content 8.779 — 57.722 IU. After 0.831. And in these 18 girls, the means of PLH, PFSH and UGn content be 0.784, and for PFSH and the second urinary FSH (SUFSH) content 0.754, and for PLH and the second urinary LH (SULH) content 0.043 — 0.821 IU, FUFSH content 0.673 — 6.725 IU; SULH content 0.185 — 15.131 IU, SUFSH content 8.779 — 57.722 IU. After

**Conclusions:** It is concluded that double timed-12h urinary gonadotropin content assayed by ICMA during GnRHa stimulation testing provides an effective, noninvasive methods for monitoring therapy in girls with CPP.

P2-d1-718 Pituitary 2

**Different reasons for hyponatraemia in a child with panhypopituitarism**

Sharon Lim

Broomfield Hospital, Paediatric Department, Chelsmford, United Kingdom

**Background:** Growth hormone (GH) influences salt and water handling in the renal tubules. Tubular response to DDAVP is influenced by cortisol. Hypotha-lamic osmoreceptors may have reduced sensitivity from chronic Valproic acid administration, resulting in antiurea. In a child with panhypopituitarism, epilepsy and recurrent chest infections, medical management is a challenge.

**Methods:** A 10-year-old girl with panhypopituitarism and cerebral palsy secondary to Group B streptococcal meningitis as a neonate had full hormonal replacement therapy since infancy. Sodium levels were always stable in the high normal range. She became epileptic aged 7 and was started on Sodium Valproate. Recurrent chest infections occurred age 8 and she became colonised with Pseudomonas and required occasional home oxygen. In the same year, she stopped feeding orally and became totally gastrostomy fed on a fixed volume of 1000ml a day. Hydrocortisone was changed to prednisolone at aged 7 to facilitate the effects of DDAVP through the day. GH was stopped aged 9 when it appeared that she was not growing very well. She had been quite ill that year with her chest. Her weight escalated despite a calorie reduction in feeds. Prior to stopping GH, her plasma sodium was 138 mmol/L. This fell to 129 mmol/L despite sodium supplements of 3mmol/kg/day. Urine output was < 3ml/kg/hr despite dose reduction of DDAVP. Urinary sodium peaked at 133 mmol/L. She was admitted for input output assessment and blood profile whilst hydrocortisone was re-introduced 6 hourly and DDAVP and sodium supplements stopped.

**Results:** Hyponatraemia and natriuresis persisted till GH was reintroduced to 0.026mg/kg/day. Urinary sodium fell to <10 mmol/L in the first week of treatment. Urine output was < 3ml/kg/hr on no DDAVP.

**Conclusions:** There are a number of reasons for this complex child to have hyponatraemia, the most influential one being GH deficiency. This, coupled with the antidiuretic effect of valproic acid must not be underestimated. 6-hourly dosing of hydrocortisone ensures residual DDAVP works effectively.
P2-d1-720 Pituitary 2
Anterior pituitary hormone deficiency in GHD children with pituitary stalk interruption syndrome
Hongshuang Che1; Minlian Du2; Boning Luo2
1The First Affiliated Hospital of Sun Yat-sen University of Medical Sciences, Paediatric Department, Guangzhou, China; 2The First Affiliated Hospital of Sun Yat-sen University of Medical Sciences, Radiology Department, Guangzhou, China
Objective: To investigate the anterior pituitary hormone secretion in growth hormone deficiency children with pituitary stalk interruption syndrome (PSIS).
Method: By reviewing the data of GHD children with PSIS in our hospital for recent 10 years, we analyze the incidence of the other anterior pituitary hormone deficiencies in those GHD children with PSIS, both before and after rhGH treatment.
Results: There were 69 growth hormone deficiency children with PSIS (53 boys, 16 girls) out of 348 growth hormone deficiency patients who were carried out MRI scans of the hypothalamo-hypophyseal tract. Of the 69 children with PSIS, 66 were complete growth hormone deficiency, and 33 were multiple pituitary hormone deficiency. MRI scans showed that 30 out of 69 PSIS children were with thin stalk and 39 with missing stalk. No statistically significant difference was found in the ratio of CPHD between the thin stalk group and missing stalk group (93.33% vs. 97.44%, P>0.05), but the ratio of multiple pituitary hormone deficiency in the thin stalk group were lower than that of the missing stalk group (83.33% vs. 97.44%, P<0.05).
Conclusion: The result indicated that the majority children with PSIS were MPHD. MRI scans of the hypothalamo-hypophysial tract should be carried out for all GHD patients. Carefully monitoring the other anterior pituitary hormone deficiencies is clinically important for GHD children with PSIS in order to early diagnose and adequately manage the possible deficiency happened later during rhGH treatment.

P2-d1-721 Pituitary 2
Nocturnal urinary gonadotropin in evaluation of precocious puberty in girls
Zhuanghui Xu1; Yaqing Ma1; Tingting Zhang2; Qing Wang3
1the Fourth Affiliated Hospital of Soochow University, Pediatrics, Wuxi, China
Background: GnRH test is a gold standard for confirming the diagnosis of central precocious puberty (CPP), an accurate but at times not always comfortable method.
Objective and hypotheses: To assess the diagnostic value of the nocturnal urinary gonadotropin for precocious puberty in girls.
Methods: Sixty-three girls with precocious puberty, in which 42 girls with CPP, other 21 girls with non-CPP, were hospitalized for gonadotropin releasing hormone analogue stimulating test. Timed 12-hour nocturnal spontaneous urine samples were collected before the test. Serum samples, which were obtained at midnight before the test and 0 min during the test, were respectively regarded as the samples of spontaneous nocturnal and diurnal gonadotropin. Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in serum and urine were assayed by immunochemiluminometric assay.
Results: The correlation coefficient between the urinary LH quantity (concentration×volume) and serum peak LH (PLH) was 0.597 (P<0.001), for diurnal spontaneous serum LH and PLH 0.514 (P<0.001), for nocturnal spontaneous serum LH and PLH 0.423 (P<0.01). The values under the receiver operator characteristic curves of urinary LH quantity, diurnal spontaneous serum LH, nocturnal spontaneous serum LH for the diagnoses of CPP were 0.825, 0.680 and 0.654, respectively. The sensitivity and specificity for the diagnoses of CPP were respectively 71.4% and 90.5% when urinary LH quantity was no less than 0.113IU.
Conclusions: Noninvasive determination of timed 12-hour nocturnal spontaneous urinary gonadotropin by immunochemiluminometric assay can be as a screening tool for CPP in girls, the value of nocturnal urinary LH quantity may be higher than that of spontaneous LH.

P2-d1-722 Pituitary 2
Factors associated with social outcomes in patients with hypotalamic pituitary conditions and growth hormone deficiency
Helena Gleeson1; Peter Jonsson1; Peter Clayton2; Marta Korbonits3; Maria Kollowazska-Haggstrom1; Andy Toogood1; Ann-Charlotte Akerblad4; Leahster Royal Infirmary, Department of Endocrinology, Leicester, United Kingdom; 1KIMS, Pfizer Endocrine Care, Sollentuna, Sweden; 2Royal Manchester Children’s Hospital, Manchester Academic Health Sciences Centre, Manchester, United Kingdom; 3Barts and the London School of Medicine, Department of Endocrinology, London, United Kingdom; 4Pfizer Endocrine Care, KIMS, Sollentuna, Sweden; 5Queen Elizabeth Hospital Birmingham, Department of Endocrinology, Birmingham, United Kingdom
Background: Physical but not social outcomes in patients with growth hormone deficiency (GHD) have been studied. Objective: To describe the social outcomes of growing up with GHD.
Methods: KIMS patients (n=5675) who completed a Patient Life Situation Form (KIMSLPSF) were divided by age of hypothalamic pituitary condition onset (childhood onset (CO) <16yrs, late adolescence/young adulthood onset (YAO) 16–25yrs, adult onset (AO) ≥25yrs). Data from individual patients were analysed in 3 age bands (25-35, 35-45, 45-55), using data closest to the middle of each age band. A patient can be represented in more than one age band but only once in each age band. Chi2 test was used for pairwise proportions and forward stepwise regression to find factors.
Results: CO and YAO were less likely to live independently, get married and have children compared with AO patients (figure).

Factors associated with independent living and marriage in age bands 25-45 were male gender, older age at condition onset, fewer pituitary hormone deficits, lower BMI and taller height. The only difference in the age band 45-55 was that women were more likely to be married than men. Longer duration of GH therapy was significant only for independent living in age bands 25-45. Having a non acquired aetiology (GHD not secondary to tumour or radiotherapy) was a factor for being married in age bands 25-35 and 45-55 and
for living with parents in oldest age band. Previous surgery was a factor for independent living and being married in age band 25-35 and irradiation for living with parents in age band 35-45.

Factors associated with both having children were older age at condition onset, fewer pituitary hormone deficits and longer duration of GH-treatment.

Conclusions: Patients affected by a hypothalamic pituitary condition at a younger age with more severe hypopituitarism are less likely to achieve social milestones.

### Table P2-d1-723 Pituitary 2

<table>
<thead>
<tr>
<th>Aetiologies and clinical characteristics of childhood central diabetes insipidus (Geneval et al.; Pourfarzam et al.; Ermel Ulusoy); Ayca Altintil; Atilla Buyukgebiz; Ece Bober</th>
</tr>
</thead>
<tbody>
<tr>
<td>1Dokuz Euly University, Pediatric Endocrinology, Izmir, Turkey; 2Dokuz Euly University, Pediatrics, Izmir, Turkey; 3Bilim University, Pediatric Endocrinology, Istanbul, Turkey</td>
</tr>
</tbody>
</table>

Background: Central diabetes insipidus is characterized with deficiency in vasopressin secretion and extremely large volumes of dilute urine that results in polyuria and polydipsia. Common causes of childhood diabetes insipidus are central nervous system (CNS) neoplasms, neurosurgical intervention, Langerhans’- cell histiocytosis, CNS malformations, CNS infections and trauma. Approximately 50% of cases of childhood DI are idiopathic.

Objective and hypotheses: To evaluate the clinical, anthropometric, hormonal and radiological characteristics of children with central diabetes insipidus.

Methods: Case records of 34 children (22 males) with documented central diabetes insipidus were reviewed. The mean age at diagnosis was 76.5±67.5 months (range 1-192 months). All the patients underwent anterior pituitary function assessment and magnetic resonance imaging of pituitary at diagnosis. The median duration of follow-up was 94.4±54.1 months.

Results: The etiology of central diabetes insipidus was organic in 22 patients (64.7%), trauma in 2 patients (5.9%) and idiopathic in 10 patients (29.4%). Organic causes consisted of craniopharyngioma in 7 patients, Langerhans’- cell histiocytosis in 4 patients, germinoma in 4 patients, holoprosencephaly in 1 patient, cavernous hemangioma in 1 patient, Rathke’s cleft kist in 1 patient and autoimmune polyendocrinopathy in 1 patient. Anterior pituitary hormone deficiencies were documented in 18 patients (53%). Organic central diabetes insipidus group had a greater proportion anterior pituitary hormone deficiency when we compared with the idiopathic group (respectively, 66% & 10%, p=0.007). The final height of patients with organic etiology were significantly lower than the idiopathic group (155 cm and 178 cm respectively, p=0.021).

Conclusions: Central nervous system tumors are the most frequent cause of organic etiology. Findings in this study suggest that accompanying anterior pituitary hormone deficiencies and short stature may be considered as indicators of organic etiology.

### Table P2-d1-724 Pituitary 2

<table>
<thead>
<tr>
<th>Hormone deficiency</th>
<th>Years since tumor surgery (mean ± S.D.)</th>
<th>Years since radiotherapy (mean ± S.D.)</th>
<th>Years since chemotherapy (mean ± S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>2.9 ± 3.4</td>
<td>3.4 ± 3.5</td>
<td>3.8 ± 3.7</td>
</tr>
<tr>
<td>GH</td>
<td>3.9 ± 2.8</td>
<td>4.1 ± 2.1</td>
<td>4.4 ± 2.8</td>
</tr>
<tr>
<td>ACTH</td>
<td>2.6 ± 3.9</td>
<td>3.6 ± 4.4</td>
<td>5.2 ± 5.5</td>
</tr>
<tr>
<td>LH/FSH</td>
<td>7.3 ± 3.7</td>
<td>8.1 ± 3.1</td>
<td>8.7 ± 3.6</td>
</tr>
</tbody>
</table>

Conclusion: Children undergoing treatment for central nervous system tumors are at risk of hormonal deficiencies, as well as obesity, which should be assessed throughout follow-up.

### Table P2-d1-725 Pituitary 2

<table>
<thead>
<tr>
<th>Hyperprolactinaemia in the paediatric age group. Clinical description and management in 12 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laura Losada; Miquel Guisany; Diego Yeste; Mariam Alibusu; Lina Velázquez; Antonio Carrascosa</td>
</tr>
</tbody>
</table>

Background: Hyperprolactinaemia is an uncommon diagnosis in childhood and adolescence.

Objective and hypotheses: A single-centre experience in the diagnosis and treatment of this entity is presented.

Methods: Patients: 12 patients (2 boys, 10 girls; age range 10-18 years) diagnosed with hyperprolactinaemia and a follow-up of 6 months to 22 years.

Results: Mean prolactin values in girls were: 146.12 ng/ml (59-343 ng / ml). Clinical findings were: galactorrhoea (n:3), oligomenorrhoea (n:3), primary amenorrhea (n:2) and secondary amenorrhea (n:2). Mean prolactin values in boys were: 463 ng/ml (380-546ng/ml) and manifest delayed puberty (n:1) and puberty and growth arrest (n:1). Function was within normal range. Ophthalmological and neurological impairments were not present at diagnosis or during follow-up. MRI confirmed the presence of a tumour in 6 of 12 patients, macroadenoma: in 1 boy and 2 girls and microadenoma in 3 girls. Drug therapy was indicated in 9 patients (7 girls, 2 boys): bromocriptine (n:3) at doses from 2.5 to 15 mg / day and cabergoline (n:6) at doses of 1 to 2 mg / week. 3 patients did not require drug therapy: 2 received risperidone indicated by a psychiatrist, and 1 was a microprolactinoma asymptomatic at the time of diagnosis. With a dose reduction or even discontinued at resolution of symptoms or after 2 years, with reduction prolactin and disappearance and / or tumor shrinkage. Prolactin levels after the onset of treatment at 1 to 1.5 months were within normal limits, symptoms were resolved between 3 and 6 months in all groups.

Conclusions: Prolactinomas are rare in children and adolescents, with a higher prevalence in girls. In our experience, pubertal development abnormalities are primarily associated with boys. Whereas in girls, symptoms are associated with menstrual cycle alterations. Prolactin values > 250 ng / ml are associated with macroprolactinomas.

### Table P2-d1-726 Pituitary 2

<table>
<thead>
<tr>
<th>Pituitary duplication and precocious puberty in a boy</th>
</tr>
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<tbody>
<tr>
<td>Sarah Castets; 1Mirjam Dirlewanger; 1Tristan Zand; 1Valérie Schwitzgebel</td>
</tr>
</tbody>
</table>

1Geneva University Hospital, Pediatric Endocrinology and Diabetology, Geneva, Switzerland; 2Geneva University Hospital, Pediatric Radiology, Geneva, Switzerland

Background: Pituitary duplication is a rare malformation. Most of the cases are associated with severe congenital craniofacial, neural and arterial midline anomalies, but in some cases pituitary duplication is isolated. Its association with precocious puberty is well established in girls.

Poster Presentations

224 Horm Res 2012;78(suppl 1)
Objective and hypotheses: To describe the first case of pituitary duplication with precocious puberty in a boy.
Methods: We used a combined analysis of MRI and CT to visualize the hypothalamic and pituitary area and to reconstruct 3D images.
Results: This communication describes precocious puberty in a boy without evident dysmorphias, for whom MRI shows two separate glands, two respective stalks, ectopic neurohypophysis, tubomamillary fusion, fenestration and duplication of the basilar artery and vertebral anomalies from C1 to C7. The patient was treated successfully with an LHRH agonist. A majority of patients described in the literature have an abnormal hypothalamic area with thickening of the hypothalamus, sometimes described as a pseudo-hamartoma, and sometimes as a tubomamillary fusion, as is the case here. The embryological mechanisms of pituitary duplication are not well understood. The pituitary gland develops at an early stage (25-26 days), from an adhesion of neuroectodermal and stomodeal ectoderm, closely related to the rostral end of the notochord and the prechordal plate. Various hypotheses have been proposed to explain the malformation, including duplication of the prechordal plate and rostral end of the notochord, or primary disruption in the area of the neuroectodermal adhesion.
Conclusions: Even if more and more genes involved in pituitary development are identified, with advancements in the understanding of the physiopathological basis of pituitary hormone disease, all known genes so far are involved in pituitary hormone deficiency and pituitary hypoplasia, and to date no gene has been associated with pituitary duplication and precocious puberty.

**P2-d1-728 Pituitary 2**

**Prolactinomas in children and adolescents: a single centre experience**

Vrinda Saraff; Wolfgang Hogler; Nick Shaw
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Background: Prolactinomas are uncommon pituitary tumors in the paediatric population, however they account for 50% of the pituitary adenomas. They are more common among adolescent girls.

Objective and hypotheses: To establish the mode of clinical presentation, MRI findings and response to treatment of the children who presented with a diagnosis of prolactinoma to a tertiary paediatric centre over a period of 9 years between 2003 to 2011.

Methods: Retrospective case note review was performed for the 12 paediatric patients who were identified and treated for a prolactinoma between 2003 to 2011.

Results: The mean age at presentation was 13.8 ± 1.5 years (11-16yrs) with 2 boys and 10 girls. 11 patients (91%) were diagnosed to have a macroadenoma. The most common clinical presentation was headache in 58% of the patients, with galactorrhea and secondary amenorrhea in 50%. Visual disturbances and lethargy were less common presenting symptoms (16%). Hypothyroidism was the most common comorbidity seen in 50% of the patients, whilst growth hormone deficiency and diabetes insipidus occurred as sequel to surgical intervention in 1 patient. All the patients were initially commenced on Cabergoline (average dose of 500 micrograms/week) with prolactin levels halved by three months of treatment in all 12 patients. Shrinkage of the prolactinoma on MRI scan at 6 months post drug treatment was seen in 75% cases. Improvement in symptoms was noted by 50% of the patients by 3 months. Two patients who failed medical treatment with persistently raised prolactin levels and lack of shrinkage of the adenoma underwent surgery with one patient requiring additional radiotherapy.

Conclusions: The majority of patients showed a good response to medical treatment within six months. Absence of significant response to medical treatment biochemically and on pituitary imaging by 12 months was more likely to require surgical intervention.

**P2-d1-727 Pituitary 2**

**A case of Shapiro's syndrome treated successfully with a combination of clonidine and propranolol: a 1-year follow up**

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Background: Shapiro syndrome is a disorder characterized by episodes of spontaneous periodic hyperthermia and hyperhidrosis. The agensis of the corpus callosum is usually but not always present. Some patients exhibit polyuria and polydipsia during the attacks. There are only about 50 cases reported in the literature. There is no definite data about the treatment of the syndrome due to its rarity. Anticonvulsants, clonidine, cyproheptadine, glycopyrrolate, bromocriptine, chlorpromazine, or sympathectomy has been used, with varying responses.

Case: A 2-year-old-girl was admitted to the hospital due to complaints of profuse sweating and cooling attacks associated with polyuria and polydipsia for two months. Body temperature was 33-34°C during these episodes which occurred almost daily and lasted for about 2 hours. She did not respond to heating with warm clothes. Laboratory findings including urinanalysis, total blood count, serum glucose and electrolytes, renal and liver function tests, acute phase reactants, thyroid function tests, and serum cortisol levels were all normal excluding any infectious or endocrinological disease, particularly diabetes insipidus. Cranial magnetic resonance imaging was normal. The patient was diagnosed with Shapiro’s syndrome. She had no response to carbamazepine (20 mg/kg) treatment. Clonidin (100 mcg/1.73 m2/d) was used with partial reduction in frequencies of episodes. After addition of propranolol (0.5 mg/kg) to the treatment, the intervals of the episodes further prolonged and became two to three months. No adverse effect occurred during a one year follow up.

Conclusions: Although rare, Shapiro’s syndrome should be considered in the differential diagnosis of patients with polyuria and polydipsia. We describe our experience with a case of Shapiro’s syndrome successfully treated with a combination of clonidine and propranolol.

**P2-d1-729 Pituitary 2**

**Low-dose mitotane in pediatric Cushing’s disease**

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Background: The main clinical feature of pediatric Cushing’s disease is growth retardation. The conventional treatment is the transphenoidal adenectomy yet with an important 50% failure rate. It is therefore necessary to control the cortisol secretion through a medical treatment. Mitotane is an adrenolytic drug used in metastatic adrenocortical carcinomas.

Objective and hypotheses: The aim of this study is to describe its efficacy and safety in pediatric Cushing’s disease as an alternative to the transsphenoidal surgery.

Methods: This is a retrospective study reporting 26 pediatric Cushing’s disease patients, 7 out of 26 were treated with mitotane. I compared growth ve
locity, height, body mass index and puberty in «cured after surgery» and «mitotane» groups.

Results: 1) 69% of the patients were cured after surgery and 22% relapsed. Surgeon experience and visualization of the adenoma on MRI were predictive factors of successful adrenalectomy. Postoperative corticosterone deficiency was associated with successful surgery (p=0.001). 2) After 3 months of treatment, the cortisol secretion was controlled. In our hands, mitotane was safe, except for transient adrenal insufficiency in some patients. We found no correlation between urinary cortisol and mitotane blood levels, which should not be used to monitor the treatment. 3) Low-dose mitotane treatment restores the growth velocity, pubertal development and improves the body mass index z-score. Moreover, in one patient, we observed the progressive growth of the pituitary adenoma on MRI over the 40 months of treatment, which allowed a successful surgery.

Conclusions: Low-dose mitotane may be used in pediatric Cushing’s disease, after surgery failure or in patients without adenoma identified on MRI. There is a need for a multicenter clinical trial to demonstrate the efficacy and safety of mitotane after these pilot observations.

P2-d2-730 Programming/Epigenetics 2  
Birthweight is directly related to body mass index and inversely related to blood pressure levels in school children  
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Background: Since the so-called Barker Hypothesis, which pointed to the intrauterine life environment an important determinant of metabolic conditions, much has been published about the association between birthweight, hypertension and obesity. However, few studies have explored this association in children, especially in developing countries.

Objectives and hypotheses: To evaluate the relation among birthweight, childhood body mass index (BMI) and blood pressure (BP) levels in schoolchildren from a medium-sized city in southeast, Brazil.

Methods: In a sample of 175 children aged 6-13 years, weight, height and BP levels were measured three times. BMI and BP levels were converted to standard deviation scores (SDS) adjusted to sex and age (BMI) or sex, age and height (BP levels). Birthweight was accessed through parents’ interviews and hospital registries (child’s card). Pearson’s test, One Way ANOVA and linear regressions were performed on statistics.

Results: It was observed a positive and linear correlation between the present BMI SDS and the birthweight SDS (p=0.001). BMI SDS got average +0.5, +0.2 and +0.7 in children classified as small, adequate or large for gestational age, respectively (p<0.009). Blood pressure levels SDS were positively influenced by the child’s BMI (p=0.003 for systolic and p=0.005 for diastolic BP). By the other side, there was a negative and linear association between birthweight and systolic BP levels SDS (p=0.03). Hence, the most important predictor of BP levels was the weight gain from birth to school age, which explained 5% (p=0.019) of systolic and 4% (p=0.001) of diastolic BP variation.

Conclusions: In this sample, the combination of low birthweight and high BMI in school age is an important predictor of increased blood pressure levels in children.

P2-d2-731 Programming/Epigenetics 2  
Health profile of young adults born preterm: negative effects of rapid weight gain in early life  
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Background: Early postnatal weight gain is associated with determinants of cardiovascular disease (CVD) and type 2 diabetes (DM2) in adults born term. However, this association remains to be elucidated in adults born preterm.

Objective: To investigate the association of weight gain during different periods, and weight trajectories in early life after preterm birth with determinants of CVD and DM2 in early adulthood.

Methods: Observational study using longitudinal data collected in the PREMS study in 162 healthy participants born preterm (gestational age <36 weeks), aged 18 to 24 years. Associations between early and first-year growth, tempo of weight gain, and determinants of CVD and DM2 in young adults born preterm were determined.

Results: Weight gain, adjusted for length, in the period from birth up to term age and in the first 3 months after term age, was positively associated with body fat percentage and waist circumference at 21 years. Weight gain in the first 3 months after term age was in addition positively associated with total cholesterol and LDL-c levels in early adulthood. Subjects with the highest gain in weight from birth to term age (highest quartile) had higher body fat percentage, waist circumference, acute insulin response, and disposition index in early adulthood than the subgroups with moderate and low gain in weight. Rapid catch-up in weight during the first 3 months after term age, resulted in a higher fat percentage, waist circumference and serum triglycerides level than slower catch-up in weight. (Figure 1)

Conclusions: Accelerated neonatal weight gain compared to gain in length after preterm birth (immediately after birth and during the first three months after term age) is associated with risk factors for cardiovascular disease in early adulthood, and should therefore be avoided.

P2-d2-732 Programming/Epigenetics 2  
Children conceived by ovarian stimulation have shorter stature  
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Background: Approximately 5% of children in the developed world are conceived with the help of fertility drugs for ovarian stimulation alone (OSA). This is in addition to the 2 to 4% of children conceived by IVF. Ovarian stimulation is also part of the IVF process, and studies have shown that IVF children are taller than naturally conceived children.

Objective and hypothesis: We aimed to determine if children conceived with OSA would differ from naturally conceived children of fertile (time to conception<12 months) and subfertile (time to conception>12 months) parents. We hypothesised that OSA children would be taller than naturally conceived children.

Methods: Children aged 3–10 years (term, singletons) were recruited and allocated into 3 groups: i) conception following OSA, & naturally conceived children of ii) subfertile and iii) fertile parents. All children had height, weight,
body composition by DEXA scan and fasting serum IGF-1, IGF-2, IGFBP3, lipids, glucose and insulin levels recorded. Children’s heights & BMI were expressed as SDS and corrected for genetic potential.

Results: 352 children (mean age 7.25±0.2 years) were studied: 84 OSA subjects, 54 subfertile and 214 fertile controls. Naturally conceived children of subfertile and fertile parents did not differ in measured outcomes. OSA children were shorter than subfertile (SDS score -0.08 ±0.09 vs 0.32 ±0.07,P<0.001) and fertile (SDS score -0.08 ±0.09 vs 0.45 ±0.10,P<0.004) control children. OSA children had lower corrected BMISDS than subfertile (SDS score -0.90 ±0.15 vs -0.37 ±0.17;P<0.05) and fertile (-0.90 ±0.15 vs -0.34±0.10,P<0.008) controls. The only detected difference in serum metabolites between groups was that fasting glucose was lower in OSA children than in fertile controls (4.62 ±0.07 vs 4.81 ±0.04,P<0.006).

Conclusions: Children conceived by ovariian stimulation are, on average, 2 to 3 centimetres shorter than naturally conceived children. We speculate that this height difference may be due to ovariian stimulation leading to changes in per-conceptual imprinting and consequent altered fetal programming.

P2-d2-733 Programming/Epigenetics 2
First born children have reduced insulin sensitivity and taller stature
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Background: There is a strong trend towards couples having fewer children, leading to an increase in the population of first born compared to later born children.

Objective and hypotheses: We aimed to determine if birth order influences childhood physical or metabolic parameters. We hypothesised that first born children would have a different asexualogical and metabolic profile to later born children.

Methods: Prepubertal children aged 3–10 years, (born at full term and not SGA) were recruited and grouped by birth order. All children had height, weight, body composition by DEXA scan and fasting serum IGF-1, IGF-2, IGFBP3, lipids, leptin, adiponectin, glucose and insulin levels recorded. Children’s heights and BMI were expressed as an SDS, and corrected for mean parental height and BMI SDS. A subgroup of children underwent 24 hr ambulatory BP monitoring and a frequently sampled IVGTT to determine insulin sensitivity with the minimal model. Results are expressed as mean ±SEM.

Results: 394 children (mean age 7.4±0.9 years) were studied: 188 first, 146 second, and 60 third borns. First borns were taller than second (HISS-DS-MPHSIDS 0.41±0.06 vs 0.18±0.07, P<0.002) and third borns (HISS-DS-MPHSIDS 0.41±0.06 vs -0.03±0.16, P<0.001), when adjusted for their genetic potential.

Second borns were also taller than third borns (P=0.011). First borns (n=32) were less insulin sensitive than second and third borns together (n=45) (Si 10.7±0.82 vs 13.10±0.94, P<0.033). Across all birth order groups, there were no differences in BMI, body composition, ambulatory BP or any measured metabolites.

Conclusions: Birth order has a graded effect on height, with incremental height reduction from first to third birth order. The additional novel finding of reduced insulin sensitivity in first born children may be a risk factor for later development of type 2 diabetes in this growing population.

P2-d2-7335 Puberty and Neuroendocrinology 2
Efficacy of the single luteinizing hormone level after GnRH agonist administration for the therapeutic monitoring of girls with central precocious puberty
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Background: The effectiveness of gonadotropin releasing hormone (GnRH) agonist therapy in central precocious puberty (CPP) depends on the suppression of leuteinizning hormone (LH) secretion. The intravenous GnRH stimulation test is the gold standard for evaluating LH suppression, however, it is difficult for pediatric patients because of the multiple blood sampling.

Objective and hypotheses: The purpose of this study was to determine the utility of single luteinizing hormone level after GnRH agonist injection for the therapeutic monitoring of CPP.

Methods: One hundred and forty-eight females with CPP who have been treated with GnRH agonist were included. During the therapy, it was assessed whether their pubertal development was suppressed by assessing their height standard deviation score (SDS), bone age, and pubertal stage. Every six months their serum LH and follicular stimulating hormone (FSH) were measured using immunoradiometric assay. Their estradiol was also assayed using radioimmunoassay two hours following GnRH agonist administration.

Results: The mean of the onset age, bone age, and chronological age were 7.2±0.93, 10.1±1.1, and 8.2±0.94 years, respectively. There were eight patients with pathologic intracranial lesions including hormatoma, hydrocephalus, meningitis, astrocytoma, and Rathke’s cleft cyst. The basal LH and peak LH levels were 1.56±1.1 and 12.8±12.1 IU/L, respectively. In 39 females with central precocious puberty, the pubertal development was not sufficiently suppressed even after one year of therapy. The receiver operating characteristic (ROC) curve shows that the cutoff value of LH for pubertal suppression is less than 2.5 IU/L. The area under the curve (AUC) is 0.674.

Conclusions: The cut-off value of 2.5 IU/L of the two-hour LH following subcutaneous GnRH agonist injection, is adequate for therapeutic monitoring of females with central precocious puberty because of its convenience and cost effectiveness.
Objective: Girls with precocious puberty have high LH levels and advanced bone age more than 1 year above chronological age. Obese children enter puberty at earlier ages than nonobese children. The mechanisms whereby obese children grow faster since early childhood are not well defined. We analyzed the effects of obesity on luteinizing hormone secretion to gonadotropin-releasing hormone (GnRH) tests in girls with precocious puberty.

Methods: Clinical data was collected retrospectively by chart review from the Pediatric Endocrine Unit at Ajou University Hospital. A total of 673 subjects with idiopathic precocious puberty who completed a gonadotropin-releasing hormone stimulation testing between 2008 and 2010 were included in the study.

Results: In Tanner 2 girls, peak stimulated LH levels on GnRH test were 8.5 ± 7.2, 7.1 ± 5.5, and 6.0 ± 4.9 mIU/mL among normal weight, overweight, and obese subjects, respectively (P < 0.001 for all comparisons). In Tanner 3 girls, peak stimulated LH levels were 13.4 ± 11.9, 8.8 ± 7.4, and 7.6 ± 7.2 mIU/mL, respectively (P < 0.019 for all comparisons). However, in Tanner 4 and 5 girls, peak stimulated LH levels were not significantly different among normal, overweight, and obese children. On multivariate analysis, BMI was significantly and negatively associated with peak LH (β = -0.432, P = 0.001).

Conclusion: In girls with precocious puberty, obesity affects peak stimulated LH levels. In addition, obesity may directly modulate skeletal growth and sexual maturation in early puberty.

Background: Puberty is a period characterized by growth spurt and rapid change in body composition. The effect of GnRH agonist therapy for central precocious puberty on bone mineral density is unclear.

Objective and hypotheses: We demonstrated changes of bone mineral density and body composition in subjects with central precocious puberty who were treated with GnRH agonist for more than three years.

Methods: One hundred ninety-five Korean girls with central precocious puberty were treated with GnRH agonist and, among these subjects, 39 patients were treated for more than three years. The changes in bone mineral density and body compositions were tested with analysis of variance with repeated measures to identify statistical significance over the treatment period.

Results: The crude values for the bone mineral density at the lumbar spine, at the femur neck, of total body and of total body less head were increased. The parameters for chronological age tended to decrease near the mean for the treatment period, however, they increased significantly for bone age excluding bone mineral apparent density. An increment of the BMI was not significant for their chronological ages.

Conclusions: Three-year treatment with GnRH agonist in central precocious puberty patients demonstrated a positive effect on bone maturation. Early treatment and administration of GnRHa in subjects who have more advanced bone age can improve their bone mineral density outcome.
age; neuropsychological testing (IQ, verbal and visual memory, visuo-spatial ability, cognitive executive functions, processing speed); emotional reactivity (computerized emotional distractibility task), behavioral measures (parents questionnaires); and HRV (inter-beat intervals recorded by Polar®).

**Results:** CPP patients displayed significantly increased emotional reactivity (p < 0.05), and higher HRV (p < 0.01) compared to healthy controls.

**Conclusions:** CPP girls treated with GnRHa did not differ in basic cognitive functioning from matched healthy controls. However, they showed greater emotional reactivity than healthy children. The significant differences regarding HRV might indicate a direct effect of GnRHa treatment on heart action through its cardiac receptors. Longitudinal studies comparing pre- and post-treatment stages are needed to establish precise effects of GnRHa on possible emotional problems and heart function.

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**P2-d2-740 Puberty and Neuroendocrinology 2**

**Three Chinese cases of familial male-limited precocious puberty (FMPP) caused by a heterozygous mutation (M398T) in luteinizing hormone/choriogonadotropin receptor gene (LHCR)**

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**Background:** Familial male-limited precocious puberty (FMPP) is an autosomal dominant form of gonadotropin-independent precocious puberty caused by heterozygous constitutively activating mutations of the luteinizing hormone/choriogonadotropin receptor gene (LHCR). There were only a few cases reported from China.

**Objective and hypotheses:** To present three cases of FMPP from China with the same heterozygous mutation (M398T) in LHCR gene.

**Methods:** The patient 1 and patient 2 were both 5-year-old boys who started to develop penile enlargement and accelerated height velocity at the age of 4 years. They both had elevated serum testosterone levels, but exhibited a pre-pubertal response of gonadotropins to GnRH. The patient 3 was the father of patient 1. He reported to have experienced precocious puberty and his height remained unchanged after the age of 11 years. His measured height was 160 cm. Father and one paternal uncle of patient 3 and a paternal cousin of patient 2 were found to have similar history. Their reported adult heights ranged from 158 cm to 164.5 cm. There is no history of short stature and precocious puberty in the family of patient 2. The LHCR gene was analyzed by direct DNA sequencing of amplified PCR products from the patient 1 and his parents, patient 2 and his father.

**Results:** All the three patients were found to carry a heterozygous c.1193T>C (M398T) mutation, which was not found from the mother of patient 1 and father of patient 2. The three patients carried the same mutation in LHCR with a previous report from north China.

**Conclusions:** Being different from the reported most common mutation (A578G) in LHCR gene found in FMPP patients, so far all the four reported Chinese FMPP patients who had undergone genetic analyses had the same heterozygous mutation (M398T) in LHCR gene.

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**P2-d2-741 Puberty and Neuroendocrinology 2**

**McCune-Albright syndrome: experience in a pediatric population**

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**Background:** McCune-Albright syndrome (MAS) is characterized by fibrous dysplasia (FD), skin hyperpigmentation (café-au-lait spots) and autonomous hyperfunction of endocrine organs, frequently seen in females as gonadotropin-independent precocious puberty (GIPP). In MAS the mosaicism of activating somatic mutations of the alpha-subunit of Gs results in a variable pattern of clinical presentation.

**Objective:** To describe the clinical manifestations and treatment of patients with MAS.

**Methods:** Ten female patients with MAS characterized by café-au-lait spots and GIPP, followed for a mean of 6.6 years (1-15 yrs).

**Results:** All patients were diagnosed before 3 years of age with GIPP. Elevated estradiol levels (mean: 40,3±9 mg/ml; normal:<24 pg/ml), prepubertal gonadotropin levels and large ovarian follicles at ultrasound. Tamoxifen was used in 9 cases to improve the final height (FH) through the interruption of bone age (BA) acceleration. The patients treated with tamoxifen evolved without vaginal bleeding and with stabilization of BA maturation. There was a significant difference between the FH predicted at the beginning (144,7 cm±9,32; Z-s:-2,88±1,56) and at the last evaluation (156,8±6,1 cm; Z-s:-0,86±1,62; p<0,01). Oophorectomy was required in one patient, never treated with tamoxifen, due to a large ovarian cyst. One patient had adenomatous goiter and two hyperthyroidism, both requiring total thyroidectomy after failure of antithyreoid drugs. FD was treated with pamidronate, vitamin D and calcium in four cases. FD resulted in walking disability in two patients and amanuasia in one of them. The treatment with tamoxifen or the FD did not interfere significantly with bone mineral accretion as the Zs of BMD was higher than -2.0 in all patients. Liver dysfunction was noted in 4 patients (two with colestasis and two with increased liver enzymes).

**Conclusions:** The patients with MAS display a broad clinical spectrum of MAS, which may complicate the diagnosis and follow-up. In our patients tamoxifen improved the FH prediction and did not affect significantly the bone mass.

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**P2-d2-742 Puberty and Neuroendocrinology 2**

**Is “intermediate thelarche” a new entity following a different clinical course than premature thelarche and central precocious puberty?**

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**Background:** The spectrum of precocious puberty (PP) is broad. Intermediate forms between benign premature thelarche (PT) and central precocious puberty (CPP) are common. We describe an entity of “Intermediate Thelarche” (IT) as breast development in girls <8 yr with features of CPP including pubic hair, and/or bone age advancement (adBA) but lack pubertal LH secretion (basal ≥0.3 ultrasensitive LH by ICMA or peak LH ≥5 mU/mL, at luteal phase).

**Objective:** 1) Describe diagnosis in a large cohort of girls <8 yr referred for evaluation of PP; 2) Compare baseline clinical and biochemical characteristics in patients with idiopathic CPP (iCPP), PT and IT and 3) Describe the natural history of progression of PT and IT.

**Methods:** Retrospective chart review of 269 girls referred for PP 2006-2011, 42 were excluded due to incomplete data. 64 girls who met criteria for iCPP, PT or IT were analyzed for baseline and followup characteristics. iCPP was defined as B≥2, PH≥2 and/or adBA (≥2SD) and prepubertal LH (baseline<0.1, peak<5); IT as B≥2, PH≥2 and/or adBA (≥2SD) and prepubertal LH (baseline<0.3, peak<5).

**Results:** Of the 64, 8 (12.5%) had iCPP, 17 (26.5%) PT and 39 (61%) IT. Of the remaining 163, 98 had precocious adrenarche, 30 prepubertal, 26 with brain pathology, 9 peripheral PP. At presentation, IT girls were similar in age to PT but younger than iCPP (IT:6.62 yr [5.0-7.91] vs CPP:7.54 yr [6.33-7.91] p<0.05). Height and BMI Z-scores were not different among groups, neither was degree of adBA in IT and iCPP. Basal LH was higher in iCPP (Mean±SD: 2.5 ±4.47), than in IT (0.04±0.05) p<0.01, but not different in IT vs PT (0.05±0.07). Over the course of 26 mos IT girls showed adBA in 30% and pubertal LH in 23% of patients. Groups were compared by one way ANOVA and post hoc multiple comparison test.

**Conclusion:** IT is a common clinical entity that does not fit criteria for PT or CPP. Despite prepubertal LH levels IT girls may be at risk for pubertal progression.
P2-d2-743 Puberty and Neuroendocrinology 2
Melatonin deficiency and disrupted circadian rhythms in pediatric survivors of craniopharyngioma
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Background: Craniopharyngioma (CP) are rare embryonic malformations of the sellar area with low-grade histological malignancy. Patients frequently suffer from endocrine deficiencies, sleep disturbances and severe obesity due to pituitary and hypothalamic lesions.

Objective and hypotheses: We hypothesized that disrupted sleep patterns in patients with CP result from dysfunction of the hypothalamic circadian pace-maker located in the suprachiasmatic nucleus. Daily variations in levels of the pineal hormone melatonin serve as a marker of the function of this system.

Methods: Salivary melatonin was evaluated in 37 childhood CP patients and 34 controls. Body weight was evaluated by calculating the body mass index (BMI) [BMI=weight (kg)/height^2 (m^2)]. Expression of the BM1 as a standard deviation score. Saliva was collected at 3 time points: morning, midday, night. Salivary melatonin concentrations were measured by a commercially available direct saliva melatonin RIA (Buhllmann Laboratories AG, Switzerland). The Epworth Sleepiness Scale (ESS) was used to assess subjective daytime sleepiness.

Results: CP patients with severe obesity had higher scores on ESS (p<0.01) in comparison with less obese or normal weight CP patients, indicating increased daytime sleepiness. Average nocturnal melatonin level in CP patients was markedly decreased (14.8±5.4 pg/mL) as compared to controls (40.7±19.1 pg/mL), p=0.001. Morning melatonin level was decreased in only severely obese CP patients (3.6±1.04 pg/mL) as compared to controls in the same group (12.0±2.5 pg/mL) p<0.01. Morning and nighttime melatonin levels in CP patients were related to BMI (R=-0.8, p<0.001 and R=-0.9, p<0.001) and patient’s ESS score (R=-0.6, p<0.001 and R=-0.4, p<0.01).

Conclusions: We assume that hypothalamic lesions might be responsible for both obesity and increased daytime sleepiness. Our findings suggest that increased daytime sleepiness in patients with childhood CP was related to decreased nocturnal melatonin level and the degree of obesity.

P2-d2-744 Puberty and Neuroendocrinology 2
Vitamin A and iron as an adjuvant therapy in addition to GnRH agonist in precocious puberty
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Background: To examine the effect of vitamin A and Iron supplementation on growth outcome of central precocious puberty (CPP) patients who receive GnRH agonist.

Methods: 36 female CPP patients were randomized in control (17 cases) and trial (19 cases) groups. Both groups received GnRH agonist and the trial group received iron (10mg/day) and vitamin A 6000 U/ week as well. The patients were revisited every 3 months, their weights, height, BMI were measured, and their bone age was determined in the beginning and end of the study. Statistical analysis was performed between groups and in each group.

Results: The mean age of the patients was 106.7±10.57 vs. 102.7 ± 13.7 months in trial and control groups. No statistical difference was observed in the base-line age, weight, height, BMI, bone age and predicted adult height (PAH). Height Z score (1.22±0.9 vs. 0.39±0.7, p value=0.01), and height velocity Z score (1.42±2.1 vs -0.36±1.9, p value<0.01) were significantly higher in the trial as compared to the control group at the end of the study. PAH-SDS had no significant changes in each group and between the two groups (trial: -0.29±0.9 vs. control: -0.55±1.1, p value>0.05).

Conclusions: In CPP, adjuvant therapy with Vitamin A and iron in combination with GnRH agonist could be considered to improve height velocity.

P2-d2-745 Puberty and Neuroendocrinology 2
Isolated giant café-au-lait spot: an unusual presentation of McCune-Albright syndrome
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Background: McCune-Albright syndrome (MAS) is classically revealed by precocious puberty, most often associated with bone fibrous dysplasia and cafe-au-lait skin lesions.

Objective and hypotheses: We report here a very unusual case of MAS revealed by an isolated cafe-au-lait spot.

Methods: This 5-year-old girl was first referred to dermatologists for a cafe-au-lait spot located at the upper back. This child was born at term with a birth length of 51 cm and a birth weight of 3040 g. Clinical examination found an irregular spot situated to the left of the midline and extending from D4,D5 to the posterior face of the left shoulder, which challenged dermatologists. Although the skin lesion seemed isolated, MAS was suspected. She was thus referred to our Pediatric Endocrinology Unit. Pubertal development was S1,P1, height was 117 cm (+2.8 SD), and weight was 20.3 kg (+1.2 SD). The growth curve showed acceleration over the last year. Bone age was 5 years and 6 months. Basal LH and FSH were both <0.5 mU/mL (N<1.5, respectively). Plasma E2 level was 20.8 pmol/L (N<35). IGF1 level was 271 ng/mL (N<250).

Results: The size of the cafe-au-lait spot, especially in association with slight growth acceleration, led us to perform Gsu gene analysis. A R201H substitution was found in DNA extracted from blood, establishing the diagnosis of MAS. Basal TSH, T4L and PRL levels were normal. Bone radiographs revealed no bone lesions.

Conclusions: The minor clinical presentation of MAS in this girl is very unusual. These data confirm the existence of dissociated forms of MAS and demonstrate the usefulness of Gsu gene analysis in the management of these children who may indeed benefit, even in these very minor forms, of screening for other autonomous endocrine hyperfunctions, as well as for bone lesions.

P2-d2-746 Puberty and Neuroendocrinology 2
Ovarian and uterine ultrasonography and relation to puberty in healthy girls between 6 to 16 years in Turkish population: a cross-sectional study
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Background: Awareness of female reproductive system changes around puberty has acquired great importance, especially with the global trend of precocious puberty.

Objective and hypotheses: Pelvic ultrasonography is mostly emphasized as a safe and non-invasive method; more up-to-date information is needed, since the quality of ultrasound has improved everyday. We investigated uterine and ovarian ultrasonography in prepubertal-pubertal girls and established reliable cut-off limits for Turkish population. Methods: The study was performed on 90 healthy girls (mean age ± SD, 10.48 ±2.68 years) with bone age and hormonal evaluation and pelvic ultrasound. Total uterine length (TUL), anteroposterior diameters of corpus (COAP), anteroposterior diameters of cervix (CEAP), fundus/cervix ratio (F/C), uterine volume (UV), ovarian volume (OV) and morphology were obtained.

Results: The data was stratified according to various ages and pubertal stages. Age-related increases of pelvic organs were noted after 10-11 years. Significant correlation was detectable between age and OV, TUL, UV in pubertal girls, but age only correlated with OV in prepubertal girls. Ovarian and uterine sizes in post-menarche cases were significantly greater than the pubertal
cases without menarche. A cut-off of 4 cm for TUL, 2.57 cm3 for UV and 1.58 cm3 for OV were the best discrimination values of pubertal status.

**Conclusion:** Assessment of uterine volume is valuable in pubertal stages and menarche should be taken into consideration in evaluating pelvic organs. The data herein may be useful in screening cases around puberty when continuous changes take place.

<table>
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<tr>
<th>Age (year)</th>
<th>Number</th>
<th>TUL (cm)</th>
<th>COAP (cm)</th>
<th>CEAP (cm)</th>
<th>FV ratio</th>
<th>UV (cm3)</th>
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<td>1</td>
<td>12</td>
<td>2.85 ± 0.6</td>
<td>0.72 ± 0</td>
<td>0.60 ± 0.1</td>
<td>1.2 ± 0.2</td>
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<td>6</td>
<td>3.10 ± 0.9</td>
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<td>1.1 ± 0.1</td>
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<td>1.2 ± 0.8</td>
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<td>5</td>
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**P2-d2-747 Puberty and Neuroendocrinology 2**

**Clinical and hormonal determinants of dysfunctional uterine bleeding in precocious puberty girls**

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**Background:** It was previously shown that course of dysfunctional uterine bleeding depends on time of puberty onset. Aims: To highlight clinical and hormonal pattern of dysfunctional uterine bleeding appropriate to precocious puberty girls. Methods: 120 girls (12-17 years) with dysfunctional uterine bleeding (DUB) were under investigation. Physical examination included height, weight, waist circumference and blood pressure measurements, pubertal development (Tanner stage) estimation. Blood samples for insulin (IRI), gonadotropins (FSH, LH and prolactin (PRL), testosterone (T) and estradiol (E2)) measurements were taken in fasting state. Dicriminant analysis was performed to obtain set of variables pertaining to course of uterine bleeding in girls with normal and precocious puberty. Data are given as standardizing coefficients of discriminant function (CDF).

**Results:** It was found out that in normal puberty girls uterine bleeding courses on the background of increased level of gonadotropins: FSH (CDF = 0.17); LH (CDF = 0.08), PRL (CDF = 0.23). In normal puberty girls DUB distinguish by late menstrual history onset (CDF = 0.67). In precocious puberty girls DUB accompanies by increased level of T (CDF = 0.14) and E2 (CDF = 0.11), and IRI (CDF = 0.32). Excessive menstrual bleeding since early menarche onset (CDF = 0.57), excess of body mass (CDF = 0.51) and higher body mass at birth (CDF = 0.18) were notable in these patients.

**Conclusions:** It was found out that depend on time of patient’s puberty onset DUBs have different history, clinical manifestation and hormonal background. In normal puberty girls increased level of gonadotropins indicates on central regulation disorders of menstrual cycle. In precocious puberty girls metabolic dysfunction affects sex steroids production and creates background for DUBs.
analyzed with logistic regression adjusting for maternal menarche, smoking in pregnancy and socio economic status. **Results: Fat % (both the current fat % and the fat % 4 years earlier) was positively correlated to earlier puberty (B2+ and PH2+). Girls with fat % above mean at early school age developed breasts 7 months earlier and pubic hair 4 months earlier than girls with fat% under the mean (figure 1). Fat % increase (AZ-score) from 3 months to 7 years was also positively associated with early PH2+.

**Conclusions:** A higher fat % at early school age was associated with earlier pubertal onset indicating a correlation between the increased prevalence of overweight and the trend of earlier puberty among girls. Secondarily it reflects that timing of puberty may be determined years before the actual first signs.

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**P2-d2-750 Puberty and Neuroendocrinology 2**

**Effectiveness of leuprolide acetate 3-month depot (11.25 mg) in the treatment of patients with central precocious puberty: experience of 3 years**

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**Background:** Depot GnRH agonists are the first-line therapy of central precocious puberty (CPP). One-month depot preparations have been shown to be effective and safe. In the last years, 3-month decots have become available allowing prolonged injection interval.

**Aim:** To evaluate the clinical and hormonal response of patients with CPP treated with leuprolide acetate 3-month depot (LA 11.25 mg) given every 3 months in comparison with the 1-month 3.75 mg formulation. Patients and Methods: 48 children (45 girls) with clinical and hormonal diagnosis of progressive CPP were included. Two groups of patients were evaluated: group 1 - children receiving leuprolide acetate (LA) 3.75 mg monthly with adequate control (n=42); group 2 - all children from group 1 who migrated to 3-monthly LA 11.25 mg and 6 girls who started therapy with 3-monthly depot leuprolide acetate (n=48).

**Results:** In girls, the mean chronological age at onset of puberty was 5.6 ± 1.8 yr and at start of therapy was 7.3 ± 1.5 yr. The mean bone age at start of therapy was 8.8 ± 2 yr. The mean duration of therapy was 2.5 ± 1.4 yr. In all but one patient, who migrated from 1- to 3-monthly therapy, mean growth velocity was similar during both regimens, breast development and testicular enlargement remained unchanged and slower bone age advancement was observed. Basal LH levels were suppressed and mean LH levels 2 h after both LA 3.75mg and 11.25 mg injection indicated adequate hormonal suppression. Basal E2 and testosterone levels were suppressed. In only one girl (BMI>97.5th percentile) LH and E2 levels were not suppressed during 3-month LA therapy, and 1-month LA therapy was restarted in this patient resulting in satisfactory suppression. All 3 boys achieved adequate pubertal suppression. Two patients (4.2%) had transient mild local reaction with LA 11.25 mg.

**Conclusions:** Clinical and hormonal parameters of children with CPP during therapy with either 1- or 3-monthly LA therapy were similar, confirming that 3-monthly depot preparations are effective and safe therapy for CPP in most of patients.

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**P2-d2-751 Puberty and Neuroendocrinology 2**

**Persistent high frequency of PCOS, hirsutism, menstrual disorders and hyperandrogenism in T1DM adolescents**

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**Background:** Polycystic ovarian syndrome (PCOS), hirsutism and menstrual disorders are frequently described in type 1 diabetes mellitus (T1DM) adolescent. Little is known about their prospective evolution.

**Objective and hypotheses:** To evaluate at 1 year of follow up the clinical characteristic, hormonal profile and the prevalence of PCOS (according to Rotterdam criteria), hirsutism (H) and menstrual disorders (MD) in adolescent girls with T1DM.

**Methods:** 78 adolescents with T1DM (12 to 17 years old, Tanner IV-V) were included at first examination (V1). Data from 54 adolescents were analysed at second examination (V2).

**Results:** A similar high prevalence of PCOS (50% and 37%, p=0.5), Hirsutism (20.5% and 32.6% p=0.12) and Menstrual Disorders (44% and 26% p=0.1) were found at V1 and V2 respectively.

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**Poster Presentations**

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232 Horm Res 2012;78(suppl 1)
Conclusions: Reproducibility of the clinical and biological differences in time suggests that they are strong features that should be investigated in all T1DM adolescents. Large scale studies are needed to assess the role of diabetes on hormonal disorders and allow for predictive diagnostic.

P2-d2-752 Puberty and Neuroendocrinology 2
Predictive markers of complete recovery in anorexia nervosa
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Background: Anorexia Nervosa (AN) is an eating disorder affecting most adolescent characterized by a decreased caloric intake and low weight that lead to metabolic and hormonal complications. Weight gain and improvement of hormones do not necessarily involve the normalization of gonadal function.

Objective and hypotheses: Aim of this study is to evaluate the link between hormonal changes and resumption of menses.

Methods: We enrolled 30 patients, aged 15-25 (mean 20.03±3.06), with active or past diagnosis AN according to DSM IV. Anorexic patients were divided into 3 groups, CA (10 grade A), AA (10 grade acute, with amenorrhea), RA (10 recovered with amenorrhea), RM (10 recovered, eumenorrheic). Mean BMI was 17.97±3.38. We evaluated hormonal parameters (serum cortisol, sexual steroids, thyroid hormones, IGF-1, PTH) and markers of bone turnover (vit. D, osteocalcin, beta-cross-laps). Total body BMD was determined using Dual Energy x-ray absorptiometry (DEXA) and was expressed as T-score.

Results: In the AA group a positive correlation was found between IGF-1 and BMI (r=0.06), fat mass (r=0.06) and osteocalcin (r=0.11); in the RA group a positive correlation was found between IGF-1 and osteocalcin (r=0.01), BMI (r=0.01) and area under curve of LH during GnRH test (AUC LH) (r=0.04). In the RM group a positive correlation was observed between estradiol and fat mass/lean mass ratio (r=0.04), IGF-1 (r=0.03) and osteocalcin (r=0.044); osteocalcin was also positively correlated with BMI (r=0.06), fat mass/lean mass ratio (r=0.025), IGF-1 (r=0.04) and T-score (r=0.07).

Conclusions: Our data show that the weight gain alone, measured as BMI, does not mean normalization of all compromised parameters and does not represent recovery from AN. Markers of bone metabolism, positively correlated with restoring normal nutritional conditions, as IGF-1, which is correlated with recovery of gonadal function, may be more representative. This evidence may suggest that BMI plus osteocalcin may be a predictive marker of complete healing in recovering of AN.

P2-d2-753 Puberty and Neuroendocrinology 2
Assessment of gonadotropin suppression in patients treated with GnRH analogue for central precocious puberty
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Background: GnRH stimulation test is the gold standard for the diagnosis and assessment of gonadotropin suppression during the therapy in patients with CPP. However the test is costly and uncomfortable for the patients. Therefore, LH determination in a single sample at 90 min after GnRH enjection is suggested to control the therapeutic efficiency. In this study, we aimed to compare the single LH cut-off >2.5 mIU/mL at 90 min after GnRH enjection with the classical GnRH stimulation test for the evaluation of gonadotropin suppression.

Patients and methods: Study group consisted of 31 girls and 2 boys with CPP who were treated with intramuscular sc Leuprolide acetate (LA) every 28 days. LH level at 90 min after 3rd dose of LA was measured. If LH level >2.5 mIU/mL, was also performed classical iv GnRH stimulation test.

Results: At the time of diagnosis, mean chronological, height and bone ages were 8.9±0.6(7.3-10), 9.8±1(7.5-12), 11.1±0.9(9.12) years, respectively. Nineteen patients (57.6 %) had tanner stage 2, 12 (36.4 %) had stage 3 and 2 (6.1 %) had stage 4 pubertal development at the time of diagnosis. Two (6.1 %) patients were presented with menarche before the age of 10 years. The mean postmenarche LH level was 3.9±1.9(2.5-10.9) mIU/mL and mean of peak LH levels of classical GnRH stimulation tests was 1.92±0.96 (0.94-8.80) mIU/mL. 28(85 %) patients had suppressed LH level <2 mIU/mL at classical GnRH test although their LH levels at 90 minute after GnRH enjection were >2.5. Only 5 patients (15 %) did not achieved gonadotropin suppression with respect to both tests.

Discussion: For evaluation of therapeutic efficiency of CPP clinical findings are very important. Additionally we need laboratory confirmation. A single LH level >2.5 mIU/mL at 90 min after GnRH enjection seems not a reliable marker alone. In these patients classical GnRH stimulation test should be performed for confirmation.

P2-d2-754 Puberty and Neuroendocrinology 2
Aromatase expression in patients with pubertal gynecomastia
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Background: Gynecomastia represents a benign proliferation of the breast glandular tissue and can be detected in up to 60% of boys during puberty. This clinical condition is thought to result from an imbalance between the estrogen androgen effects and the androgen inhibitory effects at the breast tissue level.

Objective and hypotheses: Previous studies on patients with prepubertal gynecomastia have demonstrated that aromatase plays a role in the development of this condition. The aim of this study was to try to evaluate whether aromatase expression and activity are involved in the pathogenesis of pubertal gynecomastia.

Methods: 10 patients with pubertal gynecomastia were studied. DNA and proteins were extracted from peripheral blood and glandular tissue. Aromatase expression was analyzed by Western Blotting. Sequencing of the aromatase gene was performed using the ABI 310 genetic analyzer. The promoter region was studied following the 5th Race protocol.

Results: Patients with pubertal gynecomastia presented a higher peripheral blood aromatase expression in comparison with normal controls (242380 ± 40387 vs 18796 ± 785, mean ± SD, P<0.001). Sequencing of the aromatase gene did not reveal any mutation of the coding region, although a polymorphism in exon 3 was detected. Amplification of the promoter region both in peripheral blood and glandular tissue showed the presence of L3 and PI1 promoters and both of them presented a normal sequence.

Conclusions: Patients with pubertal gynecomastia presented increased expression of aromatase in peripheral blood but this finding was not accompanied by alterations of the aromatase gene and promoter region sequences. The cause of the increased aromatase expression in peripheral blood is not clear, but it can be hypothesized, based on previous studies, that it is the result of abnormalities in the hormonal milieu.

P2-d2-755 Puberty and Neuroendocrinology 2
A prospective study of pubertal growth in children with inflammatory bowel disease
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Background: Puberty is understood to be commonly affected in Crohn’s Disease (CD) and ulcerative colitis (UC).

Objective: Determine the impact of CD and UC on pubertal status.

Methods: Prospective study of 63 children: CD-M(23); CD-F(22); UC-M(12) and UC-F(6) with a median (range) age at diagnosis and age at baseline (T0) of 10.9; 10.9; 11.8; and 11.9yrs, and 13.4; 13.9; 13.4; and 13.2yrs, respectively. Nineteen patients (57.6 %) had Tanner stage 2, 12 (36.4 %) had stage 3 and 2 (6.1 %) had stage 4 pubertal development at the time of diagnosis. Two (6.1 %) patients were presented with menarche before the age of 10 years. The mean postmenarche LH level was 3.9±1.9(2.5-10.9) mIU/mL and mean of
The median HVSDS was 0.1 (-2.3;3.6), -0.4 (-4.4;7.3), 0.3 (-4.6;2.3) and 2.5 (-2.8;2) respectively in CD-M, CD-U, UC-M and UC-F. A statistically significant negative impact on parameter, Ht12SDS (p=0.05) was seen in CD-M. Individually, 7/23 CD-M cases had one or more parameter affected: 6 had HtADSDS < -2, 3 had H0SDS and Ht12SDS < -2, and 1 had HVSDS < -2. 2/22 CD-F cases had one or more parameter affected:1 had H0ADSDS < -2, 3 had H0SDS and Ht12SDS < -2, and 1 had HVSDS < -2. In each of UC-F and UC-M 1 subject had HVSDS < -2. In post-pubertal CDM, urinary LH:Cr and FSH:Cr were significantly lower than the healthy population (p<0.01 and p=0.0001).

Median ESR showed a significant association with HV in the whole group (r=0.355; p=0.01) and median PCDAI showed a significant association with HVSDS in CD-M and CD-F (r=0.404; p=0.015).

Conclusion: Disorders of the pubertal growth spurt are more likely to occur in CD and may be related to disease activity. There is a need for detailed biochemical evaluation in these patients.

**P2-d2-756 Puberty and Neuroendocrinology 2**

**Estradiol levels in young girls with premature thelarche: a west Swedish study**

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2. Sahlgrenska Academy, Gothenburg University Institute clinical science, Department of Pediatrics, Growth Research Center, Gothenburg, Sweden

**Background:** Premature thelarche is defined as breast development without any other signs of puberty in a young girl. Premature thelarche is usually a benign condition but can create clinical problems if still seen after the age of 2 years or, if there is a progress. We need to diagnostic tools separate benign premature thelarche from pubertal precocity and other pathological conditions in young girls. This is 2nd rapport from the ongoing study to ESPE.

**Objective and hypotheses:** Study estradiol levels in girls with breast developmental younger than 5 years in relation to clinical outcome.

**Methods:** Since 2002 a study of girls with premature thelarche in the western part of Sweden is ongoing. All serum samples of for estradiol determinations in girls aged 10 months – 4 year due to thelarche that were sent to the laboratory at Gothenburg Pediatric Growth Research Center Laboratory, also with the analyses result, a questions was sent to the referral about the outcome of thelarche. The estradiol where analysed with a high sensitive extraction RIA method that measures estradiol down to 4 pmol/L. The analyses result, a questions was sent to the referral about the outcome of thelarche. The estradiol where analysed with a high sensitive extraction RIA method that measures estradiol down to 4 pmol/L.

**Results:** 150 girls qualified for the study and 98 of these girls parents accepted to participate in the study. Three girls had high estradiol levels 74, 90 and 114 pmol/L and were diagnosed with pubertal precocity, hamartoma and McCune Albright syndrome. The other the girls considered to have benign premature thelarche: 3 girls had an estradiol of 30-31 pmol/L and 7 girls had estradiol of 25-30 pmol/L. The remaining 85 girls had estradiol under 25 pmol/L. We received 67 growth charts and 14 of the girls showed a growth-acceleration (½ SD increase during 6 months). No association with the estradiol levels.

**Conclusions:** Girls aged up to 4 year with breast development without any other signs of puberty and estradiol values of 30 pmol/L or less determined with highly sensitive extraction RIA is considered to have benign premature thelarche.

**P2-d2-757 Puberty and Neuroendocrinology 2**

**Mutational analysis of KISS1 and KISS1R genes in idiopathic central precocious puberty**

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**Background:** The genetic background of idiopathic central precocious puberty (ICPP) is not well understood. The genetic activation of pubertal onset is sought to arise from the effect of multiple genes. Kisspeptin and its receptor are important stimulators of GnRH secretion and puberty onset. Mutations in KISS1 and KISS1R genes have been reported in rare cases of ICPP.

**Patients and methods:** ICPP was defined by pubertal onset before 8 yrs of age, and a pubertal LH response to GnRH testing. Twenty eight girls with ICPP were included in the study (age at diagnosis 5.7±2.59; bone age 6.1±2.81). Height SD at the start of treatment was 0.90±1.48 for chronological age. LHHR test was performed and was pubertal in all the subjects (LH20.35±32.37 mIU/ml; FSH 23.32±15.72 mIU/ml). Genomic DNA was extracted from peripheral leukocytes and the entire coding and boundary regions of KISS1 and KISS1R were amplified and sequenced.

**Results:** No rare variants were detected in KISS1 or KISS1R in the 28 subjects with ICPP.

**Conclusions:** Our results confirm that mutations in KISS1 and KISS1R are not a common cause for ICPP.

**P2-d2-758 Puberty and Neuroendocrinology 2**

**Letrozole treatment prevents development of gynecomastia and leads to normal growth in a boy with aromatase excess syndrome**

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University Hospital Ulm, Paediatric Endocrinology, Ulm, Germany

**Objective:** To describe a family with aromatase excess syndrome (AES) and the effect of letrozole in affected growing boys.

**Case report:** At the age of 8 years the index patient presented pseudopubertas praecox with gynecomastia, accelerated growth velocity and a bone age (BA) of 13 ½ years (+5.9 SDS). He underwent mastectomy twice. In late puberty increased estradiol levels (54 ng/l) became apparent. Serum testosterone was below normal range (1.4 µg/l). Presuming an AES, at the age of 18 years a therapy with letrozole 2.5 mg daily was initiated. Hereby estradiol levels decreased (6.4 ng/l) and testosterone levels raised (8.64 µg/l). At the age of 3 years a younger brother also showed an accelerated growth velocity (7.75 cm/year) and BA (5 ½ years). Suspecting an AES, he was started on a therapy with letrozole 2.5 mg daily at the age of six years, which is continued to present (0.3 mg daily). Several other male and female family members showed early puberty and relatively short final height (around 150 cm) over three generations. Mutation analysis is pending.

**Results:** Treatment with letrozol of the younger brother resulted in a decline of growth velocity (7.93 cm before/ 2.86 cm under therapy) and a dramatic attenuation of BA acceleration (2002: chronological age (CA) 7 years/ 7 months, BA 5 years). BA was 3 years a younger brother also showed an accelerated growth velocity (7.75 cm/year) and BA (5 ½ years). Suspecting an AES, he was started on a therapy with letrozole 2.5 mg daily at the age of six years, which is continued to present (0.3 mg daily). Several other male and female family members showed early puberty and relatively short final height (around 150 cm) over three generations. Mutation analysis is pending.

**Conclusion:** AES is an autosomal dominant disorder. In males it is characterized by elevated systemic estrogen levels, short final stature, prepubertal gynecomastia and testicular failure. As shown here, therapy with letrozol can normalize growth, attenuates bone age acceleration with a probable increase of final height and prohibits the development of gynecomastia.
P2-d2-759 Puberty and Neuroendocrinology 2

Precise description of pubertal development and clinical practices in women with early premature ovarian failure

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Background: Early Premature ovarian failure (ePOF) defined by cessation of ovarian function before age 18 is a rare condition. The link between puberty progression and POF hasn’t been explored in details. Aim of study: To describe pubertal development and clinical practices of women with ePOF in a referral center within the first two years follow-up.

Method: A mixed retrospective and prospective study was performed. A total of 358 consecutive POF patients were followed from 1997 to 2010. From this cohort (86% of patients with ePOF, young girls, adolescents < 18 years of age at diagnosis of POF) with karyotype excluding Turner syndrome, and no iatrogenic cause are the focus of our study. Their clinical (age, pubertal evolution, circumstance diagnosis), hormonal (FSH, LH, E2) and morphological features (pelvic ultrasonoscopy, laparoscopy) were analyzed. We also documented their management’s characteristics (type of/age of hormonal treatment).

Results: Primary amenorrhea (PA) was more often associated with Tanner breast’s stage 1-2-3 (73.3%) than breast’s stage 4-5 (26.3%). Secondary amenorrhea (SA) was always associated to stage 4-5 (100%), (p<0.001). PA was more often associated with partial and delayed pubertal development than normal and conversely for SA (p<0.001). SA’s mean age was 16.22 (15-18) years with menarchy at 13.56 (10.5-17) years. The diagnoses are made on high FSH and mean level was 94.76 IU/L and estradiol 17ng/ml, LH level was higher with normal pubertal trend (p=0.002). Both estradiol and LH level were higher for 4-5 breast stages (p=0.02) than 1-2-3 stages. Mean age at start of hormonal treatment was 17.55 (15-28) years, prostogest’s onset was one year later. Combined treatment started at 18 years old. During these two years 1/5 of patients were lost for follow-up.

Conclusion: The fact to complete puberty doesn’t exclude PA. However in SA a normal puberty is most often found then in PA. Suboptimal care of these ePOF is documented therefore widespread guidelines to improve care of patients with early POF are needed.

P2-d2-761 Puberty and Neuroendocrinology 2

Curcumin helps in treatment of neurodegenerative disorders

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Background: Curcumin is a polyphenol extracted from the rhizome of Curcuma longa and well known as a multi-functional drug with antioxidative, anti-cancerous and anti-inflammatory activities. Curcumin’s antiaging and neuroprotective potential is widely reported.

Objective: To study the effect of curcumin in neurodegenerative disorders.

Observations: In the present study, effect of curcumin treatment dose 30 mg/kg (11 day) was investigated against aluminium neurotoxicity in young and old animals. Direct and indirect intakes of aluminium have been reported to be involved in the etiology of several neurodegenerative disorders like Alzheimer’s and Parkinson’s diseases. Long term Al was administered through drinking water at a dose of 50 mg/kg/day for 6 months in both young (4 months) and old (18 months) male Wistar rats.

Results: Result obtained demonstrates that curcumin treatment attenuates the Al-induced alterations at biochemical, behavioral and ultrastructural levels which was well reflected in the electrophysiological recordings. Our results indicate that curcumin’s ability to bind redox active metals and cross the blood-brain barrier could be playing crucial role in preventing against Al-induced neurotoxicity.

P2-d3-762 Sex Differentiation 2

48 XXY syndrome in a newborn with ambiguous genitalia

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Background: Ambiguous genitalia are a complex medical problem that requires a multidisciplinary approach and may represent in the newborn period a medical emergency. The first problem is the appropriate sex of rearing, the second one is to prevent the associated metabolic imbalances. Sex chromosome aneuploidies are the most frequently occurring chromosome abnormalities and involve the addition/ deletion of an X or Y chromosome to a normal karyotype. The addition of more than one extra sex is extremely rare and in particular the 48 XXY constitution is 1:50000 among newborns.

Case report: We present the case of a newborn with ambiguous genitalia and a 48 XXY constitution. He was born at term by cesarian section with a birth weight of 2480 gr and a birth length of 47.0 cm. On physical examination he showed mild dysmorphic features and ambiguous genitalia with penis length 2.5 cm, bifid scrotum, scrotal hypospadias and both testes palpable in the scrotum (Fig. 1). Hormonal results were normal but karyotype analysis evidenced the presence of 48 XXYY aneuploidy. No renal malformations were detected. An X-ray of the left wrist showed radio-ulnar synostosis. He was discharged by the postnatal ward after rearing normal male sex and surgical follow-up was suggested in order to plan the timing of corrective genital surgery.

Conclusions: The peculiarity of our case report is represented by the fact that a patient with 48 XXYY polyosomy has been diagnosed in the newborn period, due to genital ambiguity. Most of patients with KS and rarer aneuploidies are diagnosed mainly during prenatal period by prenatal cytogenetic examination or after adolescence. The rate of diagnosis in prepubertal age is extremely low.
and the common elements that trigger the diagnosis at this stage are represent-
ed by neurodevelopmental and psychological features. Ambiguous genitalia
is an exceptional clinical presentation of 48,XXY syndrome that has never
been reported in the literature.

Conclusions: SF-1 gene plays an important role in human gonadal differen-
tiation and development. The detection of SF-1 gene is important for the early
diagnosis of the 46,XY: external genitalia ambiguous or female genital with
testicular dysgenesis.

P2-d3-765 Sex Differentiation 2
Is 46 XY gonadal dysgenesis dependent
on microdeletion of the short arm of a
chromosome 8? Report of one case and review
of the literature
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Objective: Chromosome 8 deletions, especially of the short arm, are associ-
ated with varying phenotypic expression: cardiac abnormalities, mental and
behavioural problems with variable morphotype. Associated genitourinary
abnormalities are mentioned in 25% of the cases and two cases of XY DSD
have been reported until now. Describing a third case, we tried to establish a
relationship with the above mentioned deletion.

Design: Case report, literature review.

Methods end results: Our case concerns a boy born with insufficient masc-
culisation, 46, XY DSD and few other associated signs. Imaging, pathol-
ogy and hormonal exploration suggested gonadal dysgenesis. The child’s
further development made genetic studies necessary (mental developmental
delay, microcephaly, dysmorphic facies, but no cardiac abnormality). Three
standard karyotypes were considered normal but a high resolution analysis
showed an interstitial deletion on chromosome 8’s short arm: 46, XYdel(8)
p(23.1p23.1). We compared the phenotype and genotype of our case with the
61 previously reported, especially with cases reported after 1990 (molecular
analysis). 81% of them had mental problems, 35% dysmorphic disorder, 50%
cardiac anomalies, 25% genitourinary anomalies. The phenotype of our pa-
tient with 8p microdeletion can be explained, for the genital abnormalities, by
the haploinsufficiency of the genes, such as GATA4 and SOX7, included in
the deleted area, whereas the small distal size of the deletion may explain the
absence of cardiopathy.

Conclusion: Compared with the data from the literature, this third case of
severe XY DSD raises the question of the role played by 8p deletion in go-
nadal dysgenesis. If genitourinary abnormalities are common, severe sexual
differentiation disorders are rare. Further genetic studies are necessary.
Background: The incidence of CAIS revealed by inguinal hernia in little “girls” is variable due to the clinical heterogeneity of the series.

Objective and hypotheses: The aim of this study is to estimate the percentage of CAIS in children with female phenotype who underwent bilateral inguinal herniotomy.

Methods: This is a retrospective study based on a population of 129 “girls” treated for bilateral hernia repair. The gonads are assessed either by US or by histology. Diagnosis of CAIS was confirmed by direct AR gene sequencing (exons 1-8) and/or a measurement of aromatase activity on tissue samples.

Results: We identified 2 cases of CAIS (mutations pS204N+delR615 and del 440_441insC). One of these mutations was present in both girls. The parents were heterozygotes for the same mutation. Both girls underwent a feminising genitoplasty.

Conclusion: Bilateral hernia repair is done in order to diagnose CAIS, especially in children with gonadal content on both sides.
Background: Bone health represent a clinical concern in women with complete androgen insensitivity syndrome (cAIS). Reduced BMD has been reported, but methodological issues may give some inferences on data interpretation (methods of BMD assessment or AIS molecular diagnosis). Another problem can be the use of female (phenotypic sex) or male (genetic/gonadal sex) references values to evaluated BMD status.

Objective and hypotheses: To evaluate BMD in women with molecular diagnosis of complete AIS.

Methods: 28 women (age 15-47 years) with cAIS (diagnosis based on phenotype, 46,XY karyotype, hormonal pattern and androgen receptor gene mutation); 7 patients were not gonadectomised at BMD assessment, while the others were. The women with removed gonads were on hormone replacement therapy (HRT). BMD (lumbar spine (L2-L4), femoral neck (FN), total body (TB)) were assessed by DXA. The values are expressed as T-score in comparison with normative values for females.

Results: Mean BMD values (SDS) in the whole group are: L2-L4 -1.57 ± 1.17 (p<0.001 vs 0); FN -0.62 ± 1.29 (p<0.002 vs 0); TB 0.68 ± 1.37 (p=NS vs 0). BMD was significantly reduced in women with removed gonads in comparison with women with intact gonads (FN, SDS; gonadectomized -0.98 ± 1.04 vs not gonadectomized 0.63 ± 1.38 (p<0.003); L2-L4: gonadectomized -1.86 ± 0.90 vs not gonadectomized -0.55 ± 1.51 (p=0.0095); TB: gonadectomized -0.75 ± 1.07 vs not gonadectomized 1.35 ± 1.65 (p<0.0006). Good compliance with HRT was associated with better BMD values.

Conclusions: Gonadal removed is associated with poorer bone health in women with cAIS. HRT may improve BMD status in cAIS women who had gonads removed. Testicular protein hormones (f.e. INSL3) may have a role on bone health. Larger series of homogeneous patients will be investigated to obtain conclusive data and clear indications for the optimal management of people with cAIS.

Bone mineral density (BMD) in women with complete androgen insensitivity syndrome

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Background: Infantile autochthonous TPO antibody expression is a very rare condition. From the clinical and laboratory findings we conclude that the girl showed an unusual early presentation of Hashimoto thyroiditis with consecutive severe hypothyroidism. Monogenic polyglandular syndromes (e.g. APS type 1, IPEX) where discussed but not considered at the moment due to the current lack of associated symptoms.

Case report: A girl presented with apathia, feeding problems and weight stagnation at an age of 9 months. Laboratory tests revealed an elevated thyroid stimulating hormone (TSH) level (> 200 mIU/l), an extremely low free-thyroxine (FT4) level and slightly elevated TPO-antibodies 140 U/ml. The infant’s development was normal. Ultrasound showed an orthotop normal-thyroid gland. Retrospectively, newborn screening was normal. A treatment with levothyroxine (LT4) 75 µg/d was started immediately. In the course we observed a successive rise of TPO-antibodies up to at last 1100 U/ml while TSH and FT4 amounts normalized on L-thyroxine substitution. The girl shows a normal development, hearing tests, ultrasound of the heart, kidneys and thyroid remained unremarkable. The child’s mother was diagnosed with severe hypothyroidism from Hashimoto thyroiditis can cause transient hypothyroidism in the newborn. Here we present a case of a 9 month old infant with severe hypothyroidism due to highly elevated TPO antibodies but absent TPO antibodies in the mother.

Conclusions: We suppose that the reasons for the ambiguity may be the small size of the translocated Y chromosome region and the effect of random inactivation of X chromosome including SRY.
Introduction: Graves’ disease (GD) is rare in children, being diagnosed more frequently in adolescents. It has been suggested that the clinical presentation in prepubertal children would be more severe than the pubertal with regard to the presenting symptomatology.

Objective: Our objective was to determine whether differences exist in the presentation of Graves’ disease between these two age groups. Method: The diagnosis of GD in 27 prepubertal children (Median, Q1-Q3) (7, 5.7-9.3) was compared with that in 31 pubertal patients (12.7; 10.9-14). The medical records of the patients (46 girls) diagnosed between years 1992 and 2011 at Pontificia Universidad Católica de Chile were retrospectively investigated.

Results: At diagnosis, 46.5% of patients were prepubertal with ages between 2.9 and 17.1 years (10.35 years; 6.92-13 years; P<0.0001), female to male ratio 4/1. Height-SDS (Median, Q1-Q3) ([0.67; -0.52-1.86]/vs [0.32; -0.12-0.87]; P=NS) and BMI-SDS ([0.18; -0.97-0.75]/vs [0.18; -0.82-0.62; P=NS] did not differ between prepubertal and pubertal. The most common clinical presentations between both groups were diffuse goiter (96.3%/96.6%; P=NS), hyperactivity (63%/41.9%; P=NS), frequent bowel movements (48.1%/51.6%; P:NS), sleep disturbances (44.4%/54.6%; P=NS) and palpebral fissures (37%/48.4%; P=NS). The most frequent ocular manifestation were exophthalmus (48.1%/58.1%; P=NS) and eyelid retraction (14.8%/16.1%; P=NS). Values of TSH (uIU/ml) ([0.01; 0.01-0.02])/vs (0.01; 0.01-0.02; P=NS), free T4 (ng/dl) ([2.24; 1.61-5.43]/vs [3.42; 2.18-6.35]; P=NS) and T3 (ng/dl) ([0.09; 258.5-644.8]/vs [410; 223-572]; P=NS) did not differ between groups.

Conclusions: We did not find any differences at presentation of GD among prepubertal and pubertal patients. Neuropsychiatric symptoms such as hyperactivity and sleep disturbances, together with exophthalmus are common features in children with GD.

P2-d2-775 Thyroid 2

Evaluation of CD4+CD161+-CD196+ and CD4+IL-17+ Th17 cells in the peripheral blood of young patients with Graves’ disease and Hashimoto’s thyroiditis

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Background: Up till now, altered balance of Th1 and Th2 immune cells has been postulated to play an important role in the pathogenesis of autoimmune thyroid diseases (AITD). However, recent studies on thyroid diseases suggest a new role for Th17 (T helper 17) cells that have been classified as a new lineage, distinct from Th1, Th2 and Treg cells. Despite wide interest, role of Th17 cells in the pathogenesis of inflammatory autoimmune diseases is still debated. Th17 cells are involved in immune responses against extracellular pathogens and have the ability to secrete cytokines: IL-17, IL-17F, IL-22 and IL-21. Th17 cells can be characterized by several surface markers, i.e. CCR6 (CD196), IL-23R, IL-12Rbeta2 and CD161.

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P2-d2-774 Thyroid 2

Impacts of triiodothyronine and α-tocopherol treatment in a patient with SBP2 mutations

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Background: Selenocysteine insertion sequence binding protein 2 (SBP2) plays a crucial role in selenoprotein synthesis. Selenoproteins, such as iodothyronine deiodinases and glutathione peroxidases, have physiological functions in thyroid hormone metabolism and antioxidant defense, respectively. The phenotypes of SBP2 deficiency are considered to be mediated by tissue-specific selenoprotein deficiencies and impaired antioxidant defense.

Objective: To investigate the effects of triiodothyronine (T3) and α-tocopherol (E) treatment for a patient with SBP2 mutations.

Methods: An 11-year-old Japanese boy with compound heterozygous SBP2 mutations (p.M515fsX563/Q79X) was treated with T3 (5 µg/day) and E (100 mg/day). The patient showed short stature, delayed bone maturation, easy fatigability, and characteristic thyroid hormone abnormalities, and had been receiving GH (0.175 mg/kg/week) since 4 years old. We monitored patient growth and bone age, along with various laboratory values, including levels of oxidative stress markers.

Results: Six-month T3 treatments slightly improved height score from -1.8 SD to -1.6 SD. Although GH monotherapy was unable to narrow the gap between chronological age and bone age, combined therapy T3 with GH advanced bone age by 22 months during an 8-month period that included 6 months of T3 therapy. Abnormal results for thyroid function tests were almost normalized after commencement of T3 therapy. Easy fatigability of the patient was not ameliorated after initiating treatment. Cardiovascular hyperactivitities, such as tachycardia, were not recognized during treatment. In terms of liperoxidation, total hydroxyoctadecanoic acid levels did not decrease, but 7β-hydroxycholesterol levels decreased after administration of E.

Conclusions: T3 replacement therapy appears safe and effective for normalizing thyroid function test results and advancing longitudinal bone growth and maturation, although positive effects on easy fatigability are lacking. E may decrease oxidative stress to some extent in SBP2 deficiency disorder.
Introduction: FOXP3 is a critical determinant of T regulatory cells (Tregs) development and function. Treg cells play a crucial role in modulating potentially self-reactive clones, and dysfunction of this cell type contributes to autoimmune disease such as Graves’ disease (GD) and Hashimoto’s thyroiditis (HT). The aim of our study was to estimate the association of three polymorphism of FOXP3 gene with the predisposition to GD and HT in Polish population.

Description of methods: The study was performed in the group consisting of 98 patients with GD (mean age, 17.3±6), 39 patients with HT (mean age, 18.4±5) seeking medical care from the endocrinology outpatient clinic and 158 healthy volunteers (mean age, 16.3±3). DNA was extracted from the peripheral blood leukocytes using a classical salting out method. The three SNPs rs3761549 (~2383C/T), rs3761548 (~3279G/T) and rs3761547 (~3499T/C) in the FOXP3 gene were genotyped by TaqMan SNP genotyping assay using the real-time PCR method. The levels of thyroid hormones, TSH and anti-thyroid autoantibody were determined using chemiluminescence method.

Results and conclusion: In our study the frequencies of -3279G/T polymorphism were significantly different in patients with HT (14.4%) and healthy volunteers (6.2%); p < 0.05. There was no difference in the distribution of other analyzed polymorphisms of FOXP3 gene between the studied groups. This result may suggests that -3279G/T polymorphism in FOXP3 gene could have a protective role in predisposition to HT.

P2-d2-777 Thyroid 2

Iodine supply and prevalence of thyroid autoimmunity and autoimmune thyroiditis in children and adolescents between 1 and 16 years old

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Background: Thyroid autoimmunity is related to iodine supply. Iodine nutrition has improved in our country, but the prevalence of autoimmune thyroiditis in our children is unknown.

Objective and hypotheses: To determine the status of iodine nutrition in children and adolescents in our city. To calculate local prevalence of thyroid autoimmunity and autoimmune thyroiditis in pediatric ages and to research into associated factors.

Methods: Cross-sectional epidemiological study. By a multistage probability sampling 1387 children and adolescents aged between 1 and 16 were selected. Physical examination was carried out including neck palpation. Parents were asked about eating habits as well as about social and demographic aspects. Urinary iodine, free thyroxine, TSH, antiperoxidase and antithyroglobulin antibodies were measured. Thyroid autoimmunity was diagnosed when any antibody was positive and autoimmune thyroiditis when autoimmunity was associated with impaired thyroid function or goitre. Results are shown using percentages (and its 95% confidence interval). To study associated variables with thyroid autoimmunity and with urinary excretion of iodine we used multiple logistic regression, quantifying the relation with odds ratio (OR), and multiple linear regression, respectively.

Results: Median urinary iodine concentration was 199.5 mcg/L. The prevalence of thyroid autoimmunity and autoimmune thyroiditis were 3.7% (2.4-5.0) and 1.4% (0.4-2.4). Thyroid autoimmunity is associated with female sex (OR 2.78; p<0.001) and age (OR 1.30; p<0.001). Iodine status is associated with milk and dairy products (p<0.001) and vegetable intake (p=0.021), but not with use of iodated salt at home (p=0.1).

Conclusions: The iodine supply in children and adolescents in our city is optimal. Milk and dairy products are the most important iodine sources. Thyroid autoimmunity and autoimmune thyroiditis are prevalent in pediatric ages in our city mainly in females and older subjects.

P2-d2-778 Thyroid 2

Effects of selenium in early stage of autoimmune thyroiditis in childhood: an open-label pilot study

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Background: Evidence mostly declared in adults suggests that selenium (Se) could be useful as an adjunctive therapy in autoimmune thyroiditis.

Objective and hypotheses: To evaluate the role of Se supplementation in childhood autoimmune thyroiditis regarding its effect on thyroid-stimulating hormone (TSH), free T4 (fT4), thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TgAb) and thyroid volume.

Methods: We performed an open-label study in newly diagnosed 23 out-patient euthyroid children (mean age: 12.3±2.4 years) with Hashimoto’s thyroiditis (HT). They received only 50 µg L-selenomethionine per day, orally for 3 months. The baseline urinary iodine level, serum Se, TSH, fT4, TPOAb, TgAb concentrations and thyroid morphology by ultrasound were detected. We reanalyzed our group at the third month about TPOAb and TgAb changes, and compared with 30 healthy individuals (mean age: 12.1±2.1 years) at the sixth month about thyroid volume and echogenicity changes.

Results: Serum TPOAb, TgAb titers and thyroid echogenicity were unchanged according to the baseline with Se supplementation (Table 1). In the sixth month, prominent decrease in thyroid volume was noteworthy in our subjects with the ratio of patients with 34.8% (2%3) of whom had thyroid volume regression rate of ≥30% (Table 2); thyroid volumes were similar to healthy children.

Conclusions: In terms of TPOAb and TgAb, Se may not be effective in euthyroid period of HT but, Se seems to lead regression of thyroid volume in children with HT. Besides, our data showed that the role of Se in childhood autoimmune thyroiditis should be further investigated.

Table 1. The laboratory parameters before and after Se supplementation

<table>
<thead>
<tr>
<th>Study group</th>
<th>Baseline</th>
<th>3.month</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum selenium (µg/L)</td>
<td>88.52 ± 17.5</td>
<td>70.10 ± 17.5</td>
<td>0.77</td>
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<tr>
<td>TSH (mU/L)</td>
<td>4.12 ± 2.94</td>
<td>3.61 ± 2.01</td>
<td>0.61</td>
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<tr>
<td>fT4 (ng/dl)</td>
<td>1.31 ± 0.23</td>
<td>1.18 ± 0.15</td>
<td>0.92</td>
</tr>
<tr>
<td>TPO Ab (IU/ml)</td>
<td>406</td>
<td>220</td>
<td>0.53</td>
</tr>
<tr>
<td>Tg Ab (IU/ml)</td>
<td>148</td>
<td>123</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Table 2. Thyroid volume changes in study group with Se supplementation

<table>
<thead>
<tr>
<th>Study group</th>
<th>Baseline</th>
<th>6.month</th>
<th>p</th>
<th>Mean thyroid volume regression (%)</th>
<th>The ratio of patients with volume regression ≥30%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid volume (cm3)</td>
<td>10.46 ± 6.28</td>
<td>4.77 ± 4.01</td>
<td>0.007</td>
<td>45.7%</td>
<td>34.8% (2%)</td>
</tr>
</tbody>
</table>
The long-term effects of T4 plus T3 treatment in children with congenital hypothyroidism with inappropriately elevated TSH

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Background: Inappropriately elevated TSH levels have been reported in 20-50% of L-T4 (levothyroxine) treated cases with congenital hypothyroidism (CH), despite clinical euthyroidism and normal thyroid hormone concentrations.

Objective and hypotheses: We have previously demonstrated that, combined T4 plus T3 treatment achieved euthytoprinemia without causing clinical hyperthyroidism in children with CH who have inappropriately elevated TSH on L-thyroxine treatment (1). Our initial report included 10 patients who completed 1 year on combination treatment. Here, we present long-term evaluation of this treatment of 8 patients who completed 5 years on combination treatment.

Methods: Eight cases (5M, 3F) with CH (6 dygenesis, 2 goitrous) whose TSH levels were persistently elevated despite high-normal fT4 levels and can only be normalized with supraphysiological fT4 levels were included in the study. After five years follow up, we investigated anthropometric parameters, thyroid hormone levels and changes in the bone age.

Results: TSH levels normalized at the end of the first year of combination treatment and remained within normal ranges during consecutive years. Mean TSH and fT4 levels were significantly lower (p<0.005) during combination treatment compared to those during the last 1 year of LT4-only regimen (Table 1). The mean change in bone age in patients was 1.0±0.3/year for last 2 years under L-T4 treatment only and 1.15±0.3/year for 5 years with T4 plus T3 treatment (p=0.3). Height SDS did not show a significant change but BMI SDS decreased at the end of the first year of combination treatment and remained so, for the following 5 years.

Conclusion: Combined T4 plus T3 therapy is successful in suppression of resistant TSH and has positive metabolic effects continued in the long term with no demonstrable adverse outcome.

<table>
<thead>
<tr>
<th></th>
<th>T4-only treatment-mean of last 1 year</th>
<th>T4 plus T3-mean of 1st year</th>
<th>T4 plus T3-mean of 2nd year</th>
<th>T4 plus T3-mean of 3rd year</th>
<th>T4 plus T3-mean of 4th year</th>
<th>T4 plus T3-mean of 5th year</th>
<th>p value (T4-only vs. 5th year of T4 plus T3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (IU/ml)</td>
<td>19.95 ± 0.84</td>
<td>4.90 ± 0.66</td>
<td>6.66 ± 0.79</td>
<td>7.89 ± 0.33</td>
<td>7.25 ± 3.30</td>
<td>3.32 ± 2.81</td>
<td>&lt;0.001</td>
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<tr>
<td>fT4 (1.7 ng/dl)</td>
<td>7.33</td>
<td>4.03</td>
<td>7.05</td>
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<td>3.22</td>
<td>3.21</td>
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<tr>
<td>fT3 (2.6-4.4 pg/ml)</td>
<td>1.53 ± 0.21</td>
<td>1.05 ± 0.13</td>
<td>1.03 ± 0.16</td>
<td>1.00 ± 0.10</td>
<td>1.00 ± 0.96</td>
<td>0.96 ± 0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>Equivalent T4 dose</td>
<td>3.36 ± 0.24</td>
<td>4.31 ± 0.14</td>
<td>3.98 ± 0.61</td>
<td>4.17 ± 0.78</td>
<td>4.07 ± 3.64</td>
<td>0.088</td>
<td></td>
</tr>
<tr>
<td>T4 dose (IU/ml)</td>
<td>0.94</td>
<td>0.96</td>
<td>0.80</td>
<td>1.21</td>
<td>0.85</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>Height SDS</td>
<td>-0.67 ± 0.40</td>
<td>-0.55 ± 0.50</td>
<td>-0.50 ± 0.56</td>
<td>-0.56 ± 0.50</td>
<td>-0.50 ± 0.61</td>
<td>-0.61 ± 0.58</td>
<td>-0.38 ± 0.03</td>
</tr>
<tr>
<td>BMI SDS</td>
<td>0.60 ± 0.50</td>
<td>-0.00 ± 0.00</td>
<td>0.00 ± 0.13</td>
<td>0.13 ± 0.06</td>
<td>-0.05 ± 0.34</td>
<td>0.34 ± 0.00</td>
<td>-0.03 ± 0.00</td>
</tr>
</tbody>
</table>


Assessment of IL-17 and IL-23 levels in dynamics of autoimmune thyroid diseases in pediatric patients

Beata Sawicka1; Artur Bossowski1; Hanna Borosyewicz-Sanczyk2; Edyta Pietrewicz2; Anna Bossowska2

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Background: Autoimmune thyroid diseases(AITD) account for 30% of all organ-specific autoimmune disorders.Genetic background, environmental and endogenous factors play an important role in determining the activation of immune cells or the efficacy of the immunoregulatory pathways.

Objective and hypotheses: In recent years the world literature also underlined the correlation between inflammatory response against the thyroid gland and raised cytokines secretion. The aim of the study was to estimate the concentration of IL-17 and IL-23 in serum in patients with Graves' disease(GD), Hashimoto’s thyroiditis (HT) and in healthy control subjects.

Methods: The research was performed on the group of 22 patients with GD (average age 11.5±5.7years old),37 HT patients (13.8±6.2years old) and 21 healthy children(14.3±2.2years old). Laboratory analysis included the assessment of cytokines serum concentration, levels of anti-thyroid antibodies and basic hormone values.

Results: In untreated patients with autoimmune thyroid diseases we observed a significant elevation of IL-23 concentration in comparison to control group (GD:156.29±118.22 vs 69.04±38.23, p=0.004;HT:135.04±140.19 vs 69.04±38.23, p=0.046). The thyrotropin level in Graves’ disease led to decrease of cytokines levels in a period of 6-12 months. However, during 6-24 months of L-thyroxine therapy in Hashimoto’s thyroiditis there wasn’t any reduction of IL-23 concentration compared with healthy children. The analysis of IL-17 showed increased levels of this cytokine in cases with HT in comparison to the controls,(17.17±10.49 vs 11.38±2.99, p<0.021), which normalized in a process of treatment. The examined relationships between cytokines concentrations, anti-thyroid antibodies and hormone values in the cases of untreated GD revealed positive correlation between IL-23 and anti-TPO (r=0.368, p=0.038) as well as between IL-23 and TRAK (r=0.478, p=0.014).

Conclusions: Both IL-17 and IL-23 cytokines inducing inflammatory processes play an important role in developing of autoimmune thyroid diseases in children.
patients of the same group. No polymorphism was found in 80 children of healthy group but CT heterozygote mutation was detected in 20 ones of the same groups. It was found that gene polymorphism TTF1 (2084283 C/T) are not a risk factor for this disease. No polymorphism was detected on TTF-2 (rs98532) gene region in 94 children of congenital hypothyroidism group; GA heterozygote mutation in 4 children and GG homozygote mutation in 2 children were detected in the same group.

Conclusions: No polymorphism on the mostly seen regions of PAX-8, TTF-1, and TTF-2 genes which shows found in children with congenital hypothyroidism due to thyroid dysgenesis.

P2-d2-782 Thyroid 2
Bone status assessment in children with untreated idiopathic subclinical hypothyroidism
Raffaella Di Mase1; Manuela Cerbone2; Andrea Esposito3; Flavia Barbieri4; Martina Rezzuto5; Carla Ungaro6; Francesco Porcari7; Ciro Mainolfi1; Mariacarolina Salerno1
1University of Naples, Department of Pediatrics, Naples, Italy; 2University of Naples, Department of Radiology, Naples, Italy

Background: TSH is a negative regulator of skeletal remodeling by reducing formation and increasing resorption of bone. Therefore, even mild elevations of TSH may affect bone health. Dual-energy X-ray absorptiometry (DXA) is the most widespread diagnostic tool to assess bone status.

Objective and hypotheses: To evaluate whether untreated idiopathic subclinical hypothyroidism (SH) may affect bone health in childhood and to compare two different diagnostic tools such as DXA and quantitative ultrasound (QUS) in children.

Methods: Twenty-five children and adolescents (11 males) aged 9.8 ± 3.5 years (range 4.2-18.7) with untreated idiopathic SH were enrolled in the study. SH was diagnosed on the basis of normal FT4 levels with TSH concentrations between 4.2 and 10 mcU/ml. Children have been followed for 3.3 ± 0.3 years from the time of SH diagnosis. Twenty-five healthy children, aged 9.8 ± 3.3 years and sex-matched, were enrolled as controls. Patients and controls underwent DXA to evaluate lumbar spine bone mineral density (LS-BMD) and QUS to assess bone quality, measured as amplitude-dependent speed of sound (Ad-SoS) and bone transmission time (BTT).

Results: Mean LS-BMD z-score was −0.4 ± 1.4 in patients and −0.2 ± 1.2 in controls. Mean Ad-SoS z-score was 0.01 ± 1.0 in patients and 0.1 ± 1.2 in controls and mean BTT z-score was −0.03 ± 0.8 and 0.04 ± 1.1 respectively. All values were within the normal range, both in patients and in controls. There were no statistically significant differences between the two groups.

Conclusions: Bone health, evaluated by DXA and QUS, is not impaired in our children, despite long-term duration of idiopathic SH. Data about bone status provided by QUS are comparable to those provided by DXA. Therefore, QUS may provide a good, cheaper and safer screening test for bone evaluation in children with SH.

P2-d2-784 Thyroid 2
Thyrotoxicosis in prepubertal compared with pubertal children
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Background: Graves disease (GD) is the main cause of thyrotoxicosis in childhood. It is rare at this age and diagnosis and management of GD is more complicated in children than in adults.

Objective and hypotheses: To determine the incidence, clinical presentation and remission rate of thyrotoxicosis in childhood and to compare the clinical course between pre and pubertal group of patients.

Methods: We conducted a chart review of patients with GD admitted to our institution between 1996-2011. We collected data on their symptoms, physical examination, thyroid hormones levels at diagnosis and treatment. For separate analysis, we divided them into two groups according to pubertal stage at diagnosis.

Results: The study population consisted of 56 patients aged 11.8±4.0 years, M/F ratio was 13/43. Family history was positive in 62% of patients and 22% of patients were prepubertal. The average symptom duration was 10.5 months. The remission was achieved in 18 % of patients after 1.5-5 years and remission rate of thyrotoxicosis in childhood was compared to adults. We noticed the increased incidence of GD, especially at young age. There is a delay in diagnosis, ATD therapy is associated with adverse effects and remission rate is very low in this group of patients.

P2-d2-785 Thyroid 2
Autoimmune diseases induced by antithyroid drugs in childhood: is it time for close autoimmune follow-up?
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Background: Rheumatic manifestations are a rare side effect of antithyroid drugs (ATD) in hypothyroidism, especially propylthiouracil (PTU). Few cases have been reported in adults, but more rarely in childhood.

Objective and hypotheses: We report a case of PTU induced lupus in a young girl and we review the literature focusing on childhood.

Case presentation: A 167/12 year old girl was referred to our department with a 2-month history of arthralgias and conjunctivitis. She had a history of Graves disease, treated with PTU and Methimazole (MM) alternatively. She had a palpable non tender goiter, migrant polyarthralgia, especially to right hand. The erythrocyte sedimentation rate and serum C-reactive protein level were both normal. ANA, p-ANCA and c-ANCA antibody were positive. The perichondral discharge test was negative. The renal and respiratory function remained normal. At the computed tomography there was no evidence of glomerulonephritis and MRI showed endolymphatic duct and sac enlarged. The SLC26A4 gene analysis showed two mutations (1197delT, FS400 stop 431 and 1614 + 1G>A). Her partner is deaf without goiter or hypothyroidism. A perichondral discharge test will be performed. Computed tomography showed EVA. She presented two mutations in the SLC26A4 gene (L597S and Q706X). The second one is not reported in literature yet. After genetic counselling they decided to procreate and five moths ago was born a deaf male. She presented a normal neonatal screening for TSH, not goiter and normal thyroid function in all examinations. The SLC26A4 gene analysis is ongoing.

Conclusion: The phenotypic variability has been reported for SLC26A4 related-diseases and in some cases other genes can be postulated (FOXI1, KCNJ10) to explain the different intrafamiliar expression. Some authors suggested to review the classification in syndromic and non syndromic EVA.
P2-d2-786 Thyroid 2
R320H mutation in the thyroid hormone receptor beta (TRβ) with autoimmune thyroid disease in a Turkish family
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1Akdeniz University, Pediatric Endocrinology, Antalya, Turkey; 2Akdeniz University, Medical Biology And Genetics, Antalya, Turkey

Background: Resistance to thyroid hormone (RTH) is rare and dominantly inherited syndrome of reduced responsiveness of target tissues to thyroid hormone (TH). It is characterised by raised circulating free thyroxine (fT4) and serum thyrotropin (TSH) levels. The TRβ gene mutations is associated with RTH. Hashimoto’s thyroiditis is the most common autoimmune thyroid disease (AITD). The combination of RTH with AITD is reported that rare, approximately 1 in 1.3 million. However, RTH can be easily overlooked in the AITD.

Objective and hypotheses: We present R320H mutation of the TRβ gene in a Turkish family with RTH and AITD.

Methods: The patient was admitted to the pediatric endocrine department for evaluation of hyperthyroidism and palpable goiter at the 13 years of age. He showed elevated level of sT3, sT4 and TSH. Anti-Tg and anti-TPO antibodies were slightly positive, suggesting AITD. His brother, aged 20 years, showed elevated levels of TSH and sT4 who had positive anti-Tg and anti-TPO antibodies with palpable goiter. Their mother had non palpable goiter, euthyroidism with AITD. Heterozygous R320H mutation was identified in all cases in the genetic analysis.

Results: To date, more than 150 TRβ gene mutations have been identified. Molecular analysis, showed that R320H mutation was known disease-causing mutation in the TRβ gene, but is the first published in the Turkish population. In addition RTH and coincidental AITD has not been reported with R320H mutation of the TRβ gene. Moreover, the same mutation can result in considerable heterogeneity in the clinical manifestations. The reason is unknown but the same laboratory findings of both disease may be the presence of thyroid autoantibodies with RTH often leads to misdiagnosis and treatment.

Conclusion: As the case of our patients shows, hight serum TH and TSH levels with diagnosis of AITD, should consider the question of RTH and must be corrected with molecular analysis.

P2-d2-787 Thyroid 2
A boy with thyroid hormone resistance: from diagnosis to final height
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1Faculty of Medical Science - University of Campinas (Unicamp), Endocrinology Unit - Pediatric Department/CIPED, Campinas, Brazil; 2University of Campinas (Unicamp), Laboratory of Human Molecular Genetics - CBMEG, Campinas, Brazil

Background: Thyroid Hormone Resistance is a rare inherited disease, caused by mutations in thyroid hormone receptor β gene (THRβ). The variable magnitude of hormone resistance in the different tissues is responsible for the diversity of phenotypes. Therefore, clinical and laboratory evidence of thyroid hormone (TH) excess and deficiency may coexist.

Objective: We report a six-year-old boy presenting goiter, high levels of THs with the initial diagnosis of hyperthyroidism. Aggressive and hyperactive behavior and learning difficulty have been reported by his parents.

Methods: Clinical findings included hyperkinetic behavior, goiter, normal resting pulse and low weight-for-height (Zsc= -1.85). THs serum levels were always increased with normal TSH secretion (basal and after TRH) and normal levels of thyroid-binding globalin. At the age of 10 years, T3 therapy was started in order to ameliorate the attention-deficit hyperactive disorder, despite clinical euthyroidism.

Results: After 6 months of treatment his parents reported behavior improvement: he was doing better in school and his hyperactivity was reduced. During the treatment, he presented bone age acceleration and concluded his puberty in 19 months, reaching a final height of 169.3 cm (Zsc= -1.7) - target-height of 170.0 cm (Zsc=0.9). THRβ gene was amplified and sequenced. The molecular analyses identified a leucine to valine substitution in codon 454 (L454V).

Conclusion: The clinical presentation of Thyroid Hormone Resistance ranges from asymptomatic and euthyroid patients to variable signs of thyrotoxicosis and hypothyroidism. The same mutation may exhibit different clinical manifestations. We describe a boy with signs of hypothryoidism (learning disability and initial delayed bone age) presented along with hyperactivity (suggesting excess of TH). The most likely explanations for these findings are the dominant negative effect of a mutant THRβ (mTHRβ) interfering with a normal THRβ and the impaired association of mTHRβ with cofactors (co-activators and corepressors) that modulate receptor-dependent action of TH.

P2-d2-788 Thyroid 2
Normal values of thyroid volume, TSH, T3 and T4 in school children aged 5-18yrs living in a long-standing iodine replete area; Relation to BMI
Irene Kaloumenou; Antonis Voutetakis; Maria Alevizaki; Leonidas Duntas; Dimitrios Chiotis; Christos Ladopoulos; George Matorakos; Catherine Damou-Voutetakis
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Background: The definition of normal values of thyroid function indices in the pediatric population has created controversies and therapeutic dilemmas, especially with regard to TSH, and its relation to BMI.

Objective and hypotheses: To outline the mean as well as the 5th and 95th percentile values of thyroid hormones, TSH and thyroid volume, at different ages, in a cohort of school children, after excluding all subjects with any objective evidence of thyroid abnormality, and to also determine whether or not in this “normal” sample, TSH is related to BMI.

Population and/or methods: Out of 440, apparently healthy school children, aged 5-18yrs, 69 were excluded on the basis of any abnormal laboratory results. The relation of TSH to BMI SDS was calculated. The relation of TSH to BMI SDS was also determined.

Results: Table 1. Results in the entire group (males and females)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>mean (±SD)</th>
<th>5th percentile</th>
<th>95th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH mcU/ml</td>
<td>2.0 (0.96)</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>T3 ng/dl</td>
<td>1.67 (0.33)</td>
<td>1.1</td>
<td>2.18</td>
</tr>
<tr>
<td>T4 mcg/dl</td>
<td>8.7 (4.5)</td>
<td>6.5</td>
<td>10.74</td>
</tr>
<tr>
<td>Thyroid volume (ml)</td>
<td>4.82 (2.63)</td>
<td>2.16</td>
<td>11.11</td>
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</tbody>
</table>

No relation of TSH to BMI SDS was detected in this sample (in either males or females) in which the mean±SD values of BMI SDS were in males 0.17± 1.17 and in females 0.08± 1.0, whereas there was relation of BMI to thyroid volume (P 0.012), Pearson correlation.

Conclusions: We consider the range of values in this, specifically selected cohort, as representing reference values for thyroid indices at this developmental stage. Moreover, the lack of correlation between TSH and BMI indicates that although, reportedly, TSH values may be higher in obese children, in children within the normal BMI range, TSH is not related to BMI.
Do children with Hashimoto’s thyroiditis need a life-long treatment with l-thyroxine?

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1Regional Hospital of Bolzano, Department of Pediatrics, Bolzano, Italy; 2Institute G. Gaslini, University of Genova, Department of Paediatrics, Genova, Italy; 3Microcitemico Hospital, ASL Cagliari, Paediatric Endocrinology Unit, Cagliari, Italy; 4Bambin Gesù Children’s Hospital, IRCCS Roma, Unit of Endocrinology and Diabetes, Roma, Italy; 5Institute San Raffaele, Milano, Department of Pediatrics, Milano, Italy; *S.Orsola Malpighi, Bologna, Department of Pediatrics, Bologna, Italy; 1Regional Hospital of Pisa, Department of Pediatrics, Pisa, Italy; *University of Naples Federico II, Naples, Department of Pediatrics, Napoli, Italy; 6Regina Margherita Children Hospital, Torino, Department of Paediatric Endocrinology, Torino, Italy

Background: Recent studies on the natural history of Hashimoto’s thyroiditis (HT) showed that in many patients thyroid function recovers over the years. Moreover the criteria to start a treatment with l-thyroxine have changed (TSH > 10 TAGGontoffTAgymfromnTAGGontoffTAGGistdfonU/mL).

Objective and hypotheses: To verify after discontinuation of treatment, how many patients needed to resume it, based on the TSH and FT4 levels.

Population and methods: We evaluated 51 children and adolescents (9 months–18 years) affected with HT and in treatment with l-thyroxine for at least 1 year, who were examined in 5 Italian Centres of Paediatric Endocrinology. TSH and FT4 serum level were assayed at baseline and after 2, 6 and 12 months.

Treatment with l-thyroxine was restarted when TSH raised above 20 µU/ml and FT4 serum level were assayed at baseline and after 2, 6 and 12 months.

Preliminary results: at baseline TSH was in the normal range in all 51 patients; treatment was restarted after 2 months in 15/51 (29.4%) patients, after 6 months in 1/51 (2%) patients, after 12 months in 1/51 (2%) patients (see figure).

Conclusion: from our preliminary data it seems that not all children affected with Hashimoto’s thyroiditis need a life-long therapy.

Background: Central endocrine dysfunction is a hallmark of PWS. However, it may evolve over time, as shown by the contrast between the normal mini-puberty of infancy (reference 1) and the hypogonadotropic hypogonadism commonly seen at later ages. Central hypothyroidism has recently been reported to occur in infants with PWS (reference 2), but whether it is present at birth is unknown.

Research question: Is thyroid function normal at birth in PWS?

Methods: We retrieved the newborn screening blood spot to measure total T4 in 21 patients with genetically-confirmed PWS born between 2002 and 2011. The results of blood spot TSH, which is the primary screening test for congenital hypothyroidism in our jurisdictions, were also analyzed. The results of each patient were compared to those of 4 healthy neonates born on the same day and matched for sex, birth weight (±200 g) and age at screening (±2 h). To correct for T4 decay in stored blood spots over time, T4 results are expressed as the ratio of the value measured in the neonate with PWS to that of the 4 matched controls.

Results: The median ratio of T4 of the neonates with PWS to that of the matched controls was 1.09 (range: 0.17 to 2.03, p = 0.20, t-test). Likewise, median TSH (mU/L whole blood) was similar in neonates with PWS and controls: 2 (range 0 to 5) vs 3 (range 0 to 12), p > 0.20, Mann-Whitney test.

Conclusions: We found no evidence for central hypothyroidism at birth in PWS. Further study is needed to determine how frequently it occurs at later ages, when screening should start and whether treatment affects the PWS phenotype.

A patient with Allan-Herndon-Dudley syndrome due to a complete deletion of exon 1 of the MCT8 (SLC16A2) gene

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Background: In 1944, Allan, Herndon and Dudley described a severe form of X-linked mental retardation with a particular thyroid hormone profile that was later known as AHD syndrome. Years later, mutations in MCT8 (SLC16A2), a gene that codes for a thyroid hormone transporter, were found to cause this syndrome. Since then, affected males from 47 families carrying an hemizygous mutation in MCT8 have been described.

Objective and hypotheses: 30 month old patient, second son of a non-consanguineous couple, delivered by C-section at 39 weeks. The patient’s neonatal screening for hypothyroidism was reported normal. At 3 months of age, he was somnolent and difficult feeding, which required a gastrostomy. At 2 years old he was central hypotonia, not cephalic support, wide anterior fontanel, depressed nasal bridge, telecanthus, bulbous nose, prominent upper lip and is unable to speak. Thyroid tests show a particular profile: high T3, T4 in the lower limit of normal range, and normal TSH, sugest AHD syndrome.

Methods: The molecular study of MCT8 was performed by amplifying each of its six exons, following the method described by Schwartz 2005.

Results: The genomic DNA sample of this patient only allowed the amplification of five exons of MCT8. Despite many attempts, the expected 773 pb product of exon 1 was never obtained. The molecular study of MCT8 was the same in the mother.
Conclusions: The results are consistent with a deletion that completely spans exon 1 of MCT8. To our knowledge, this would be the 48th family in which a MCT8 mutation has been identified. Of all mutations, 52% are point mutations, 31% small indels and the remaining 17% large deletions. The complete deletion of exon 1 has been found in 4 different families, the rest are private mutations. This recurrence of the complete exon 1 deletion could be indicative of a genomic region prone to deletions. The loss of exon 1 predicts a complete inactivation of the MCT8 transporter and is associated with a severe phenotype where independent walk or speech are never attained. Our patient presents this severe phenotype.

P2-d2-792 Thyroid 2

Approach to the etiologic diagnosis of dyshormonogenesis
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Background: Defects in thyroid hormone biosynthesis, which accounts for 15-20% of the primary Congenital Hypothyroidism (CH) cases, has been linked to mutations in the sodium iodide symporter (NIS), thyroid peroxidase (TPO), dual oxidase 2 (DUOX2), DUOX maturation factor 1 (DUOXA2), iodothyronine deiodinase 1 (DEHAL1) and thyroglobulin (TG) genes.

Objective and hypotheses: Approach to the etiology of hormone biosynthesis defect in patients with congenital hypothyroidism and thyroid orthotopic.

Methods: 50 infants with CH and thyroid gland in place were included in the study. Children older than 2 years old, and still undergoing the L-thyroxine (LT4) treatment underwent a diagnostic algorithm. After LT4 was discontinued for three weeks, thyroid function tests (TFT) were obtained. A scintigraphy with I123 and perchlorate discharge test (PDT) was performed. 

Results: 43 patients (23 men and 20 women) completed the trial. Among these children, eight had transient CH. Among patients with permanent CH, nine had total iodine organisation defect with positive PDT. Six showed partial organisation defect (Duox, Tpo partial). Six showed TG deficit. One had a mutation in the NIS (normal thyroidal stimulation and absence iodine uptake in thyroid), three had other dyshormonogenesis with negative PDT and ten displayed hypertirotiropinaemia when reevaluated. Table: Values and limits of in thyroid), three had other dyshormonogenesis with negative PDT and ten displayed hypertirotiropinaemia when reevaluated. Table: Values and limits of

<table>
<thead>
<tr>
<th></th>
<th>TSH (n)</th>
<th>TSH (r)</th>
<th>T4L (r)</th>
<th>TG</th>
<th>Perchlorate discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPO</td>
<td>(mIU/mL)</td>
<td>(mIU/mL)</td>
<td>(ng/dL)</td>
<td>(ng/mL)</td>
<td></td>
</tr>
<tr>
<td>(n: 9)</td>
<td>(63 - 685)</td>
<td>(426 - 295)</td>
<td>0.29</td>
<td>964</td>
<td>83.1%</td>
</tr>
<tr>
<td>TG</td>
<td>(n: 6)</td>
<td>(75 - 605)</td>
<td>(0.2 - 0.5)</td>
<td>0.41</td>
<td>2</td>
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<tr>
<td>DUOX / TPO</td>
<td>(n: 6)</td>
<td>(13 - 268)</td>
<td>(3.8 - 27.2)</td>
<td>0.89</td>
<td>1.59</td>
</tr>
<tr>
<td>Duox partial</td>
<td>(n: 6)</td>
<td>(13 - 268)</td>
<td>(3.8 - 27.2)</td>
<td>0.89</td>
<td>1.59</td>
</tr>
<tr>
<td>Transient</td>
<td>(n: 8)</td>
<td>(48 - 223)</td>
<td>(2.1 - 4.2)</td>
<td>1.2</td>
<td>1.59</td>
</tr>
<tr>
<td>Hypertirotiropinaemia</td>
<td>(n: 11)</td>
<td>(18.1 - 586)</td>
<td>(6.2 - 55.0)</td>
<td>0.7 - 1.59</td>
<td>272.26</td>
</tr>
<tr>
<td>MS (n: 1)</td>
<td>&gt; 100</td>
<td>&gt; 378</td>
<td>&lt; 0.1</td>
<td>50</td>
<td>not catchment</td>
</tr>
</tbody>
</table>

Conclusions: The diagnostic reassessment by analytical determination, scintigraphy and perchlorate discharge test guides the etiologic diagnosis of patients with dyshormonogenesis, prior to genetic testing.

P2-d1-793 Turner Syndrome 2

Uterine development in patients with Turner syndrome: relation to hormone replacement therapy and karyotype
Heba Elsedly; Rasha Hamza; Mohamed Farghaly; Mohamed Ghazy; 'Ain Shams University, Pediatrics, Cairo, Egypt; 'Ain Shams University, Radiodiagnosis, Cairo, Egypt

Background: It is not clear from previous studies whether impaired uterine development in Turner syndrome (TS) patients is due to delayed estrogen replacement, too low dosage, or is related to karyotype.

Objective and hypotheses: To assess uterine development in TS patients and its relation to dose and type of estrogen therapy; and karyotype.

Methods: Pelvic ultrasound was used to assess uterine size and shape, and ovarian volume in 40 TS patients. Information on hormone replacement therapy (HRT) was collected from patients’ notes.

Results: Among 40 studied subjects, 57.5% started estrogen therapy and 30% were taking progestins. Sixty five% had immature uterus, 17.5% had fully mature uterus and 17.5% had transitional uterus. Uterine volume was associated with age (p<0.001), height (p=0.002), weight (p=0.001), years of estrogen use (p<0.001), estrogen dose (p=0.016), current estrogen use (p<0.001) and Tanner breast stage (p<0.001). Uterine volume was not affected by type of estrogen used (p=0.40) and Karyotype (p=0.40).

Conclusions: Patients with TS treated with estrogen (adequate dose and duration) may attain a normal, mature uterine size and configuration even at a late start of HRT and regardless of karyotype. Table 1 Immature versus mature uterus in TS patients (n=40). Fig. 1: Correlation between immature uterus and duration of estrogen therapy Fig. 2: Correlation between uterine volume and dose of estrogen therapy.

<table>
<thead>
<tr>
<th>Immature uterus</th>
<th>Mature uterus</th>
<th>t/x2</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>16.1 ± 3.7 (9.7 – 24.3)</td>
<td>23.9 ± 1.5 (21.8 – 26.3)</td>
<td>6.18</td>
</tr>
<tr>
<td>Karyotype, 45X, n (%)</td>
<td>1(43.2)</td>
<td>2(28.6)</td>
<td>12.15</td>
</tr>
<tr>
<td>Karyotype, 46X (Xq), n (%)</td>
<td>5(19.2)</td>
<td>1(4.2)</td>
<td>3.65</td>
</tr>
<tr>
<td>Currently taking HRT, n (%)</td>
<td>10(38.5)</td>
<td>7(100)</td>
<td>16.34</td>
</tr>
<tr>
<td>Uterine length (cm)</td>
<td>3.6 ± 0.6 (2.5 – 4.9)</td>
<td>7.0 ± 0.4 (6.5 – 7.6)</td>
<td>13.55</td>
</tr>
<tr>
<td>Uterine width (cm)</td>
<td>1.4 ± 0.7 (0.7 – 3.0)</td>
<td>3.4 ± 0.5 (2.9 – 3.8)</td>
<td>11.12</td>
</tr>
<tr>
<td>Uterine thickness (cm)</td>
<td>1 ± 0.4 (0.5 – 1.7)</td>
<td>2.3 ± 0.5 (1.8 – 2.6)</td>
<td>10.38</td>
</tr>
<tr>
<td>Uterine volume (mL)</td>
<td>3.4 ± 3.1 (0.6 – 10.3)</td>
<td>27.9 ± 4.4 (20.2 – 33.2)</td>
<td>17.21</td>
</tr>
<tr>
<td>FCFS</td>
<td>1.1 ± 0.1 (0.9 – 1.5)</td>
<td>1.4 ± 0.8 (1.3 – 1.5)</td>
<td>4.99</td>
</tr>
</tbody>
</table>

51st Annual Meeting of the ESPE
Horm Res 2012;78(suppl 1)
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P2-d1-794 Turner Syndrome 2

**Combined treatment of recombinant human growth hormone and stanozolol improve growth velocity and final adult height in girls with Turner syndrome**

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**Objective:** To evaluate the effect of combined treatment with recombinant human growth hormone (rhGH) and low dosage stanozolol on growth velocity (GV) and final adult height (FAH) in young patients with Turner syndrome (TS).

**Methods:** Forty-three Chinese girls with TS, aged (12.6 +/- 1.9) yr, were treated with daily subcutaneous injections of rhGH (1.0-1.1 IU/kg/w) and oral stanozolol (0.02-0.04 mg/kg/d) for 0.5-5 years. GV, height standard deviation score (SDS) by reference of healthy Chinese girls (HtSDSNor) and height SDS by reference of untreated Chinese TS girls (HtSDSTS) were evaluated regularly. Of the forty-three girls studied, thirteen had discontinued the treatment after a mean duration of (2.9 +/- 1.2) years when GV was less than 2 cm/yr or when patients were satisfied with the achieved height. FAH or near-final height, which defined as the most recent available height after discontinuation of treatment, and the height gain for the thirteen girls were evaluated.

**Results:** GV increased from <4 cm/yr to (8.8 +/- 2.3) cm/yr in the first sixth month, and GV for the 1st year, 2nd year, 3rd year, 4th year and 5th year was (8.6 +/- 2.0) cm/yr, (6.4 +/- 1.6) cm/yr, (5.5 +/- 1.5) cm/yr, (4.7 +/- 2.1) cm/yr, and (4.4 +/- 0.1) cm/yr respectively. HtSDSNor also increased from (-4.2 +/- 1.0) to (-3.4 +/- 1.0) in the first year, and (-2.8 +/- 1.0), (-2.4 +/- 0.8), (-2.5 +/- 0.5), (-2.3 +/- 0.3) respectively in the subsequent year. The change of HtSDSTS was similar to HtSDSNor. The 13 girls predicted adult height (PAH) was (142.8 +/- 4.2) cm before treatment. FAH was (151.7 +/- 4.3) cm, which was significantly higher than PAH (P < 0.001), the mean height gain was (8.9 +/- 2.8) cm (5.1-12 cm). FAHSDSNor increased to (-1.6 +/- 0.8) from (-3.8 +/- 0.8).

**Conclusions:** For Chinese girls with TS above approximately 9 yr of age, combined therapy with rhGH and the low dosage stanozolol significantly increase growth velocity and improve final adult height.

P2-d1-795 Turner Syndrome 2

**Selected factors in the development of atherosclerosis in patients with Turner syndrome**

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**Background:** Coronary heart disease (CHD) is the most common cause of death in Turner syndrome (TS). Generally known risk factors for atherosclerosis such as obesity, diabetes, hypertension and dyslipidemia although appear in adults with TS are rarely observed in children. The increased synthesis of factors predisposing to the development of atherosclerosis such as homocysteine (HC), endothelin1 (ET) and ADMA can be one of TS features.

**Objective and hypotheses:** The estimation of the selected parameters of development of atherosclerosis in patients with TS.

**Methods:** 44 patients with TS aged 12.5 +/- 4.5 years were analyzed. Anthropometric data were as follows: mean height 135.2 +/- 22.1 cm, height SDS -1.8 +/- 0.9, weight 38.4 +/- 15.3 kg, BMI 19.7 +/- 3.57 kg/m2, BMI SDS 0.3 +/- 1.1. 15 parents matched with age and weight constituted control group. The analysis of serum biochemical parameters (CRP, cholesterol, triacylglycerol [TGI]) was performed immediately; plasma for estimation of HC, ET and ADMA was frozen and subsequently analyzed with immunoenzymatic methods.

**Results:** Mean concentration of HC in TS (7.925.2 µmol/l) was significantly higher than in control group (6.5 +/- 2.4 µmol/l), p = 0.03. Mean concentration of ET in TS (24.7 +/- 45.4 pg/ml) was also significantly higher than in control group (3.6 +/- 0.4 pg/ml), p = 0.00035. There was no similar difference in ADMA level. The concentration of HC correlated with age (r = 0.53), height (r = 0.46) and weight (r = 0.46) in patients with TS. Concentrations of ET and ADMA did not correlated with anthropometric parameters, but only with TG level (r = 0.41, r = 0.40). A significant correlation between ET and ADMA (r = 0.40) was found.

**Conclusions:** Levels of HC and ET are higher in young patients with TS despite of unchanged body mass and normal concentration of lipids. The estimation of them in youth is therefore important in the prevention of CHD.

P2-d1-796 Turner Syndrome 2

**Results of molecular genetic studies on latent mosaicism and parental origin of X chromosome in girls with Turner syndrome**

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1Republican specialized research and practical medical center of endocrinology, laboratory of endocrine diseases epidemiology and organization of endocrinological service, Tashkent, Uzbekistan; 2Republican specialized research and practical medical center of endocrinology, endocrinology, Tashkent, Uzbekistan

**Background:** The determination of latent mosaicism and parental origin of X chromosome in girls with Turner syndrome is very important from the viewpoint of setting correlations between a phenotype and karyotype.

**Objective and hypotheses:** Identification of latent mosaicism and determination of a parental origin of an X chromosome in TS patients in Uzbek population.

**Methods:** Molecular genetic studies are carried out in 35 patients with TS (26 with monosomy, 9 with mosaicism) at the age of 7 to 16 and their parents with a set of DIATOMTM DNA prep 200 reagents. DNA amplification was performed in Applied Biosystems thermocyclers. PCR products were subjected to electrophoresis on 12% acrylamide bis-acrylamide gel (29:1) with subsequent DNA staining with ethidium bromide and visualization by a BioDocAnalyze (Biorad) system.

**Results:** Three X-linked markers (DMD 49, AR and DX1283E) were studied on the basis of their high level of heterozygosis (varying from 88.6 to 93.3%), a number of alleles (11 to 19) and localization both on a short and long X chromosome arm. The results obtained confirm that the use of these primers (DMD 49, AR and DX1283E) will allow enhancing a probability of obtaining an informative marker and detection of latent X-mosaicism. Monozogy on all 3 markers indicates the presence of only one X chromosome that in female patients will correspond to true monosomy (X0). Heterozygosis of one marker suggests on the presence of an additional second X chromosome or a part of an X chromosome which is observed both in 46XX karyotype (healthy) and in mosaic variants of chromosomal anomalies (45X0-46XX, 45X0-46XY).

**Conclusions:** A comparative analysis of polymorphic markers in TS patients and their parents enable us to establish the origin of an X chromosome and determine in gametogenesis of which parents meiotic impairment occurred. Identification of mosaicism in Turner syndrome is very important from the viewpoint of setting correlations between a phenotype and karyotype.

P2-d1-797 Turner Syndrome 2

**Time distant effects of growth hormone treatment in patients with Turner syndrome: the influence on anthropometric parameters and metabolic status**

**Hanna Magnuszewskak, Maria Szymanska, Piotr Wisniewski, Dorota Birkholz-Walerzak, Maria Korpal-Szczyszka, Krzysztof Sworczak**

1Medical University of Gdansk, Department of Paediatrics, Hematology, Oncology and Endocrinology, Gdansk, Poland; 2Medical University of Gdansk, Department of Endocrinology and Internal Medicine, Gdansk, Poland

**Background:** Beneficial effect of growth hormone (GH) therapy on height in patients with Turner syndrome (TS) is confirmed. Data suggest also other advantages: reduction of overweight, decrease in body fat mass (BFM) and serum lipids level. Influence on carbohydrate metabolism, especially after discontinuation of GH therapy is still discussed, the more that patients with TS are at increased risk of metabolic disturbances.
Objective and hypotheses: Evaluation of time distant results of GH treatment in TS, including height, weight, body composition and metabolic status.

Methods: 49 girls with TS: 33 after GH treatment (45X: 39%, mosaic: 36%, abnormal X: 24 %, age 20.8±3.7 yrs) and 16 girls never treated GH (45X: 31%, mosaic: 56%, abnormal X: 13%, age 21.3±5.9 yrs). Age on start of GH therapy in treated group was 11.8±2.7 yrs, treatment duration 5.2±3.4 yrs. Interval between GH discontinuation and study 4.3±3.1 yrs. All included patients received estrogen replacement therapy or were after spontaneous puberty. Height, weight, BMI, waist to hip ratio (WHR), BFM were measured. Serum lipids, thyroid hormones, oral glucose tolerance test (OGTT) were performed. Indices of insulin sensitivity and β-cell function were calculated (HOMA-IR, Matsuda index (MI) and HOMA-β).

Results: TS patients previously treated GH were higher (154.6±6.2 vs 148.1±5.7 cm, p=0.001), the difference was also significant when compared with parental height (hSDS - mp hSDS: -1.3±0.9 vs -2.2±0.9, p=0.01). TS treated with GH had lower BFM (27.3±5.9 vs 31.7±6.25%, p=0.04), BMI, WHR, serum lipids didn’t differ significantly between groups. Indices of insulin sensitivity and β-cell function derived from fasting state were similar, but considering MI derived from OGTT, the percentage of insulin resistant patients in GH treated group was lower (33.3% vs 62.5%, p=0.05).

Conclusions: GH therapy in TS significantly improves height, decreases BFM and insulin resistance. Benefits maintain after years of discontinuation of treatment.

P2-d1-799 Turner Syndrome 2
Medical follow-up of young women with Turner syndrome in the transition phase is still inadequate
Aneta Gawlik; Agnieszka Zachurzok-Buczynska; Barbara Kaczor; Halia Kaminska; Ewa Malecka-Tendera
Medical University of Silesia, Department of Paediatrics, Paediatric Endocrinology and Diabetes, Katowice, Poland

Background: Smooth transition from pediatric to adult health care is a critical point for patients with chronic disorders.

Objective and hypotheses: The aim of the study was to evaluate the quality of medical follow-up of the young women with Turner syndrome (TS) a few years after the guidelines introduced by the TS Study Group.

Methods: A questionnaire study was performed in 59 TS adults selected from a database of 117 patients. Twenty-two of them, aged 23.0±2.8 yr, consented to participate.

Results: 19 (86.4%) patients were followed up by general practitioners (GPs) who were not aware of the TS diagnosis in 14 (63.6%) cases. Eight (36.4%) patients were seen regularly by the relevant specialists, 4 (18.2%) were followed up by both endocrinologist and gynecologist. Adequate medical assessment varied from 5% (celiac serology) to 74% (gynecology assessment) and 82% (ear-nose-throat assessment) of participants. None of the patients had undergone all of the recommended investigations. Height deficiency, BMI, age of TS diagnosis and level of education did not correlate with the number of assessments performed (p =0.687; p =0.810; p =0.641, p =0.568, respectively). Eighteen (81.8%) responders had regular meals while on HRT: thirteen (59.1%) received estrogen and progestagens delivered by transdermal routes and five (22.7%) were treated with oral contraceptive pills.

Conclusions: It is concluded that three years after the guidelines introduction medical follow-up in the transition phase is still inadequate. Improvements in transitional health care is warranted through patients’ better education, referring to physicians caring for adults with TS and better cooperation with GPs with wider popularization of the TS recommendations among them.

P2-d1-800 Turner Syndrome 2
Turner syndrome and Madelung deformity: influence of GH treatment and karyotype
Alessia Stilemi; Alessandra Nicolosi; Valeria Panebianco; Stefano Passanisi; Maria Andaloro; Manuela Caruso Nicoletti
University of Catania, Department of Medical and Pediatric Sciences, Catania, Italy

Background: Madelung deformity (Md) is a marker of the bone dysplasia present in Turner Syndrome (TS). We previously reported that Md, not clinically evident, detected by measure of Ulnar Tilt (UT), Lunate Subsidence (LS), Triangulation index (T) in hand and wrist X-Ray is frequent in TS patients (Horm Res 2012;78(suppl 1).P2-d1-828). Response to GH treatment is variable and influenced by several factors.

Objective and hypotheses: To assess the relationship between the response to GH treatment in TS patients, Madelung deformity (detected measuring UT, LS and T) and karyotype.

Methods: We analyzed in 21 TS patients: Karyotypes, height SDS and age at start of GH treatment, GH dose, length of treatment, parents height and final stature SDS. We evaluated the presence of Md by measuring UT, LS and T (McCarroll HR Jr et al., J Hand Surg Am, 2005).

Results: Mean final height SDS was -2.1±1; mean height SDS gain was 0.44±1. No correlation was found between these parameters and Md measures. Patients with 45,XO/46,XisoXq karyotype showed the worst final height and the worst UT and LS values, compared to patients with others karyotype (45,X0, mosaicism, other X chromosome anomalies).

Conclusions: Our data suggest that response to GH treatment is not significantly affected by the presence of minor hand and wrist bone dysplasia; however we found that patients with 45,X0/46,XisoXq karyotype had both worst final height and UT and LS values; therefore we cannot exclude that this karyotype is more frequently associated with bone dysplasia and that this negatively influence response to GH treatment.

P2-d1-799 Turner Syndrome 2
The utility of ultrasound examination in diagnosis of autoimmune thyroid disorders in girls with Turner syndrome
Aneta Gawlik1; Aleksandra Januszek-Trzciakowska2; Tomasz Gawlik2; Agnieszka Zachurzok-Buczynska3; Ewa Malecka-Tendera1
1Medical University of Silesia, Department of Paediatrics, Paediatric Endocrinology and Diabetes, Katowice, Poland; 2Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Department of Nuclear Medicine and Endocrine Oncology, Gliwice, Poland

Background: Turner’s syndrome patients (TS) are known to have an increased risk for thyroid disorders, especially Hashimoto’s thyroiditis (HT).

Objective and hypotheses: The aim of the study was to analyze the utility of ultrasound examination (US) in diagnosis of autoimmune thyroid disorders in TS girls.

Methods: Eighty six TS patients with a median age of 10.6 years (mean 10.0±4.0; range from birth to 17.4) were followed for 4.6±3.0 years. Out of them, 31 (36%) had positive thyroid autoantibodies (TAb) and 27 (31.4%) had subclinical hypothyroidism. HT was diagnosed in 15 girls. US examination was performed at least once during follow-up period and diffuse low echogenicity was considered as an indicator of thyroid autoimmune disorder.

Results: US showed thyroid hypoechogenic pattern in 32.5% of all subjects. Typical decreased thyroid echogenicity was present in 66% of TS patients with autoimmune thyroiditis (HT) and in 14 % of TS girls without thyroid disturbances (p =0.008). In 4 (26.6%) TS girls with HT and in 2 (12.5%) with only positive TAb, characteristic hypoechogenicity was ahead of biochemical markers of autoimmune thyroid disorders. Positive and negative predictive value, sensitivity and specificity for low echogenicity as an indicator of HT were 45.4%, 91.4%, 66.7% and 81.5%, respectively.

Conclusions: It is concluded that thyroid ultrasound examination could be a valuable tool for the diagnosis and follow-up of thyroid disorder.
**P2-d1-801** Turner Syndrome 2

**Pelvic magnetic resonance imaging in Turner syndrome**  
Maria Cristina Maggio¹; Anita De Pietro²; Francesca Serraino²; Paolo Porcelli³; Tommaso Angileri³; Giovanni Corsello¹  
¹University of Palermo, Materno-Infantile, of Andrology and Urology, Palermo, Italy; ²Villa S. Teresa Diagnostica per Immagini e Radioterapia, Diagnostic Operative Unit, Bagheria, Italy; ³Azienda Ospedali Riuniti Villa Sofia-Cervello, Operative Unit of Endocrinology, Palermo, Italy

**Background:** Adolescents with Turner Syndrome (TS) live a difficulty related to the prospective to have spontaneous pubertal development and menarche as well as to their future fertility. These questions have relevant psychological-therapeutic implications on clinical and endocrine follow-up and represent critical points in the TS management. Some patients have spontaneous menarche and do not need estrogen replacement in the first years of adolescence. This evolution is not always predictable on the basis of hormonal pattern and echographic imaging, while it is described in patients with mosaicism.

**Methods:** We studied 17 patients with TS, age: 9-16 years, caryotype 45,X in 9 patients, mosaic in 8. We did not included TS with Y chromosome, because they underwent to gonadectomy to prevent neoplasm risk. We studied caryotype, endocrine assess (FSH, LH; Prolactin, TSH, FT3, FT4, IGF-1), pelvic imaging to determine uterine and ovarian size and to compare uterine and ovarian size evaluated by transabdominal ultrasound (US) and by Magnetic Resonance imaging (MRI). We correlated the data described by imaging and caryotype, FSH, LH, estradiol levels.

**Results:** MRI revealed higher definition of uterine, ovarian volume and morphology, follicular volume, endometrial thickness, uterine body/neck ratio. MRI measured a bigger ovarian volume compared to US; ovarian follicles were detected by MRI not by US. The presence of a bigger ovarian volume and ovarian follicles was not related to caryotype (mosaicism vs. 45,X); two patients with a spontaneous pubertal development and menstrual cycles were 45,X. 8 patients with mosaicism did not show a spontaneous pubertal development and needed estrogen replacement treatment. The presence of ovarian follicles was relieved by MRI in patients with spontaneous menarche and the persistence of menstrual cycles was related to a significant ovarian volume.

**Conclusions:** We stress the utility of MRI in the pelvic study in the follow-up of TS to help in the decision of cryopreservation.

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**P2-d1-802** Turner Syndrome 2

**Case of heterokaryotic monozygotic twins discordant for Turner syndrome diagnosed with amniocentesis**  
Claudia Piona; Elena Monti; Grazia Morandi; Giulia Rodella; Evelina Maines; Giuseppina De Luca; Rossella Gaudino; Claudia Piona; Elena Monti; Grazia Morandi; Giulia Rodella; Evelina Maines; Giuseppina De Luca; Rossella Gaudino; Franco Antoniazzi  
University of Verona, department of Life and Reproduction, Verona, Italy

**Introduction:** Different karyotype in monozygotic twins is called heterokaryotic monozygosity. We describe a case of monochorial diamniotic twins both of whom have 45,X/46,XX mosaicism resulted from karyotype analysis on postnatal blood samples but differ in prenatal diagnosis of complete monosomy 45 XO in twin B and a normal karyotype 46,XX in twin A resulted from amniocentesis.

**Case report:** After a pregnancy characterized by maternal preeclampsia and discrepancy results of two karyotype and the therapeutic approach. Buccal smears could better clarify the phenotypical difference between twins, discrepancy results of two karyotype and the therapeutic approach.

**Conclusion:** Karyotype analysis on peripheral lymphocytes in monozygotic and monochorial twins may be different from prenatal karyotype. This divergence is presumably due to anastomoses between the placentae resulting in a mixture of the two cell populations in the hematopoietic tissue. Therefore it is described in patients with mosaicism.