P2-d1-618 GH and IGF Physiology 1

**IGF system is not normal in well-controlled HIV children**

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**Background:** New therapeutic strategies have contributed for better control of HIV infection, however, still a significant amount of children have growth impairment. Studies regarding the IGF system in HIV children are scarce.

**Objective and hypotheses:** To characterize serum concentrations of IGF-I, IGF-II, IGFBP-1 and IGFBP-3 in prepubertal children and their relationship with growth in two different conditions of clinical control.

**Methods:** 38 children aged 5-12yr were evaluated every 6 months during 1.5 years. Evaluation of disease control was based on the occurrence of any disease related with immunosuppression, HIV viral load and CD4+ T lymphocyte count. Two blood sample from each patient, one collected during a better clinical control (GC) and another during a worse clinical control (PC), were selected for IGF-I, IGF-II, IGFBP-1 and IGFBP-3 determinations (ELISA).

**Results:** Patients with more GC periods showed higher height velocity (HV) than those with more PC periods (5.7±1.0 vs. 4.9±1.2cm/yr; P=0.03). No difference between GC and PC was found regarding IGF-I (median: 137 vs. 131ng/ml), IGF-II (630 vs. 612ng/ml) or IGFBP-3 (131 vs. 135ng/ml), IGF-II (630 vs. 612ng/ml) or IGFBP-3 (3.7 vs. 3.8mg/l) but a trend towards lower IGFBP-1 levels in GC was observed (68 vs. 73ng/ml; P=0.04 one-tail-test). The concentration of IGF-I, IGF-II and IGFBP-3 were calculated, and obesity degree was evaluated according to International Obesity Task Force (IOTF) standard. Genomic DNA was extracted from their peripheral blood leukocytes, and GHR exon3 gene polymorphism were detected by polymerase chain reaction (PCR). Serum Fasting glucose, insulin and lipid profile were measured, and HOMA-IR and ISI were calculated using homeostasis model. All the data were analyzed by SPSS statistics software.

**Results:**

1. The frequency of d3 gene of obesity group is significantly higher than that of the control group (p<0.05).
2. In the obesity group, BMI, fasting insulin, HOMA index, total cholesterol, triglyceride of the d3-GHR (d3/d3 and d3/fl) group was significantly lower than that of the fl-GHR (fl/fl) group (p<0.05). The insulin sensitive of the d3 group is significantly higher than the non-d3 group (p<0.05).
3. In the control group, 46 subjects were d3 gene, and 160 were fl. There existed no statistical difference in BMI, fasting insulin, HOMA index, insulin sensitive index, total cholesterol and triglyceride between two genotypes.

**Conclusions:** We first report that the d3-GHR polymorphism has significant effect on children’s metabolic profile in Chinese obesity children, d3/d3 and d3/fl polymorphism might play protective effect on metabolic syndrome development sensitivity.

**P2-d1-620 GH and IGF Physiology 1**

**The growth hormone receptor (GHR) exon 3 polymorphism and its correlation with metabolic profile in Chinese obesity children**

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**Background:** The GHR exon 3 polymorphism previously must be investigated for association with a number of disorders mainly on impaired growth, its impact on the metabolic children has not been studied.

**Objective and hypotheses:** To investigate the GHR exon 3 polymorphism and its correlation with the metabolic profile in Chinese obesity children.

**Methods:** 409 obesity/overweight children and 206 normal weight children were recruited. Body weights and heights were measured, body mass indexes were calculated, and obesity degree was evaluated according to International Obesity Task Force (IOTF) standard. Genomic DNA was extracted from their peripheral blood leukocytes, and GHR exon3 gene polymorphism were detected by polymerase chain reaction (PCR). Serum Fasting glucose, insulin and lipid profile were measured, and HOMA-IR and ISI were calculated using homeostasis model. All the data were analyzed by SPSS statistics software.

**Results:**

1. The frequency of d3 gene of obesity group is significantly higher than that of the control group (p<0.05).
2. In the obesity group, BMI, fasting insulin, HOMA index, total cholesterol, triglyceride of the d3-GHR (d3/d3 and d3/fl) group was significantly lower than that of the fl-GHR (fl/fl) group (p<0.05). The insulin sensitive of the d3 group is significantly higher than the non-d3 group (p<0.05).
3. In the control group, 46 subjects were d3 gene, and 160 were fl. There existed no statistical difference in BMI, fasting insulin, HOMA index, insulin sensitive index, total cholesterol and triglyceride between two genotypes.

**Conclusions:** We first report that the d3-GHR polymorphism has significant effect on children’s metabolic profile in Chinese obesity children, d3/d3 and d3/fl polymorphism might play protective effect on metabolic syndrome development sensitivity.

**P2-d1-619 GH and IGF Physiology 1**

**Mutational screening of the AKT1 gene in patients born small for gestational age (SGA)**

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**Background:** SGA (small for gestational age) characterizes individuals with a birth length/birth weight two standard deviations below the mean of a reference population. Several homo-/-homozygous mutations in the GH (growth hormone) - IGF1 (insulin growth factor 1) axis have been described, leading to intrauterine and/or postnatal growth retardation. Proliferation, cell differentiation and modulation of apoptosis are some of the pleiotropic effects of protein kinase PKB/AKT1. Akt1 deficient mice show a growth retardation of twenty percent compared to wildtype littermates. Gain-of-function mutations in the PH-(pleckstrin homology) domain of AKT1 found in human ovarian, colorectal and breast cancer result in increased cell proliferation and induce leukemia in mice.

**Objective and hypotheses:** To find mutations in the AKT1 gene that interfere with protein kinase activation as a possible cause of growth retardation in children born SGA.

**Methods:** Seventy patients born SGA with high IGF1 serum levels and no postnatal catch-up growth were selected for mutational screening. PCR products of all exons were pre-screened using dHPLC and WAVE® Navigator Software. aberrant PCR samples were further analysed by dideoxy sequencing.

**Results:** Four not yet annotated heterozygous SNVs (single nucleotide variations) in six different patients were identified. Three SNVs were found upstream of the coding region (one in the 5’ UTR and two in the intron region between exons one and two, whereas c.1251C>T occurs as synonymous variation in three different patients.

**Conclusions:** The functional effects of the novel SNVs remain hypothetical.

**SNVs in the intron region can impact on the splicing process, while the SNV in the 5’ UTR can affect the translation efficiency or mRNA stability. Further studies in larger cohorts and functional investigations are necessary to disclose a possible relevance of the SNVs. Moreover, genetic analyses of known regulatory promoter and enhancer/silencer regions are on the way.**

**P2-d1-621 GH and IGF Physiology 1**

**Progressive reduction of growth hormone responsiveness to combined test (GHRH + Arginine or Pyridostigmine) in Prader-Willi Syndrome (PWS) children**

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**Background:** Growth hormone (GH) deficiency has been demonstrated in the majority of PWS patients, but it doesn’t seem due to obesity. GH releasing hormone (GHRH) plus Arginine (ARG) or Pyridostigmine (PD) is a potent combined provocative test to evaluate the maximal secretory capacity of pituitary somatotroph cells. No longitudinal studies have evaluated in PWS changes of GH secretion in the same subject with age.

**Objective and hypotheses:** Aim of the study was to evaluate the influence of age on GH responsiveness in PWS children using such test.

**Methods:** We performed a combined test in 10 prepubertal PWS patients (8 del, 2 UPD) at 0.7-9.9 years of age and re-evaluated after a period of 7.02±2.07 years (range: 4.6-10.7). BMI-SDS did not change during the follow-up. GH treatment was discontinued almost 4 months before retesting. All subjects underwent GHRH plus ARG (0.5 g/kg iv) or pyridostigmine (60 mg orally) test (cut-off: 20 ng/ml), IGF-1 and GH at baseline, 30, 45, 60, 90, 120 min were measured. The area under the curve of GH (AUC), BMI-
**P2-d1-622 GH and IGF Physiology 1**

**Heterogeneous clinical presentation in patients with yet-unreported type 1 IGF receptor molecular defects**

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**Background:** Fetal growth is a complex process involving various intrinsic and extrinsic factors. The Insulin-like growth factor system is critical for the control of fetal and postnatal development. However, few IGF1 and IGF type 1 receptor (IGF-1R) molecular defects have been identified in patients born with intrauterine growth retardation/small for gestational age (IUGR/SGA).

**Objective and hypotheses:** We searched for molecular anomalies of the IGF1 and IGF-1R genes in 5 patients with IUGR/SGA, postnatal growth retardation and elevated IGF-1 serum levels.

**Results:** Analysis of the patients' IGF1 gene was normal. We identified 5 IGF-1R molecular defects, 4 of which previously unreported: one patient presented a heterogeneous nonsense mutation resulting in an early truncated protein and probably a haplosufficiency for this receptor. The patient phenotype includes microcephaly, mental retardation without deafness. High dose of GH increased growth velocity. Three patients had a heterozygous missense mutations, each affecting a highly conserved aminoacid in the tyrosine kinase domain. Two of them were resistant to GH therapy and had a mild mental development impairment, whereas one showed an increased growth velocity under GH and did not show mental development delay. MLPA analysis for the fifth patient showed a heterogeneous interstitial deletion of chromosome 15q including the entire IGF-1R gene. She was microcephalic but did not have mental developmental delay. Her growth velocity increased under high dose of GH therapy. The 3 missense variations were studied using PolyPhen software and predicted to be highly damaging for the receptor function.

**Conclusions:** We report 5 patients harbouring 5 IGF-1R molecular defects (4 among them are yet-unreported variations) predicted to result in a diminished activity of the receptor. These patients all presented IUGR, microcephaly and moderate to elevated IGF-1 serum levels. The phenotype severity, the existence of a mental retardation and the GH response to treatment were variable.

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**P2-d1-623 GH and IGF Treatment 1**

**Growth response in 17 growth hormone (GH)-treated patients with congenital adrenal hyperplasia (CAH) in comparison to patients with GH-deficiency (GHD) and Turner syndrome (TS)**

Christopher J Child1; Werner F. Blum2

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**Background:** Adult height (Hi) in patients (pts) with CAH may be compromised due to glucocorticoid treatment, and early epiphyseal fusion resulting from androgen excess and secondary precocious puberty.

**Objective and hypotheses:** Previous studies with GH and GnRH analogues in CAH have shown improved height velocity (HV) and final height (FH). To determine the outcome of GH treatment in pts with CAH treated in typical pediatric endocrine practice, we evaluated 1-yr HV and FH SDS gain in pts with CAH, compared to those of pts with GHD and TS enrolled in the prospective, multinational GeNeSIS observational program.

**Methods:** Seventeen pts with CAH (10 female, 7 male; 16 from USA) who had 1-yr GH treatment HV available were identified from 16345 GH-treated pts enrolled in GeNeSIS. In addition to CAH, GHD was reported for 3 pts (18%) and TS for 2 pts (12%). Sixteen pts (94%) were reported as receiving glucocorticoids and 9 (53%) as receiving aromatase inhibitors or GnRH agonists.

**Results:** At baseline (pre-GH treatment), compared to pts with GHD and TS, pts with CAH had similar chronological age, but were taller, had significantly greater bone age SDS, Hi SDS, Ht SDS–target Ht SDS and BMI SDS; the majority of pts in all groups were pre-pubertal (data not shown). After 1 yr of GH treatment at mean dose similar to that used for pts with TS, Hi SDS gain was 0.1 ± 0.3 for CAH vs 0.5 ± 0.4 for TS (p<0.05). At FH overall duration of GH treatment was shorter for CAH, and unlike pts with GHD and TS, those with CAH had no Hi SDS gain from baseline (p<0.05 for between-group difference; table).

**Table:** Patient characteristics and growth parameters at baseline and during GH treatment (mean ± SD [95% confidence interval]).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CAH (N=17)</th>
<th>GHD (N=8151)</th>
<th>TS (N=1209)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline age (yr)</td>
<td>9.9 ± 2.2</td>
<td>9.5 ± 4.1</td>
<td>8.9 ± 3.7</td>
</tr>
<tr>
<td>Baseline bone age SDS (Growth-Pyle)</td>
<td>2.4 ± 2.0</td>
<td>1.1 ± 3.7</td>
<td>1.4 ± 1.5</td>
</tr>
<tr>
<td>Baseline height SDS</td>
<td>-0.9 ± 1.6</td>
<td>-2.2 ± 1.6</td>
<td>-1.4 ± 1.5</td>
</tr>
<tr>
<td>Baseline height SDS - target height SDS</td>
<td>-0.2 ± 1.2</td>
<td>-2.0 ± 1.2</td>
<td>-2.6 ± 1.1</td>
</tr>
<tr>
<td>Baseline BMI</td>
<td>1.1 ± 0.6</td>
<td>0.3 ± 0.3</td>
<td>0.3 ± 0.1</td>
</tr>
<tr>
<td>Pre-treatment height velocity (cm/yr)</td>
<td>5.2 ± 2.0</td>
<td>4.7 ± 2.4</td>
<td>4.9 ± 2.3</td>
</tr>
<tr>
<td>Baseline max GH peak µL/mL</td>
<td>14.1 ± 8.4</td>
<td>7.5 ± 7.7</td>
<td>13.5 ± 10.8</td>
</tr>
<tr>
<td>Initial GH dose (mg/ kg/yr)</td>
<td>0.34 ± 0.3</td>
<td>0.25 ± 0.2</td>
<td>0.25 ± 0.2</td>
</tr>
<tr>
<td>First year height velocity (cm/yr)</td>
<td>6.2 ± 2.3</td>
<td>9.0 ± 2.6</td>
<td>7.9 ± 1.9</td>
</tr>
<tr>
<td>Δ height SDS after 1 yr of GH</td>
<td>0.1 ± 0.3</td>
<td>0.6 ± 0.5</td>
<td>0.5 ± 0.4</td>
</tr>
<tr>
<td>Final height SDS</td>
<td>-0.9 ± 1.0</td>
<td>-0.9 ± 1.0</td>
<td>-1.7 ± 0.9</td>
</tr>
<tr>
<td>Final height GH gain</td>
<td>-0.1 ± 0.7</td>
<td>1.4 ± 1.1</td>
<td>1.1 ± 0.9</td>
</tr>
<tr>
<td>GH treatment duration (yr)</td>
<td>3.5 ± 2.5</td>
<td>5.0 ± 3.2</td>
<td>5.3 ± 2.7</td>
</tr>
</tbody>
</table>

*Maximum N, lower for certain parameters: N=10 (CAH), 2054 (GHD), 362 (TS); aSignificantly different from GHD and TS (p<0.05).

**Conclusions:** GH treatment, started at close to 10 yrs of age, had no beneficial effect on 1-yr GH treatment HV or FH in this small group of pts with CAH.
P2-d1-624 GH and IGF Treatment 1

Long-term efficacy of growth hormone in short Japanese children born small for gestational age
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Background: Beneficial effects of growth hormone (GH) treatment on height in short, European, small for gestational age (SGA) children have been seen in both short- and long-term studies. However, the efficacy of long-term GH treatment in equivalent Japanese children has not been studied.

Objective and hypotheses: To investigate the long-term efficacy of two doses of GH in short Japanese children born SGA.

Methods: This was a multicentre, double-blind, randomised trial comparing two doses of GH for the treatment of short stature in prepubertal (Tanner Stage 1) Japanese children born SGA. Treatment was 0.033 mg/kg/day (n=39) or 0.067 mg/kg/day (n=38) or no treatment (n=21) for an initial 52 weeks. Following this, those in the no treatment group were randomised to receive 0.033 mg/kg/day or 0.067 mg/kg/day (n=10) for a further 208 weeks. Primary endpoint was change in height standard deviation score (SDS) for chronological age (CA). Secondary endpoints included change from baseline in height velocity (HV) SDS, bone age (BA), ratio of BA/CA and metabolic parameters.

Results: Mean height SDS for CA at baseline was -2.89 and a dose-dependent increase from baseline was seen in both treatment groups. After 260 weeks (5 years) of treatment, the mean height SDS for CA increased from -3.00 to -1.78 in the 0.033 mg/kg/day group and from -2.83 to -0.82 in the 0.067 mg/kg/day group. Bone age increased during GH treatment with the mean (SD) change in bone age of 6 yrs and 7 months; years in the 0.033 and 0.067 mg/kg/day treatment groups respectively. Both doses of GH were well tolerated with few adverse events occurring related to treatment.

Conclusions: Long-term treatment with GH improved height SDS in a dose dependent manner in short, prepubertal Japanese children born SGA and was well tolerated in this patient population.

P2-d1-625 GH and IGF Treatment 1

A novel POU1F1 mutation (p.Thr168IlefsX7) associated with an early and severe form of combined pituitary hormone deficiency: functional analysis and follow-up from infancy to adulthood
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1Ha’Emek Medical Center, Pediatric Endocrine Unit, Afula, Israel; 2Hôpital Trousseau, INSERM U.933, Paris, France

Background: POU1F1 encodes a pituitary-specific homeodomain transcription factor that is crucial for development and differentiation of anterior pituitary cell types producing GH, TSH and PRL. Although the first mutations in humans were reported in 1992, to date, less than 25 different mutations of POU1F1 have been identified worldwide.

Objective and hypotheses: To describe the long-term follow-up of a 22-year-old male of Israeli Arab Muslim origin, born to a consanguineous union, with congenital hypothyroidism, who presented with life-threatening hypoglycemia and severe growth retardation from infancy. To identify the molecular basis of this severe disease.

Methods: Endocrine investigations, neuroimaging, sequencing of POU1F1 and assessment of the identified mutated POU1F1’s ability to transactivate three specific targets (POU1F1, TSHβ and PRL).

Results: Central hypothyroidism was diagnosed at the age of 2 months and GH and PRL deficiencies were documented at 9 months. MRI at 14 years revealed hypoplastic adenohypophysis. The patient underwent spontaneous but delayed puberty. A novel disease-causing mutation (c.502insT) was identified in the homoyzgous state in exon 4 of POU1F1. This insertion results in a frameshift introducing an early termination codon at position 174 (p.Thr168IlefsX7), leading to a severely truncated protein lacking the entire homeodomain. This mutation abolishes POU1F1’s transactivation properties on three target promoters.

Conclusions: This study, which identifies a novel loss-of-function mutation in POU1F1, describes the phenotype of a rare condition in a patient followed from the first weeks of life to adulthood. The severity of the central hypothyroidism should alert clinicians to assess other pituitary axes, in particular GH and prolactin.

P2-d1-626 GH and IGF Treatment 1

Short-term outcome of a patient with Majewski osteodysplastic primordial dwarfism type II (MOPD II) treated with rhIGF-1
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Background: MOPD II (MIM 210720) belongs to the primordial dwarfism group characterized by IUGR, severe proportionate short stature and microcephaly. We describe the case, diagnosed as Seckel syndrome, of a male child born preterm from healthy unrelated parents (31 weeks, W 585 gr, L 31 cm), with severe microcephaly, beaked nose and post-neocrotic cirrhosis. Biochemical evaluations (at the age of 4 yrs) showed a lack of response to an IGF-1 generation test and a low IGF-1 level (<-2 SDS). At our observation (at the age of 6 yrs and 7 months): H 63 cm (-10.3 SDS), W 4.860 gr, head circumference 41 cm (-8 SDS), delayed bone age of 4 years, fine and sparse hair, micrognathia, macronodular cirrhosis and radiological features of skeletal dysplasia. Following the clinical data, the diagnosis was revised to MOPD II syndrome. Molecular analysis of the PCNT gene showed a homozygous splicing site mutation in position 3608-2-A>G intron 18, found in heterozygosity in his parents.

Objective: We assessed the impact of the recombinant IGF-1(rhIGF-1) treatment on auxological outcome.

Methods: The patient received rhIGF-1 (Increlex TM, Tercica, Brisbane, CA, USA) starting with 0.04 mg/kg in 2 doses/day, with an increase of 0.04 mg/kg after one week until the maximum dose of 0.12 mg/kg.

Results: At six months from the start, the growth rate was 2 cm (-2.21 SDS), with an increment in bone age of 1 year and a half. No response was observed in the subsequent 6 months. Because of worsening of dysplasia, therapy was discontinued.

Conclusions: The rhIGF-1 treatment does not seem to be able to replace the physiological action of IGF-1 in MOPD-II patients with IGF-1 insufficiency. The combined recombinant GH-IGF-1 treatment could have better results in these patients, but effects on bone age maturation and dysplasia should be considered.

P2-d1-627 GH and IGF Treatment 1

Can growth hormone deficiency diagnosis be affected by the GH immunoassay used?
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Background: In current clinical practice, the diagnosis of GHD in childhood relies on biofunctional measurement of GH secretion after at least two stimulation tests in combination with auxological parameters and radiological findings. The peak GH concentration below 10 ng/ml have traditionally been used to support the diagnosis, notwithstanding the inter-assay variability of different commercial assays for measuring GH.

Objective and hypothesis: The aim of the study was to evaluate the contribution of calibrators used in GH assay in leading to different GH results and the impact on the formulation of GH diagnosis and the subsequent decision to start the GH substitutive therapy.

Method: During the last year, 23 short children (5 females and 18 males), with the clinical characteristics of a condition of GHD and requiring GH

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Horm Res 2011;76(suppl 2) 195
Conclusions: These data suggest that the use of different calibrators may have a great impact on the formulation of a diagnosis of GHD, the subsequent decision to start GH substitutive treatment and on the expenses for covering the costs of the therapy.

**P2-d1-628** GH and IGF Treatment 1

Subcutaneous rhIGF-1 significantly increases circulating IGF-1 concentrations in children with Crohn's disease induced growth failure

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Background: There is no established treatment for growth failure in Crohn’s disease (CD). Patients have low circulating insulin-like growth factor-1 (IGF-1). Recombinant human IGF-1 (rhIGF-1) improves growth in animal models of colitis and children with genetic GH insensitivity syndrome, but has never been used in CD-induced growth failure.

Objectives and hypotheses: We hypothesised that subcutaneous (SC) rhIGF-1 would increase circulating IGF-1 concentrations, and that twice daily injections would maintain them.

Methods: 8 children with active CD and growth failure were recruited for a pharmacokinetics study of rhIGF-1 (Inrelex). SC rhIGF-1 (dose 120 μg/kg) was given, and levels measured over 24 hours. The children were then studied over a 5 day period of repeated doses. Blood glucose levels were monitored. Protein losing enteropathy (PLE) was measured by stool alpha-1-antitrypsin and related to the IGF binding protein-3 and IGF-1 levels attained.

Results: The median age (range) of the children was 12.97 yrs (10.67-14.82). 4 were female, 4 male. All children had negative height velocity standard deviation scores (SDS) (mean -3.34, SD 1.13), and all were in early puberty. rhIGF-1 was well tolerated, with only one patient having an (asymptomatic) hypoglycaemic episode. 7 of 8 patients had low baseline IGF-1 (mean SDS -1.78, SD 1.37). All had low IGFBP-3 (mean SDS -1.75, SD 0.52) that was independent of stool alpha-1-antitrypsin levels (p=0.75). The 3 hour circulating IGF-1 levels increased significantly in all children following SC rhIGF-1 (mean SDS 2.70, SD 3.06) (p=0.007) and were maintained above 0.0 SDS by twice daily injections without any consistent effect on GH levels. PLE did not inhibit this response.

Conclusions: SC rhIGF-1 significantly increased circulating concentrations of IGF-1 in children with CD-induced growth retardation. These results support the initiation of trials to assess the impact of long-term rhIGF-1 replacement therapy on linear growth.

**P2-d1-629** GH and IGF Treatment 1

Efficacy and safety of growth hormone (GH) in the treatment of children with hypochondroplasia (HCP); comparison with a historical cohort of untreated children with HCP

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1Hospital Necker Enfants Malades, Pediatric Endocrinology, Paris, France; 2Hospital Necker Enfants Malades, Medical Genetics Department, Paris, France; 3Hospital Necker Enfants Malades, Pediatric Endocrinology and Diabetes, Paris, France; 4Merck Serono s.a.s, Endocrinology, Lyon, France; 5Hospital Necker Enfants Malades, Physiology Laboratory, Paris, France; 6CNRS, UPR 2147, Paris, France; 7Université Paris Descartes, Hospital Necker Enfants Malades, Pediatric Endocrinology and Diabetes, Paris, France

Background: HCP is a skeletal dysplasia, mainly caused by mutations in the fibroblast growth factor receptor 3 (FGFR3) gene expressed in the growth plates of long bones during endochondral ossification. The importance of this growth defect is variable and it is due, in part, to an inadequate pubertal growth spurt.

Objective: To determine the efficacy of GH therapy in 19 children with HCP, compared with a historical cohort of 40 untreated children with HCP.

Methods: The HCP subjects were diagnosed on specific skeletal abnormalities and confirmed by two experienced physicians of the Bone Dysplasia Center, Necker Hospital, Paris, France. From the historical cohort data, growth charts were derived and height standard deviation scores (SDS) calculated. The 19 studied patients (9 male, 10 female) with initial height ≤-2 SDS were included in the study and treated at a mean (SD) age of 9.0 (3.0) yrs (range 3–14 yrs) with a mean GH (Saizen®, Merck Serono) dose of 0.053 (0.005) mg/kg/day (dose adjusted with IGF-I levels) over 3 yrs. This Phase II study was approved and conducted according to the French legal authorities. Interim results after 2 yrs of treatment are presented.

Results: The height gain was +0.57±0.70 SDS compared with a standard population, but it was +1.43±0.96 SDS and persistent over the 2 yrs compared with the historical cohort. Upper segment increased proportionally; % fat mass decreased during the 1st yr. There was no significant change in BMI, vertebral bone mineral density or response between patients with FGFR3 mutation (n=11) and the patients without mutation. No safety signals appeared.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Gain during 1st yr treatment</th>
<th>Gain during 2nd yr treatment</th>
<th>Total gain during 2 yrs treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (SDS)</td>
<td>-2.80±0.83</td>
<td>0.42±0.33*</td>
<td>0.15±0.51</td>
<td>0.57±0.70**</td>
</tr>
<tr>
<td>BMI (SDS)/Sempe1</td>
<td>1.50±1.22</td>
<td>-0.12±0.94</td>
<td>0.21±0.72</td>
<td>0.09±1.08</td>
</tr>
<tr>
<td>Height/HCPS (SDS)2</td>
<td>-0.53±1.09</td>
<td>0.75±0.55</td>
<td>0.68±0.88</td>
<td>1.43±0.96</td>
</tr>
<tr>
<td>BMI/HCPS (SDS)2</td>
<td>-0.38±1.45</td>
<td>0.01±0.82</td>
<td>0.34±1.12</td>
<td>0.35±1.26</td>
</tr>
<tr>
<td>Upper segment (SDS)</td>
<td>-0.90±1.14</td>
<td>-0.42±0.5</td>
<td>0.61±1.05</td>
<td>1.03±0.96</td>
</tr>
<tr>
<td>% Fat body mass</td>
<td>1.13±0.81</td>
<td>-0.66±0.69</td>
<td>0.07±0.52</td>
<td>-0.59±0.73</td>
</tr>
<tr>
<td>BMD (Zscore)3</td>
<td>-1.90±1.21</td>
<td>0.034±0.6</td>
<td>0.29±0.65</td>
<td>0.32±0.72</td>
</tr>
<tr>
<td>IGF-I (Zscore)4</td>
<td>-1.07±0.89</td>
<td>1.39±0.57</td>
<td>1.48±1.60</td>
<td></td>
</tr>
</tbody>
</table>

*p<0.05; **p<0.01 1vs Sempe table values 2vs values of a non-treated historical cohort of pts with HCP 3Lumbar spine density evaluated by dual X-ray absorptiometry 4IGF-I values at M0, M12, M24

Conclusions: These 2-yr interim results suggest that GH is effective and well tolerated in improving growth in patients with HCP. The effect on pubertal growth spurt remains to be determined.
P2-d1-630 GH and IGF Treatment 1
Accurate long-term prediction of height development during growth hormone (GH) treatment in prepubertal children with growth hormone deficiency (GHD) and Turner syndrome (TS)

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Background: Treatment with GH during the pre-pubertal years is essential for improvement of the height outcome of short children. Optimizing and individualizing GH therapy requires the accurate simulation of height development based on empirical growth prediction models early during the course of treatment.

Methods: Pre-pubertal children with idiopathic GHD or TS documented within KIGS (Pfizer International Growth Database) were analysed. In a first step, cohorts which had previously been used to develop models for the prediction of height velocity (HV) during the first four pre-pubertal years of GH treatment were analyzed and a prediction algorithm for the annual gain in weight for an observed gain in height was developed. In a second step, the height simulations were validated in a separate population (validation cohort: 664 GHD and 607 TS patients from GH start up to 4 prepubertal years). The most likely height development was simulated prospectively by sequential application of the newly developed algorithms for gain in weight and the existing yearly prediction algorithms for HV.

Results: When height was simulated from GH start in GHD, the predicted mean (SD) gain after 4 years was 30.4 (3.4) cm when the first year model included GHmax, and 30.5 (2.9) cm when not, while the observed gain in height was 30.0 (5.0) cm. In TS the corresponding predicted and observed mean gains were 27.2 (2.2) cm and 26.5 (3.8) cm respectively. The simulation model was predictive in all but 22 (3.3%) of the 664 cases of the GHID validation cohort from GH start. This proportion was below 2% for all of the TS cohort or when simulation started after the first year of treatment (GHD and TS), using 98% confidence intervals.

Conclusion: Sequential application of annual prediction models permits accurate simulation of height development during the first four years of GH treatment in GHD and TS. The system is applicable for groups from GH start and for individuals after experiencing the 1st year growth response.

P2-d1-631 GH and IGF Treatment 1
Growth hormone treatment in a family with Léri Weill syndrome due to contiguous gene syndrome

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Background: Léri Weill syndrome (LWS) is a pseudoautosomal inherited skeletal dysplasia being associated with SHOX haploinsufficiency (short stature homeobox-containing gene). It is located at the pseudoautosomal region (PAR) of the sex chromosomes. Clinical findings in LWS include mesomelic skeletal dysplasia being associated with short stature and mental retardation. Altogether they have 3 affected sons, which are treated with GH starting at Tanner stage 1.

Results: In boy 1 treatment started at age 5.7 years (height -2.7 SDS). After 2.2 years height SDS gain was 0.7. Boy 2 was treated from age 4.5 years (height -2.2 SDS) for two years when a gain in height SDS of 0.8 was noted. In boy 3 treatment started at age 2.3 years (height -3.5 SDS). After 1.1 years on GH height SDS gain was 0.5.

Conclusions: The improvement of height SDS by GH substitution in these reported cases of familiar LWS depended on the age of initiation of GH therapy. Follow up examinations will show whether the effectiveness of GH for final height in these young patients will be comparable to those shown in a former study of 14 patients with SHOX deficiency, in which a height benefit of 1.1 SDS was demonstrated.

P2-d1-632 GH and IGF Treatment 1
Growth hormone treatment in a patient with Langer mesomelic dysplasia

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1University of Palermo, University Department “Materno-Infantile, of Andrology and Urology”, Palermo, Italy; 2University of Palermo, University Department, Palermo, Italy; 3University of Pisa, Pediatric Endocrinology, Division of Paediatrics, Department of Reproductive Medicine and Paediatrics, Pisa, Italy

Background: Homozygous mutation of the short stature homeobox-containing gene, SHOX, results in Langer mesomelic dysplasia (LMD). The expression of the SHOX gene in growing skeletal tissue of distal femur and tibia, ulna and radius has been determined.

Objective and hypotheses: Patients with homozygous SHOX gene deficiency have a final adult height of 130 cm, with severe short stature and skeletal deformities.

Methods: He was surgically treated for the scoliosis and at the age of 4 years, on the basis of genetic diagnosis of SHOX gene homozygous mutation, he started the treatment with GH for the poor growth, at the mean dose of 0.045 mg/kg/die.

Results: The growth velocity of the patient evidenced an improvement in the first years of GH treatment (4 cm/year), with progressive reduction of SDS of height velocity in the following years. At the age of 12 years his pubertal stage is PH2G2, his testicular volume 4 ml, his growth velocity is < 1 cm/year. The stature is 130 cm; the weight 30 kg. For the failure to achieve growth improvement, he stopped GH treatment. During the follow up however there was no worsening of the skeletal deformities.

Conclusions: Only a few cases of patients with homozygous mutation of SHOX gene treated with GH are described in the international literature. In a case with combined Turner syndrome and a deletion in the normal X chromosome authors concluded that GH treatment was not beneficial in the patient. Our patient reached a stature near the final stature reported in similar cases of homozygous mutation of the SHOX gene, even if not treated with GH. Hence these patients may not improve their linear growth with GH treatment.

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P2-d3-633 GH and IGF Treatment 2

Increlex- treated children enrolled in the Increlex Growth Forum Database (IGFD) in Europe: baseline characteristics and preliminary results on safety and efficacy

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1Linkoping University, Pediatrics, Linkoping, Sweden; 2Hôpital Necker Enfants Malades, Pediatric Endocrinology, Paris, France; 3University of Bonn, Pediatric Endocrinology, Bonn, Germany; 4Ipsen, Global Medical Affairs, Boulogne, France

Background: EU IGFD follows postmarketing safety and efficacy ofIncrelex® (measerevin[DNA origin] injection) treatment (Tx).

Objective: Report baseline characteristics and safety data for children with IGF-I Tx and 1-year height velocity (HV) in naive prepubertal patients (Efficacy subgroup).

Methods: Multicenter, open-label, observational study.

Results: 70 pats (78% prepubertal) enrolled in 7 countries from Jan 2009 to Aug 2010. Most common diagnosis is severe primary IGF-1 deficiency (76%).

Baseline Characteristics (Mean (SD) or % of pats).

<table>
<thead>
<tr>
<th></th>
<th>Total (N=70)</th>
<th>Efficacy subgroup (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>39</td>
<td>47</td>
</tr>
<tr>
<td>Age at Tx start (yrs)</td>
<td>10.3 (4.1)</td>
<td>8.2 (3.4)</td>
</tr>
<tr>
<td>HT SDS</td>
<td>-4.0 (1.6)</td>
<td>-3.8 (1.8)</td>
</tr>
<tr>
<td>WI SDS</td>
<td>-3.1 (1.9)</td>
<td>-2.7 (2.2)</td>
</tr>
<tr>
<td>Bone age (yrs)</td>
<td>7.7 (3.9)</td>
<td>6.2 (3.8)</td>
</tr>
<tr>
<td>Mother’s ht (cm)</td>
<td>156.2 (9.0)</td>
<td>154.9 (6.7)</td>
</tr>
<tr>
<td>Father’s ht (cm)</td>
<td>172.1 (7.9)</td>
<td>171.5 (8.3)</td>
</tr>
<tr>
<td>HV (cm/yr)†</td>
<td>4.7 (2.2)</td>
<td>6.1 (3.1)</td>
</tr>
<tr>
<td>Baseline IGF-1 (ng/ml)‡</td>
<td>35.7 (35.0)</td>
<td>32.4 (27.2)</td>
</tr>
<tr>
<td>Stimulated GH max (ng/ml)#</td>
<td>30.2 (30.7)</td>
<td>33.2 (32.7)</td>
</tr>
<tr>
<td>History of hypoglycemia</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>IGF-1 start dose (µg/kg BID)</td>
<td>49.4 (23.3)</td>
<td>39.3 (14.9)</td>
</tr>
</tbody>
</table>

† >50% missing data ; # 30% missing data.

Mean Tx duration was 392 (271) days (~ 68.7 pat yrs). Month 12 IGF-1 dose was 94 (30) µg/kg BID. Targeted adverse events (TAEs) were reported in 27% pats. Hypoglycemia was most frequently reported (12 pats, 17.1%) and was due to hypoglycaemia, hypersensitivity, injection site reactions (2 pats). First year HV was 7.8 (2.0) cm/yr in Efficacy subgroup.

Conclusions: EU IGFD did not show new safety signals. Frequency of re-estimated adverse events (AEs) was 1.4 pats with AEs being documented in an observational cohort of short GH-treated SGA children. Mean HV in naive prepubertal patients was 7.8 cm/yr.

P2-d3-635 GH and IGF Treatment 2

Better initial catch-up growth in very young GH-treated SGA children: data from the NordiNet® international outcome study

Isabelle Oliver1; Oliver Blankenstein; Lars Sävendahl; Henrik Thyo Christensen; Marta Snajderova; Birgitte Tannes Pedersen; Viatcheslav Rakov; Peter Lee

1Hôpital des enfants, Unité d’endocrinologie, génétique, maladies ossseuses et gynécologie, Toulouse cedex, France; 2Charité University Clinic, Department of Paediatric Endocrinology, Berlin, Germany; 3Karolinska Institutet, Department of Women and Child Health, Stockholm, Sweden; 4Odense Universitetshospital, Paediatric Endocrinology, Odense, Denmark; 5University Hospital-Motol, Paediatric Endocrinology, Prague, Czech Republic; 6Novo Nordisk A/S, Global R&D, Søborg, Denmark; 7Novo Nordisk Health Care AG, Global Medical Affairs Biopharm, Zurich, Switzerland; 8Indiana University School of Medicine, Penn State College of Medicine, Pediatrics, Indianapolis, Hershey, United States

Background: Clinical studies have demonstrated a better 2-year growth response in children born small for gestational age (SGA) started on growth hormone (GH) therapy before 4 years of age. However, no such data have been documented in an observational cohort of short GH-treated SGA children.

Objective: To describe the baseline characteristics and 2-year growth response in a cohort of GH-treated short SGA children evaluating the impact of age at treatment start.

Methods: GH-treated SGA children (n=936) were based on their age at treatment start divided into two groups: Group A—GH start before 4 years of age (n=63); Group B—GH start at and after 4 years of age (n=873). Statistical analysis was performed applying an ANCOVA model.

Results: No difference between group A and B were observed for mean gestational age (36.6±3.9wks and 36.7±1.8wks, respectively), birth weight (2011:9.689.0g and 2077.0±734.4g) and birth length (42.7±4.5cm and 42.7±4.4cm, respectively).
Temporal trends in growth hormone one year treatment response in children with GHD, born SGA and with Turner syndrome: German data from the longitudinal NordiNet® International Outcome Study

Olaf Höft1; Tilman Rohrer2; Martin Wabitsch3; Joachim Wölfle1; Christoph Brack4; Viacheslav Rako5; Birgite Tennes Pedersen; Dirk Schnabel6

1University of Lübeck, Pediatrics, Pediatric Endocrinology, Lübeck, Germany; 2Saarland University Hospital, Pediatric and Adolescent Medicine, Homburg/Saar, Germany; 3University of Ulm, Devision of Pediatric Endocrinology, Department of Pediatric and Adolescent Medicine, Ulm, Germany; 4Children's Hospital's University Hospital of Bonn, Division of Pediatric Endocrinology, Bonn, Germany; 5Gemeinschaftspraxis, Kinder und Jugendmedizin, Celle, Germany; 6Novo Nordisk Health Care AG, Global Medical Affairs Biopharm, Zurich, Switzerland; 7Novo Nordisk A/S, Global Research and Development, Soeborg, Denmark; 8Otto-Heubner-Centrum für Kinder- und Jugendmedizin, Charité, Paediatrische Endokrinologie und Diabetologie, Berlin, Germany

Background: Previous investigations from the German cohort of NordiNet® International Outcome Study (IOS), revealed a tendency towards a younger age at treatment start with growth hormone (GH) over the time period 2002-2009 in short children born small for gestational age (SGA) and patients with Turner syndrome (TS), but not in growth hormone deficient (GHD) children. Objective: To analyse whether one year height outcomes in GHD, SGA and TS children are related to any temporal trends in the German paediatric population of the NordiNet® IOS.

Methods: Patients included were treated with Nortropin® and enrolled in the NordiNet® IOS. Data were collected per year from 2002 to 2009. Trends were analyzed per indication using simple mixed linear models including random variation between both individual patients and annual mean levels.

Results: The investigated cohort comprised 1089 GHD, 690 SGA and 138 TS patients who started GH treatment in 2002-2009. During this period of time, mean age at treatment start showed no significant change in GHD children (9.6±3.8 yrs), but decreased in SGA (9.7±4.6→7.5±2.8 yrs, p=0.026) and TS patients (9.3±3.5→7.6±4.7, n.s.). Baseline HtSDS showed no significant changes for all three indications, the respective mean values for GHD, SGA and TS were 2.8±1.0, 3.3±0.7, and 3.16±0.91. No significant changes were observed for relative GH dose, with GHD, SGA and TS patients receiving mean daily doses of 29.5±6.8ug/kg, 35.1±6.0ug/kg, 45.5±12.2ug/kg, respectively. Considering one year HtSDS change, we observed a significant trend towards a greater HtSDS improvement in SGA (p=0.010) and TS patients (p=0.019) dependent on the year of GH treatment start during the time period 2002-2009. (Picture) Conclusions: The demonstrated significant temporal trend towards a greater HtSDS improvement after one year of GH treatment in the German IOS cohort may be related to a decreasing age at treatment start in SGA and TS patients over the period 2002-2009. Follow up is needed to analyse such temporal trends in the long term GH treatment outcomes.

The demonstrated significant temporal trend towards a greater HtSDS improvement after one year of GH treatment in the German IOS cohort may be related to a decreasing age at treatment start in SGA and TS patients over the period 2002-2009. Follow up is needed to analyse such temporal trends in the long term GH treatment outcomes.

The 3 groups of cytokines were similar at baseline in both groups and did not show a significant change at 6 months. Median total IGF1 at baseline showed negative associations with IL12(r=-0.65, p=0.002) and RANTES(r=-0.74,p=0.002). Median free IGF1 at baseline showed negative association with IL12(r=-0.57,p=0.01). Median IGBP3 at baseline showed negative associations with IL12(r=-0.8,p=0.0001), MIP1α(r=-0.63,p=0.04) and RANTES(r=-0.55,p=0.04). Median ALS at baseline showed negative associations with IL12(r=-0.67,p=0.002) and MIP1α(r=-0.74,p=0.004). There was no association between percentage change of total IGF1, free IGF1, IGBP3, ALS with that of IL12, MIP1α and RANTES.

Conclusions: In children with IBD, rhGH is not associated with raised systemic free IGF1 and did not change a range of systemic pro and anti-inflammatory cytokines

**Conclusion:** The demonstrated significant temporal trend towards a greater HtSDS improvement after one year of GH treatment in the German IOS cohort may be related to a decreasing age at treatment start in SGA and TS patients over the period 2002-2009. Follow up is needed to analyse such temporal trends in the long term GH treatment outcomes.

**Background:** Therapy with rhGH in IBD may be associated with an improvement in growth and disease activity but the underlying mechanisms are unclear.

**Aims:** To compare changes in systemic markers of GH action and inflammatory cytokines in children with IBD treated with rhGH and control(Ctrl).

**Methods:** 6 month RCT of 22 children with IBD(11 in rhGH); rhGH group 0.067 mg/kg/day. Markers of inflammation measured-(1)Pro-inflammatory cytokines:interleukin(IL)5,12,15;(2)Anti-inflammatory cytokines: IL10 , IL1RA, IL2R; (3)Chemokines(pro-inflammatory): MIP1α and RANTES. Results expressed as median(range).

**Results:** Median age at baseline was 14.7yrs(9.1,16.4) and 13.7yrs(8.5,15.5) in rhGH and Ctrl group, respectively. Median HV only improved in the rhGH group from 4.5(0.6,8.9)to 10.8cm/yr(6.1,15.5)(p<0.003).

**Conclusion:** In children with IBD, rhGH is not associated with raised systemic free IGF1 and did not change a range of systemic pro and anti-inflammatory cytokines.

**Conclusions:** The demonstrated significant temporal trend towards a greater HtSDS improvement after one year of GH treatment in the German IOS cohort may be related to a decreasing age at treatment start in SGA and TS patients over the period 2002-2009. Follow up is needed to analyse such temporal trends in the long term GH treatment outcomes.
growth response to three different dosing regimens of growth hormone: two-year data from the North European Small for Gestational Age Study (NESGAS)

Rikke Beck Jensen¹; Susan O’Connell²; Alyay Thakarnomy³; Jeremy Kirk⁴; Malcolm Donaldson²; Sten Ivarsson⁵; Olle Soder⁶; Robert Hoey⁷; David Dungan³; Anders Juul⁸
¹Rigshospitalet, Copenhagen University Hospital, Department of Growth and Reproduction, Copenhagen, Denmark; ²National Children’s Hospital, Department of Pediatrics, Dublin, Ireland; ³Aarhus University Hospital, Department of Pediatrics, Aarhus, Denmark; ⁴Birmingham Children’s Hospital, Department of Pediatrics, Birmingham, United Kingdom; ⁵Royal Hospital for Sick Children, Department of Child Health, Birmingham, United Kingdom; ⁶University General Hospital, Department of Pediatrics, Malmo, Sweden; ⁷Astrid Lindgren Children’s Hospital, Pediatric Endocrinology Unit, Stockholm, Sweden

Background: The optimal growth hormone (GH) dosing and duration of treatment in children born small for gestational age (SGA) without catch-up growth is matters of debate.

Objectives: The North European Small for Gestational Age Study (NESGAS) is a multicenter study involving the UK, Ireland, Denmark, Sweden, and Denmark. 110 short SGA children (69 males) were treated with high-dose GH (Norditropin; 67 µg/kg/day) for one year and then randomized into three different groups for the next two years of treatment. One group continued on high-dose (HD) 67 µg/kg/day (N=37), one group was reduced to a lower dose (LD) 35 µg/kg/day (N=31) and in one group the dose was titrated according to serum IGF-I levels (P2-d3-640) (N=36). Two-year data were available from 95 patients. Analyses of serum IGF-I and IGFBP-3 were analysed centrally using a solid-phase enzyme-labelled chemiluminescent immunometric assay.

Results: There was no difference in target height and clinical characteristics at birth and at baseline between the three groups (table 1). Growth response and changes in IGF-I levels during the first year were similar in the three groups where all children were treated with high-dose GH (table 1). After randomization into the three different dose regimens the children treated with the growth response during GH treatment.

Near adult height in children born prematurely with different GH status and size at birth
treated with growth hormone — data from KIGS
Margaret CS Boguszewski¹; Hanna Karlsson²; Hartmut Wollmann³; Giovanna Dahlgren⁴; Anita Kokken-Koelga²
¹Federal University of Paraná, Department of Paediatrics, Curitiba, Brazil; ²Pfizer, Endocrine Care, Solentuna, Sweden; ³Pfizer, Endocrine Care, Berlin, Germany; ⁴Institute for Clinical Sciences, Gothenburg University, Department of Paediatrics, GP-GRC, Gothenburg, Sweden; ⁵Sophia Children’s Hospital, Erasmus University Rotterdam, Rotterdam, Netherlands

Objective and hypotheses: The aim of this study was to evaluate the influences of prematurity and size at birth on near adult height (NAH) after growth hormone (GH) treatment in short children with different GH status using information from KIGS (Pfizer International Growth Database). Children were selected from four major KIGS diagnostic groups: idiothetic GH deficiency, idiopathic short stature, small for gestational age (SGA) without or with minor dysmorphic stigma. Available birth weight SDS and NAH was a pre-requisite. Height was expressed as standard deviation score (SDS) using Prader reference. Values are given as mean ± SD. A total of 285 children born preterm were selected, 39 of them were born SGA (birth weight ≤ -2 SDS).

Results: Information at GH start, at puberty start and at NAH is presented in the Table below. No significant difference was observed in total height gain during GH treatment for preterm AGA and preterm SGA. Parental adjusted height was normalized for the preterm AGA, whereas preterm SGA had a NAH in the low-normal range. In the total group, NAH SDS correlated with birth weight SDS (r=0.22, p=0.001), birth length SDS (r=0.21, p=0.002), max GH peak (r=-0.20, p=0.001) and height SDS at pubertal start (r=0.76, p<0.001). Delta height SDS from start of GH treatment to latest visit correlated with dose at start (r=0.13, p=0.024), parental adjusted height at start (r=-0.49, p=0.001), max GH peak (r=-0.45, p=0.001), treatment years from start of GH treatment to puberty (r=0.58, p=0.001), and treatment years from start of GH treatment to latest visit (r=0.60, p=0.001).

Conclusion: GH treatment resulted in a significant improvement in height SDS, especially during the prepubertal years. NAH appropriate for parental height was mainly obtained in the AGA children. Prematurity did not interfere with the growth response during GH treatment.

Near adult height in children born prematurely with different GH status and size at birth

Objectives: The aim of this study was to evaluate the influences of prematurity and size at birth on near adult height (NAH) after growth hormone (GH) treatment in short children with different GH status using information from KIGS (Pfizer International Growth Database). Children were selected from four major KIGS diagnostic groups: idiothetic GH deficiency, idiopathic short stature, small for gestational age (SGA) without or with minor dysmorphic stigma. Available birth weight SDS and NAH was a pre-requisite. Height was expressed as standard deviation score (SDS) using Prader reference. Values are given as mean ± SD. A total of 285 children born preterm were selected, 39 of them were born SGA (birth weight ≤ -2 SDS).

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Near adult height in children born prematurely with different GH status and size at birth

The patient with Kearns-Sayre syndrome treated with recombinant growth hormone
Monika Obara-Moszynska1; Jaroslaw Maceluch; Marek Niedziela2
1Federal University of Paraná, Department of Paediatrics, Curitiba, Brazil; 2Pfizer, Endocrine Care, Solentuna, Sweden

Background: Kearns-Sayre syndrome (KSS) is a multisystem disorder caused by dysfunction of oxidative phosphorylation system in mitochondria. Mitochondrial DNA (mtDNA) rearrangements are a key molecular feature of

Mitochondrial DNA (mtDNA) rearrangements are a key molecular feature of
this disease, which manifests a broad phenotypic spectrum.

**Objective and hypotheses:** The case report of 17 years old boy with KSS coexisting with growth hormone (GH) deficiency.

**Methods:** Clinical observation.

**Results:** The boy was born with birth weight 2500 g (-2.43 SD). From the 2nd year of life chronic progressive external ophthalmoplegia was observed. Additionally pigmentary retinopathy was diagnosed. From early childhood the boy presented short stature. In the age of 11 years the EMG revealed myogenic pattern. MRI showed hypoplasia of pituitary gland. Due to clinical picture the diagnosis of KSS was proposed. During endocrinologic diagnostics GH deficiency was recognized. In the age of 12 years the recombinant GH (rGH) therapy was started. The rGH dose was 0.018-0.024 mg/kg/d. During rGH treatment patient developed hypothyroidism. The puberty was spontaneous. In third year of rGH treatment the elevated HbA1c levels were observed. The further diagnostics revealed hyposecretion of insulin and elevated glycemia in OGTT. The GAD and anti-insulin antibodies were negative. The insulin therapy was started. IGF-I levels during rGH administration were within normal range. In the age of 15 years complete atrioventricular block was diagnosed. The patient was applied with pacemaker. Long-range PCR analysis disclosed a deletion in mtDNA in 6340-14003 nucleotide region, which confirmed KSS. During next 6 months progressive insufficiency of left ventricle was observed. In the echo sound the features of dilated cardiomyopathy were revealed. The rGH treatment is finished with the final height 163 cm.

**Conclusions:** The response to rGH therapy is very satisfactory and exception- al comparing to other children with KSS treated in our clinic. A big mtDNA deletion had not an impact on the response to rGH. This work was supported by grant from MNKaW (2M5A07030).

**P2-d3-641 GH and IGF Treatment 2**

**The efficacy and safety of growth hormone (GH) treatment used for children born small for gestational age (SGA) between 1991-2011: the experience of a regional centre**

Simon Chapman; Charles R. Buchanan

King's College Hospital, Child Health, London, United Kingdom

**Background:** GH is licensed in Europe for SGA children not catching up by 4 yrs. Although licensed at 35mcg/kg/d in Europe, a higher regimen of 67 mcg/kg has been shown to enhance catch-up growth and be well tolerated. We report the use of GH for SGA in a single UK Tertiary centre from 1991 - 2011.

**Objective and hypotheses:** Review efficacy and safety of GH up to 70 mcg/kg/d over first 3 yrs of treatment.

**Methods:** To date, 41 children started GH (any licensed product) for SGA indication. 39 pts have completed at least 1 yr of treatment (10 Silver-Russell, 4 twins, 25 prem / SGA). GH deficiency was excluded pre-treatment by Glucagon stimulation. Baseline IGF-I/BP3. glucose tolerance test, HbA1C, fasting lipids & insulin were performed, and repeated annually for 2 yrs, unless no abnormality seen.

**Results:** Of 39 patients who completed 1 year of treatment (26 Male), mean age 6.3 (+/-2.3) mean Start dose was 53 mcg/kg/d (18-77mcg). For the 20 children who completed 3 years treatment the mean start dose was 47 mcg/kg/d. GH was stopped in 4 children (1 for benign intracranial hypertension, 1 due to lack of response, 3 due to poor compliance). Mean SDS for treated patients is tabulated.

<table>
<thead>
<tr>
<th>Pre-Treatment</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height SDS ±sD</td>
<td>-3.1±0.7</td>
<td>-2.5±0.8</td>
<td>-1.9±0.9</td>
</tr>
</tbody>
</table>

Conclusions: Initial GH treatment at 70 mcg/kg/d for SGA children is generally well tolerated and achieves significant height SDS improvement within 2 -3 yrs. This supports consideration of temporary interruption of treatment to allow GH treatment withdrawal and review need for longer term GH continuation. Insulin resistance can be associated with abnormal glucose tolerance, not apparent on fasting blood samples alone and merits close surveillance.

**P2-d3-642 GH and IGF Treatment 2**

**Encephaloduromyosynangiosis leads to cranial revascularization but not somatotroph recovery in a 6.6 year-old girl with growth failure due to growth hormone deficiency as a leading sign of Moyamoya disease**

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1Pediatric Endocrinology and Diabetology, University Children's Hospital, University Duisburg-Essen, Essen, Germany; 2Saedtische Kliniken Duisburg, Neurosurgery, Duisburg, Germany

**Background:** Moyamoya is a rare cerebrovascular disease that leads to a progressing occlusion of the basal intracranial vessels. A cloud of collateral vessels develops. The disease manifests a broad phenotypic spectrum.

**Objective:** To know if early encephaloduromyosynangiosis, performed before occurrence of neurological signs, is able to restore impaired endocrine function.

**Case report:** An otherwise healthy-appearing 6.6 year-old girl presented with short stature and decreased height velocity caused by growth hormone deficiency (IGF-I 38.9 ng/ml, < 1. P., IGFBP-3 0.8 mg/L, < 0.1 P; GH max. AIT 4.0 ng/ml, GH max. clonidine test 6.3 ng/ml). Magnetic resonance imaging showed a hypoplastic pituitary gland and an unsuspected deformity of the basal vessels. Cerebral angiography led to the diagnosis of Moyamoya disease. GH therapy (0.025mg/kg/d) normalized growth and IGF-I and IGFBP-3 concentrations. Except for occasional morning headaches, the patient showed no neurological signs. Encephaloduromyosynangiosis was performed before cerebral infarction or other clinical signs of Moyamoya disease could develop. To test if residual somatotroph function had been preserved by the early surgery, GH therapy was stopped for 14 days. At the end of that interval, IGF-I (IGFBP-3) concentrations had again fallen to values < 0.1 P (< 1. P.) indicating permanent GH deficiency. GH therapy was resumed. No other endocrine dysfunctions were noted.

**Conclusions:** Our findings indicate that components of the somatotrophic axis are the structures most sensitive to vascular compromise. In the case of Moyamoya disease and hypothyalo-pituitary involvement, they are permanently damaged at an early stage, before damage of other intracranial structures develops.

**P2-d3-643 GH and IGF Treatment 3**

**Comparison of intuitiveness and ease of use for a new growth hormone injection device versus comparator devices**

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**Background:** Growth hormone (GH) is used to treat short stature in children. Improved GH injection devices may enhance treatment adherence.

**Objective and hypotheses:** We compared intuitiveness and ease of use of the GH injection pen, Norditropin® FlexPro® (FP; Novo Nordisk) versus four
other devices: easypod® (EP; Serono), Genotropin® pen (GP; Pfizer), Nutropin AQ® NuSpin™ pen (NP; Genentech) and Omnitrope® pen (OP; Sandoz).

Methods: In two non-interventional, randomised, crossover, comparative studies (INT1 & INT2), GH-treated (≥6 months) children (n=120; 10–17 years) with GH deficiency, Turner syndrome or born small for gestational age were randomly assigned to intuitiveness (INT1, n=30; n=32) or instruction (n=26; n=32) groups and performed a usability test (needle attachment, dose setting and injection into an Ependorr tube). Intuitiveness groups were briefly instructed verbally on device use; instructed groups received full instructions. Questionnaires assessed intuitiveness (four items) and ease of use (three items; 5-point scales).

Results: The majority of subjects rated FP the most intuitive device (INT1: EP: 70%; GP: 30%; OP: 9%; INT2: EP: 78%; OP: 16%; NP: 6%). FP was significantly easier to learn than the other devices in both studies. In the intuitiveness groups, FP was rated as significantly easier to use than EP or GP (p<0.001 for both) in INT1 and likewise scored higher than NP or OP (p<0.001 for both) in INT2. In the instruction groups, FP was rated as significantly easier to use than EP (p=0.001) or GP (p=0.05) in INT1 and was similarly rated easier to use than NP or OP (p=0.001 for both) in INT2.

Conclusions: At least 70% of un instructed subjects rated FP as the most intuitive of the devices tested. All subjects found FP significantly easier to learn to use than comparators. Ease of use, even without adequate training, might improve patient adherence to treatment.

P2-d3-644 GH and IGF Treatment 3
Biphasic effects of GH and IGF-I on the adipose tissue in man
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Background: In the literature GH is cited as a lipolytic hormone despite stimulating insulin secretion. In man and rats i.v. or s.c. injection of IGF raises serum FFA.

Objective and hypotheses: To determine whether the lipid mobilizing effects of hGH and IGF-I are maintained during long-term treatment.

Population and methods: In two studies populations were studied: a) 21 children (11M, 10F) with congenital IGHD, b) 20 prepubertal children (13M, 7F) with CMHFD both treated by hGH 33 µg/kg/day, and c) 9 children (4M, 5F) with Laron syndrome (LS) treated by IGF-I 150-200 µg/kg once daily.

Methods: Adiposity was estimated by measurement of subscapular skinfolds (SSK) using a Harpenden caliper. Statistical analysis was made using ANOVA with repeated measures.

Results: During the first 1½ years of hGH treatment, IGHD patients decreased their SSK from 9.4 ± 3.8 to 6.5 ± 2.5 mm (p<0.001) and the MPH patients from 10.5 ± 5 to 7.3 ± 4.2 mm (p=0.001). The LS patients treated by IGF-I reduced their SSK from 20.8 ± 7.8 to 15.9 ± 6.5 mm (p<0.001). Continuation of treatment for another 3-8 years increased the SSK from 6.3 ± 2.4 to 15.8 ± 9, 7.3 ± 2.9 to 12.8 ± 7 and from 15.9 ± 6.5 to 29.3 ± 9 mm, in the three groups respectively.

Conclusions: Both hGH and IGF-I treatment have biphasic effects on the adipose tissue. Short-term treatment reduces body fat, whereas long-term treatment has an adipogenic effect. The causes of this switch of effects cannot be explained.

P2-d3-645 GH and IGF Treatment 3
Body image, self-esteem and behavior problems in children with short stature; age-matched controlled study
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1Kyungpook National University Hospital, Pediatrics, Daegu, Republic of Korea; 2Kyungpook National University Hospital, Pediatrics, Daegu, Republic of Korea; 3Kyungpook National University, College of Nursing, Daegu, Republic of Korea; 4Kyungpook National University, College of Nursing, Daegu, Republic of Korea

Background: It has been proposed that appearance satisfaction and chronic illnesses influence emotional and behavioral development in children. Sandberg and coworkers reported that growth hormone treatment of short stature improved status of the quality of life (Hormone Research, 2005). Controlled studies on the status of emotional and behavioral development in children with short stature is necessary in clinical aspect.

Objective and hypotheses: This study was done (1) to see the differences of body image, self-esteem, and behavior problems in children with short stature compared to age-matched normal children, and (2) to provide a rationale for emotional and behavioral supports in children with short stature at early stage of treatment. We suggest that short stature is interfering emotional behavioral development in children with short stature, consequently, they also need emotional and behavioral support with a specific therapy.

Methods: Study populations consisted of thirty-eight elementary school children with short stature. Controls are thirty-eight age-matched children with normal stature. Body image was measured by Franzio’s method. Self-esteem and behavior problems were measured using Perceived Competence Scale. Problem behavior was measured using Korean-Child Behavior Checklist. Statistical analysis was done using SPSS/WIN 14.0 program.

Results: There was a significant difference in body image in short children compared to controls (126.21+/18.80 vs 137.87+/18.58, respectively) (p<0.05). Behavioral problems were also significantly higher than controls (47.39+/6.81 vs 40.24+/9.97, respectively) (p<0.05). Self-esteem was not significantly decreased in children with short children compared to controls (79.76+/13.93 vs 85.24+/10.73, respectively). Controls who were children with normal stature showed negative correlations between body image and behavior problems.

Conclusions: A specialized program which focuses in behavior problems, body images, and self esteem is necessary to support children with short stature along at the time of specific therapy.

P2-d3-646 GH and IGF Treatment 3
Response to growth hormone therapy in children with Noonan syndrome: correlation with or without PTPN11 gene mutation
Chungs Woo Chung1; Jin Lee2; Jin Ho Choi2; Hye Young Jin3; Boom Hee Lee4; Jae Min Kim5; Han Wook Yoo1
1Asan Medical Center, Pediatrics, Seoul, Republic of Korea; 2Asan Medical Center, Medical Genetics Center, Seoul, Republic of Korea

Background: Noonan syndrome (NS) is characterized by facial dysmorphism, congenital heart defects, post-natal short stature, short and webbed neck, and chest deformities. Recombinant human growth hormone (rGH) therapy in NS has been reported to be beneficial on final adult height.

Objective and hypotheses: The objective of this study was to evaluate the efficacy of rGH therapy and to evaluate the influence of genotype on response to rGH therapy in children with NS.

Methods: The study was designed as a single-arm prospective study. Eleven male and three female patients (range, 4.3-13.3 yr of age at onset of rhGH therapy) with GS with short stature whose height was less than 3 percentile for their age were included. The rhGH was administered in a dose of 0.066 mg/kg/day subcutaneously for 12-month period. Anthropometric data (height SDS and height velocity) was collected and blood sampling for biochemical analysis (free T4, TSH, IGF-1, and IGFBP-3 levels) were carried out every 3 months. Mutations in the PTPN11 gene were identified in 9 patients (64.3%). Mutations in the SOS1 (2 children, 14.3%), MEK1 (1 child, 7.1%) and KRAS (1 child, 7.1%) genes were also found. There were no clinical or laboratory differences between groups with and without mutations in the PTPN11 gene.

Results: Height SDS increased from -2.58 ±0.95 at the start of rhGH therapy to -1.83 ±1.01 after 12 months later (P<0.001). Height velocity increased from 4.96 ±0.95 cm/yr in the year before treatment to 8.23 ±2.76 cm/yr during treatment (P<0.001). Changes in height SDS, height velocity, and serum IGF-1 level were not significantly different between those with or without PTPN11 mutations.

Conclusions: The rhGH therapy significantly improved growth velocity and increased serum IGF-1 level. Long-term correlation between genotype and rhGH therapy responsiveness needs to be addressed from large population because of the short duration of therapy and small number of children in this study.
Effect of 3 years of growth hormone (GH) therapy in children with Noonan syndrome

Peter Lee1; Judith Rose2; John Germak3; Robert Gut4
1The Milton S Hershey Medical Center, Penn State College of Medicine, Department of Pediatrics, Hershey, PA, United States; 2Thomas Jefferson University, DuPont Hospital for Children, Department of Pediatrics, Philadelphia, PA, United States; 3Novo Nordisk Inc., Department of Clinical Development, Medical and Regulatory Affairs, Princeton, NJ, United States

Background: Noonan syndrome (NS) is a genetic disorder characterized by phenotypic features, including facial dysmorphology, cardiovascular anomalies, and short stature. In 2007, the US Food and Drug Administration approved the use of GH for short stature in children with NS.

Objective and hypotheses: To assess the height standard deviation score (HSDS) and change in HSDS (AHDS) for up to 3 years (Y3) of GH therapy (GHT) in children with NS.

Methods: The American Norditropin Studies: Web-enabled Research (ANSWER) Program®, a US-based registry, has collected long-term efficacy and safety information on patients treated with Norditropin® (somatropin rDNA origin, Novo Nordisk A/S) at the discretion of participating physicians. As of October 2010, 99 children (75 boys and 24 girls) with NS were enrolled and analyzed.

Results: The mean (SD) baseline age of all subjects with NS was 9.5 (3.8) years. Mean (SD) HSDS increased from -2.7 (0.7) at baseline to -1.7 (1.4) at Y3. Both male and female subjects showed increased HSDS from baseline to Y3 without significant differences between genders (Table). The mean (SD) GH dose at baseline and Y1 to Y3 was 47 (10), 51 (12), 48 (12), and 56 (19) mcg/kg/day, respectively. There was a negative correlation between baseline age and AHDS at Y1 (correlation coefficient R = -0.3102; p=0.0238) and Y2 (R= -0.4551; p=0.0069).

Conclusions: GH naïve subjects with NS from the ANSWER Program® showed continued increase in HSĐS after 3-year treatment with GH with no significant differences between genders. Baseline age was negatively correlated with AHDS at Y1 and Y2. Whether longer-term therapy will increase adult height in NS remains to be investigated with longer GH duration and a larger patient population.

Table. Mean (SD) HSDS and AHDS over Time

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Male</th>
<th>Female</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HSDS</td>
<td>ΔHSDS</td>
<td>HSDS</td>
<td>ΔHSDS</td>
<td>HSDS</td>
<td>ΔHSDS</td>
</tr>
<tr>
<td>Baseline</td>
<td>n</td>
<td>99</td>
<td>53</td>
<td>-2.7 (0.72)</td>
<td>--</td>
<td>75</td>
</tr>
<tr>
<td>Y1</td>
<td>39</td>
<td>0.36 (0.40)</td>
<td>44</td>
<td>0.38 (0.40)</td>
<td>14</td>
<td>0.32 (0.42)</td>
</tr>
<tr>
<td>Y2</td>
<td>27</td>
<td>0.66 (0.67)</td>
<td>7</td>
<td>0.69 (0.70)</td>
<td>7</td>
<td>0.54 (0.59)</td>
</tr>
<tr>
<td>Y3</td>
<td>14</td>
<td>0.94 (0.74)</td>
<td>7</td>
<td>0.94 (0.77)</td>
<td>1</td>
<td>0.89 ( )</td>
</tr>
</tbody>
</table>

Adult height of children receiving growth hormone therapy with Norditropin®

Peter Lee1; Judith Rose2; Robert Gut4; John Germak3
1The Milton S Hershey Medical Center, Penn State College of Medicine, Dept. of Pediatrics, Hershey, PA, United States; 2Cambridge University Hospitals Foundation Trust, Cambridge, United Kingdom; 3University of California, Department of Paediatrics, Cambridge, United Kingdom; 4Cambridge University Hospitals Foundation Trust, Wolfson Adult Diabetes and Endocrine Clinic, Institute of Metabolic Science, Cambridge, United Kingdom

Background: The American Norditropin Studies: Web-enabled Research (ANSWER) Program®, a US-based registry, has collected long-term efficacy and safety information on patients treated with Norditropin® (somatropin rDNA origin, Novo Nordisk A/S) at the discretion of participating physicians. Objective and hypotheses: To assess the height standard deviation score (HSDS) at baseline, Year 1, Year 2, and at adult height for all growth hormone (GH) naïve pediatric subjects in the ANSWER Program® who achieved adult height as defined by the physicians.

Methods: As of October 2010, 332 GH naïve pediatric subjects (210 boys and 122 girls) with isolated/idiopathic growth hormone deficiency/multiple pituitary hormone deficiency (GHD/MPHD, N=280), idiopathic short stature (ISS, N=27), and Turner syndrome (TS, N=25) from the ANSWER Program® who had reached adult height were included in this analysis.

Results: Baseline mean (SD) age of this population (13.0 (2.1) years) was older than the mean age of all subjects enrolled in the ANSWER Program® (10.3 years). Overall, mean (SD) HSDS increased from -2.1 (0.8) at baseline to -0.7 (0.9) at the last visit, and 93% of the children achieved AHDS~ -2. Mean (SD) adult HSDS for each indication was as follows: GHD/MPHD, -0.6 (0.9); ISS, -1.0 (0.7); TS, -1.6 (0.9). The mean duration of GHT before reaching adult height was 3.7, 3.8, 3.3, and 3.6 years for the overall, GHD-MPHD, ISS, and TS subjects. There was a positive correlation between the Year 1 change in HSDS (AHDS) and the AHDS at final visit for the overall population and for each indication (p<0.001 for all).

Conclusions: GH naïve subjects who achieved adult height in response to GH therapy experienced increased HSDS from baseline to final visit. The adult height achieved was well within the normal reference range (~ -2 SDs). The Year 1 AHDS was positively correlated with the AHDS at final visit, consistent with early treatment response as a potential predictor of longer term growth.

Results of long-term safety and efficacy of Omnitrope® Phase III study in the treatment of Spanish growth hormone deficient children

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Carlos Haya Hospital, Pediatrics Department, Málaga, Spain; Hospital de Granollers, Pediatrics Department, Granollers, Barcelona, Spain

Background: Omnitrope® is the first off-patent biopharmaceutical to receive market approval according EMA centralized procedures that includes final comparative exercises with phase III studies. Objective and hypotheses: A phase III study was designed to demonstrate the safety ad efficacy of Omnitrope® 3.3 liquid formulation administered for up to 5 years to naïve treated Spanish pre-puberal children with isolated GHD. Methods: 70 children, 44 males and 26 females, aged 4-11y participated in the study. 32 and 5 patients completed treatment 4y and 5y with Omnitrope® at a dose of 0.03mg/kg/day respectively in a multicenter, open label phase III study.

Results:

<table>
<thead>
<tr>
<th>Year</th>
<th>1</th>
<th>2nd year</th>
<th>3rd year</th>
<th>5th year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean differences in HV compared to the start of treatment (cm/year)</td>
<td>5.5</td>
<td>4.1</td>
<td>3.1</td>
<td>2.4</td>
</tr>
<tr>
<td>Mean differences in HVSDS compared to the start of treatment</td>
<td>6.3</td>
<td>3.9</td>
<td>3.2</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Mean IGF-1 serum levels increased by 123.2 ng/ml after 1 y and by 176.8 ng/ml after 2 years compared to baseline. A total of 426 AEs were reported in 55 patients. 94% of these AEs were mild in intensity, with 22 AEs considered moderate in intensity and 1 AE, toothache, was rated as severe. There were no related SAEs and no withdrawals due to AEs.

Conclusions: Omnitrope® given to CGHD children for up to 60 months, at a dose of 0.03mg/kg/day, was shown to be effective, safety and well-tolerated, both locally and systemically.

Effects of transition on insulin-like growth factor — I levels in patients with growth hormone deficiency

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Introduction: Transition is the period of time from the completion of linear growth until full somatic maturation is achieved. IGF—I levels are much higher during adolescence than any other time of life. An explanation of
growth, IGF—I levels remain high until age 25 years and may be important for maintaining lean body mass, bone mineral density and cardiovascular health. 

Objective: To evaluate the effects of transitional care on IGF—I levels in patients with growth hormone deficiency (GHD).

Materials and methods: Data from 30 individuals who have achieved final height (FH) and were restarted or continued on transition dose of growth hormone (GH) were collected from KGDS database in UK. IGF—I levels were reported in 20 patients (12 males, 16.4±1.5 yrs) before reaching FH and on paediatric dose of GH (1.7±0.66 mg/day), and in 24 patients (14 males, 18.6±1.3 yrs) while on transition dose of GH (0.9±0.61 mg/day). The latest IGF—I levels were while receiving transition dose of GH (median time period 1.3 yrs; range 0.32—5.7 yrs) and the last measurement before achieving FH were used for calculations. IGF—I levels were converted into standard deviation scores (SDS) based on population derived normative data.

Results: IGF—I levels on the transition dose of GH were markedly lower compared with paediatric dose (20.9±12.1 vs 43.2±28.4nmol/L; p<0.001). However, transition patients were older (Table1). These differences persisted when longitudinal data from 14 patients were analysed (19.7±13.7 vs 47.3±30.3nmol/L; p=0.005). Low IGF—I SDS (-2.63 SDS and -0.84 SDS) indicated suboptimal levels of IGF—I in both groups. In the transition period, females showed trends for lower IGF—I than males (2.15±2.7 SDS vs -1.5±2.3 SDS)

Conclusions: GHD patients in the early transition period receiving transition doses of GH showed suboptimal levels of IGF—I. These preliminary data suggest that GH requirement is likely to be much higher in transition as compared with later adult life.

<table>
<thead>
<tr>
<th></th>
<th>Before High</th>
<th>During Transition</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>16.4 (1.5)</td>
<td>18.6 (1.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IGF—I levels</td>
<td>59.1 (18.5)</td>
<td>68.4 (20.9)</td>
<td>0.13</td>
</tr>
<tr>
<td>BMI</td>
<td>22.9 (4.9)</td>
<td>25.2 (5.9)</td>
<td>0.11</td>
</tr>
<tr>
<td>GH dose (mg)</td>
<td>1.7 (0.86)</td>
<td>0.9 (0.61)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IGF—I SDS</td>
<td>43.2 (20.4)</td>
<td>20.9 (12.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IGF—I SDS</td>
<td>-0.84 (2.25)</td>
<td>-2.63 (1.93)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

P2-d3-652 GH and IGF Treatment 3

The results of mecasermin treatment in patients with severe IGF—1 deficiency

Elzbieta Petriczko1; Beata Wikiera1; Agnieszka Biczysko-Mokosa2; Justyna Szmit-Domagalska1; Agnieszka Biczysko-Mokosa2; Katarzyna Marcinkevicz1; Mieczysław Walczak1; Pomeranian University of Medicine, Pediatrics, Endocrinology, Diabetology, Metabolic Disorders and Cardiology, Szczecin, Poland; 2Merical University, Endocrinology and Diabetology for Children and Adolescents, Wroclaw, Poland

Background: IGF—1 deficiency is a rare cause of short stature.

Objective and hypotheses: To present two years follow-up of the first patients treated with mecasermin (rhIGF1) in our country.

Methods: 3 patients IGF-1 deficient.

Results: Patient 1. 12.25 year-old girl, 4 pregnancy, birth weight 3480 g, length 59 cm, Appgar 8. Height before treatment 128.8 cm (~4.0 SDS), bone age delay 18 months, puberty 2nd stage. Stimulated GH 35.8 ng/ml. IGF—1 50.8 ng/ml without increase in IGF—1 stimulating test. Growth velocity before treatment 4.3 cm/ year, improved during the first and second year of rhIGF1 therapy to 9.2 and 7.1 cm/year respectively. Mean dose of rhIGF1 used in the first year of therapy 0.07-0.1 mg/kg, in the second year 0.12 mg/kg (twice a day). Mild hypoglycemic episodes were noted during the first year of therapy.

Patient 2. 6.75 year-old boy, 2 pregnancy, birth weight 3400 g. Height before treatment 109.5 cm (~3.0 SDS), bone age delay 30 months, puberty 1st stage. Stimulated GH 23.9 ng/ml. IGF—1 <25 ng/ml without increase in IGF—1 stimulating test. Growth velocity before the treatment 4.3 cm/year, improved during the first and second year of rhIGF1 treatment to 7.6 and 9.2 cm/year respectively. Mean dose of rhIGF1 during observation period was 0.08 mg/kg twice a day with good growth response. No side effects were observed. Patient 3. 7.1 year-old boy, 1 pregnancy, birth weight 2700g, length 50cm, Appgar 8. Height before treatment 109.5 cm (SD –3.4), bone age delay 48 months, 1st stage of puberty. Stimulated GH 30.0 ng/ml. IGF1 28.9 ng/ml without increase in IGF—1 stimulating test. Growth velocity before the treatment 5.1 cm/year improved during the first and second year of rhIGF1 treatment to 7.2 cm/year and 6.7 cm/year respectively. Mean dose of rhIGF1 during the first year of therapy was 0.08 mg/kg, in the second year 0.12 mg/kg (twice a day). No side effects were observed.

Conclusions: Treatment with mecasermin significantly improves growth velocity in patients with IGF—1 deficiency. During two years of therapy no serious side effects was noted.

P2-d2-653 Gonads and Gynecology 1

Homocysteine and ghrelin link with polycystic ovary syndrome in relation to obesity

Tolga Altug Pen1; Recep Kokten1; Adnan Narci2; Mehmet Yilmazer2

1Pomeranian University of Medicine, Pediatrics, Endocrinology, Alepppo, Syrian Arab Republic

Background: Elevated levels of plasma homocysteine and depressed ghrelin levels have been found to be associated with insulin resistance in a number of clinical situations, such as polycystic ovary syndrome.

Objective and hypotheses: This study was designed for determining the relations of plasma homocysteine and ghrelin levels with obesity in polycystic ovary syndrome.

Methods: Forty four adolescents and young women (24 lean, 20 obese) between 16-21 years old with polycystic ovary syndrome and age matched 20 healthy adolescents and young women were participated the study. Fasting samples were collected for serum vitamin B12, folate, plasma total homocysteine and ghrelin levels. Serum levels of follicle-stimulating hormone, luteinizing hormone, dehydroepiandrosterone sulphate, insulin, 17-hydroxyprogesterone, free testosterone, sex-hormone binding globulin were measured. Also, serum concentrations of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides were determined. Oral glucose tolerance test was done, and HOMA-IR index was used to define insulin resistance.

Results: Plasma total homocysteine levels were significantly higher in women with polycystic ovary syndrome and their plasma ghrelin levels were depressed compared to control group (p<0.05). Obese adolescents with polycystic ovary syndrome had more depressed plasma ghrelin levels.
Comparison to lean ones (p<0.05). Homocysteine levels didn’t correlate with body mass index, but positively correlated with insulin resistance (p<0.05).

Conclusions: Elevated plasma homocysteine levels in polycystic ovary syndrome are independent from obesity. Adversely ghrelin levels were depressed with polycystic ovary syndrome in relation to obesity.

P2-d2-654 Gonads and Gynaecology 1
A rare cause of vaginal bleeding in childhood: benign papilloma
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Background: Vaginal bleeding is an unusual and alarming finding in childhood, and should always be promptly investigated. It can result from estrogen stimulation, infection, foreign bodies, tumors and trauma. This condition can be a source of fear and concern for the patient and her family.

Case report: We present a case of a 14-mo-old female infant with vaginal bleeding for four days. Her parents denied any history of urinary symptoms, bleeding per rectum, trauma or unsupervised play. Her family history revealed negative for endocrine or clotting abnormalities. At the admission’s clinical examination, she was a healthy, well-nourished child, not in distress. She had normal infantile external genitalia with sanguineous vaginal discharge, no other signs of precocious puberty. Sexual abuse seemed unlikely by history and examination.

Methods: Hormonal exams were performed: estradiol, progesterone, PRL, TSH, FT4 levels were within normal limits, with FSH and LH basal and after LH-RH Test showing a pre-pubertal pattern. Bleeding disorders were exclud-

Discussion: Genital tract papillomas are rare benign tumors of the cervix and/ or vagina occurring predominantly in young children, who typically present with vaginal bleeding. Their cytologic features can mimic malignant lesions, but normal infantile external genitalia with sanguineous vaginal discharge, no other signs of precocious puberty. Sexual abuse seemed unlikely. In the patient we hereby present, cytopathologic examination revealed areas exhibiting low steroid receptor density allowing no significant breast enlargement. They were associated with gynecomastia during puberty seem to explain the pronounced tissue re-

Conclusions: Vaginal bleeding in childhood is a rare condition for which there are few and conflicting studies. The diagnosis of vaginal bleeding in children should be promptly investigated. It can result from estrogen stimulation, infection, foreign bodies, tumors and trauma. There is a need for an accurate diagnosis to provide appropriate treatment with local excision. The prognosis of these conditions is good, even with recurrences.

P2-d2-655 Gonads and Gynaecology 1
High prevalence but different androgenic profiles of polycystic ovary syndrome (PCOS) in obese and type 1 diabetes girls
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Background: There are few and conflicting studies that focus on early stages of abnormal gynecological traits in obese and type 1 diabetes adolescents.
**P2-d2-657 Gonads and Gynaecology 1**

**Subclinical impairment of left ventricular function in adolescent girls with PCOS**

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**Background:** Detrimental effect of PCOS on cardiovascular system was shown in young women.

**Objective:** The study aim was to investigate whether increased cardiovascular risk (CVR) is present already at adolescence.

**Methods:** In 34 girls in the mean age 16.1±1.3 ys with PCOS diagnosed according to Rotterdam criteria and 17 healthy controls matched for chronological and gynecological age as well as the BMI value, echocardiographic assessment and 24 hours blood pressure monitoring were performed. Seventeen girls from the study group and 6 controls were obese.

**Results:** Left ventricular end diastolic dimension (LVEDD) was increased in PCOS girls compared to the controls, p=0.05. However when non-obese girls were excluded, LVEDD as well as left ventricular end systolic dimension (LVESD) were significantly higher in girls with PCOS (4.6±0.3cm vs 4.2±0.2cm, p=0.01 and 3.0±0.3cm vs 2.7±0.2cm, p=0.03 respectively). 24 hours mean blood pressure (24 h MBP) was significantly higher in PCOS girls (78.0±5.0 mmHg vs 73.0±5.0mmHg respectively, p=0.01) and so was the day BP (70.0±9.0 vs 66.0±6.0mmHg respectively, p=0.03). The difference remained significant also after exclusion of all the obese subjects from the comparative studies. There was no difference in left ventricular mass (LVM) between the groups regardless of the weight status. Obese and non-obese subjects with PCOS had increased blood glucose and insulin level at several time points of OGTT compared to the healthy controls however the difference in HOMA and FIGR were not statistically different. Girls' BMI significantly correlated with LVM (r=0.5,p=0.02) as well as with 24 h MBP (r=0.5,p<0.01) but neither with fasting insulin nor with HOMA and FIGR. Besides from higher triglycerides in the study group, lipid parameters were not statistically different.

**Conclusions:** It is concluded that in adolescent girls hormonal disturbances typical for PCOS do not impair left ventricular mass, however they may trigger the process of increasing CVR, regardless of the girls' body weight, lipid parameters and insulin resistance.

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**P2-d2-658 Gonads and Gynaecology 1**

**Evaluation of diagnostic possibility in juvenile uterine bleeding via colored doppler**

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**Background:** Transvaginal or transrectal coloured doppler (CD) ultrasound is a method of choice for non-invasive study of endometrium. Objective assessment of physiological blood supply of uterus during pubertal phase may suggest early diagnosis of endometrial pathology and a choice of optimal therapeutic method which will avoid developing of expressed anemia in girls.

**Objectives and hypotheses:** The aim of present research is the study of the possibility to apply ultrasound screening with grey scale along with CD for diagnosis of endometrial pathology accompanied by juvenile uterine bleeding (JUB) in girls of puberty period as well as prognosis of bleeding occurrence.

**Methods:** Thirty eight girls (aged 12-16 years) developing JUB and 17 healthy girls of the same age group were studied. Uterine blood supply was studied by CD accompanied with impulse-wave dopplergraphy. Uterine blood perfusion parameters were measured by common patterns of study. General blood supply was studied in the uterine artery, across endometrium and subendometrium. Resistance index as well as pulsing index were measured.

**Results:** Dopplerometric data during bleeding showed increase of absolute parameters for both the maximal systolic and end-diastolic velocities along with reduction of vascular resistance vs. healthy controls. The patients with bleeding recidives manifested increased vascular resistance due to decrease of end-diastolic velocity when compared to the data obtained during bleeding. The patients with no bleeding recidives showed parameters of uterine perfusion, pulsing and resistance indices close to the ones in control group.

**Conclusions:** The data obtained allow concluding that CD is a non-invasive and informative method for evaluation of hemodynamic alterations accompanied by JUBs. Diagnostically valuable prognostic criteria were established as revealing of high-velocity perfusion on the background of decreased vascular resistance and presence of colored loci in the zones of increased echodensity of endometrium.

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**P2-d2-659 Gonads and Gynaecology 1**

**Assessment of puberty and pituitary-gonadal axis in boys and young men with Nijmegen breakage syndrome, a cancer-prone disease with the DNA repair defect. Evidence from a longitudinal study**

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**Background:** Nijmegen breakage syndrome (NBS) is a severe chromosomal instability disorder, caused by hypomorphic mutations in the NBS1 gene, which product is critical for processing DNA double strand breaks during mitotic and meiotic recombination. It is characterized by microcephaly, growth retardation, immune deficiency and predisposition for malignancy.

**Objective and hypotheses:** Due to variable information on reproductive function, depending on the NBS1 murine model, we investigated the course of puberty with respect to humans with NBS. Previously we published data on hypergonadotropic hypogonadism in NBS females, however little is still known on male gonadal function, which will be presented in this study.

**Methods:** The study comprised 18 NBS males (ages 1.2-25.9 yrs), homозy- gous for c.657_661del5 mutation, followed between years 1993 and 2008, as well as 12 healthy male controls. Patients after chemotherapy were excluded.

**Results:** Pubertal commencement spontaneously and progressed similarly to healthy peers, however with incomplete growth spurt. Testosterone levels were within reference ranges in all age groups, whereas gonadotropins were normal in the prepubertal period. Later concentrations of FSH and LH showed an increasing trend, with adult values doubling reference norms. They amounted for mean FSH/LH concentrations as follows: 2.37±2.0/1.33±1.1 (10-13 yrs; Tanner I/II), 3.55±1.64/2.83±0.84 (11-15 yrs; Tanner II/III), 4.02±1.72/2.97±1.44 (13-18 yrs; Tanner III/IV), and 4.53±1.96/4.79±1.76 IU/l (≥ 19 yrs; Tanner IV/VA).

**Conclusions:** Despite normal pubertal development in NBS boys, increasing gonadotropin levels in older patients may be indicative of commencing gonadal dysfunction, which in the light of extending survival in patients with chromosomal instability disorders, demands further supervision.
Methods: Serum AMH increased from birth to 2-3 yr, then decreased to values in the range of 0.01-0.7 pmol/l. AMH levels were also determined by appropriate methodology in the follicular phase of 5 cycling perimenopausal women (75.7±23.7 vs 110.3±39.2 pg/mL; p<0.001). Decreased inhB levels were found in the follicular phase of 5 cycling perimenopausal women reflecting a diminished ovarian activity. A good correlation between Gen II inhB levels remained low (14.9±10.6), only in 3/21 samples inhB fell below the detection levels of 5.3 pg/mL. A transient increase was observed indicating Sertoli cell dysfunction, from early infancy (Table). The newly developed inhB assay showed to have full clinical potential to assess ovarian function in girls; due to its high sensitivity ovarian function may be monitored even during the quiescent period. However, our results show that inhB concentrations tend to be lower than those previously published in the postnatal period where a new normal range has to be established.

Results: The CYP21A2 heterozygote frequency in PCOS women and in controls was 7.6% and 8.2%, respectively (p=0.246) [Group 1: 9.7% and Group 2: 5.3% (p=0.332)]. The basal values of androgens (Testosterone, Δ4-androstenedione, DHEAS and 170IP) were higher in group 1 compared to group 2 (p=0.000).

Conclusions: 1) The contribution of CYP21A2 heterozygous mutations to the pathogenesis of PCOS is not substantiated. 2) Basal androgens are significantly higher in PCOS women with PCO sonographic findings compared to those without PCO sonographic findings. 3) 170HP values <2 ng/ml at baseline and <10 ng/ml post ACTH exclude homozygosity of CYP21A2 mutations in hyperandrogenic women.

Background: Male patients with an extra sex chromosome or autosome are expected to present primary hypogonadism at puberty owing to meiotic germ cell failure. Scarce information is available in trisomy 21, a frequent autosomal aneuploidy.

Objective and hypotheses: We asked whether trisomy 21 presents with pubertal-onset, germ cell-specific, primary hypogonadism, or whether the hypothalamic-pituitary-gonadal axis function is altered. We compared with an adequate control population, we established reference levels for AMH in 357 normal males using a recently developed ultrasensitive assay.

Results: In normal males, AMH increased from birth to 2-3 yr, then decreased to a plateau until pubertal onset, and further decreased until adulthood. The main fall was between Tanner stages 1 and 3, in coincidence with a significant main fall was between Tanner stages 1 and 3, in coincidence with a significant decrease in testis volume and serum testosterone. Serum AMH was above as-
Conclusions: In trisomy 21, primary hypogonadism involves a combined dysfunction of Sertoli and Leydig cells, which can be observed soon after birth, thus prompting the search for new hypotheses to explain the pathophysiology of gonadal dysfunction in autosomal trisomy.

Objective: The children with precocious puberty, who have expressed to high-er pollution of EEDs, are treated with traditional Chinese Medicine (TCM). It is verified that the antagonistic effects of TCM on estrogen-like activity of EEDs.

Methods: 73 girls with precocious puberty, whose serum levels of EEDs were higher, were treated by TCM. The formula consisted of Radix rehmanniae, Carapax et Plastrum testudinis, Cortex phellodendri, Rhizoma anemarrhenae, etc. All medicines were extracted and concentrated (1 ml mixture contained about 2.5 g crude extract). The dosage was 60 ml/day. The therapeutic course was 3 months. The volume of uterus and ovary, bone mineral density were measured, serum E2 and osteocalcin (OST) were determined before and after therapy. The animal model contaminated with 4-nonylphenol (4-NP) and bisphenol A (BPA) were fed the formula of TCM. The dosage was 5 ml/day. The therapeutic course was 14 days. Uterine wet weight, height of the luminal epithelium, thickness of the myometrium and the level of protein expression of proliferating cell nuclear antigen (PCNA) in rat uterine were determined.

Results: After therapy, in the girls, the volume of uterus decreased from 4.0 +/- 0.5 ml to 2.6 +/- 0.4 ml (p < 0.01), serum E2 descended from 174.84 +/- 16.40 pmol/L to 85.91 +/- 9.65 pmol/L (p < 0.01), BMD decreased from 0.537 +/- 0.067 g/cm2 to 0.417 +/- 0.056 g/cm2 (p < 0.01), serum OST descended from 16.85 +/- 3.16 ug/L to 10.06 +/- 3.37 ug/L (p < 0.01). In the contaminated animal models, the uterine wet weight decreased from 0.081 +/- 0.009 mg to 0.055 +/- 0.008 mg (p < 0.05), height of the luminal epithelium decreased from 23.27 +/- 5.64 mm to 17.45 +/- 4.30 mm (p<0.05), thickness of the myometrium decreased from 8.29 +/- 1.39 mm to 5.52 +/- 1.02 mm (p<0.05), positive cell area of PCNA descended from 5490.25 +/- 678.58 mm2 to 4301.59 +/- 464.02 mm2 (p<0.05).

Conclusion: The present therapeutic regime of TCM could effectively against the estrogen-like activity of EEDs.

Objective: Premature ovarian failure (POF) is present in only 0.01% of females <20 years of age. Most cases of POF are idiopathic and presumed to be genetic. One of the Forkhead transcription factors—FOXL2 is the first human autosomal gene of which dominant mutations have been shown to interfere with ovarian maintenance and POF.

Methods: A 16 years old female was investigated for primary amenorrhea. Thearche started at 10 years of age. No history suggestive of hirsutism, cyclic pelvic pain, cushing syndrome, thyroid dysfunction or raised intracranial tension. No significant past medical/surgical, family, drug history. Her mother had menarche at 14 years of age. On examination she appeared to be a well developed female with BMI 83%, vitals in the normal range, normal general physical and systemic examination and Tanner stage 3. Pelvic examination revealed normal uterus without any adnexal mass. USG Pelvis and MRI Pelvis done twice revealed hypoplastic uterus with no ovaries identified. Karyotype was 46,XX and bone age was 15 years. In lab analysis, LH and FSH were elevated (43, 73 mlU/ml respectively) with low estradiol 0.63 ng/dl and very low Anti mullerian hormone and Inhibin B levels. Adrenal hormones, ACTH, testosterone and thyroid function tests were in the normal range. After ruling out other etiologies, genetic studies were done on patient’s DNA to find the somatic chromosomal defects as a cause of POF.

Results: The heterozygous variants p.A179G (c.536C>G) and c.C501T (p.F167F) in FOXL2 gene were identified in patient blood. No functional analysis was available.

Conclusions: Ovarian failure associated with FOXL2 mutations results from a malfunction of granulosa cells during follicle formation. Presence of similar variants in control subjects (from the literature review) raises the possibility that environmental and other genetic factors may play an important role in determining the final phenotype and thus explain the incomplete penetration observed in inherited conditions such as POF.
P2-d3-666 Gonads and Gynaecology 2

Inhibin B (InhB) levels, as measured by a newly developed ELISA, in the assessment of testicular function in normal males and in newborns and infants with congenital multiple pituitary hormone deficiency (CMPHD)

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Background: In newborn males CMPHD, a life-threatening condition, can be suspected by signs of hypogonadism. InhB has been a valuable tool to assess testicular function from birth to adulthood. A newly developed assay, not requiring sample pre-treatment step, has become available but data on reference levels and its applicability in gonadal dysfunctions are lacking.

Objective: Our aim was to establish: (a) the normal range of inhB levels using an active® Inhibin B Gen II ELISA (Beckman Coulter, USA) in boys from birth to advanced puberty and b) the usefulness of InhB in the diagnosis of males with CMPHD.

Methods: 219 normal males and 11 boys with CMPHD aged 1-6 months were included. Serum levels of InhB were determined using Gen II and the previously used Oxford Bio-Innovation (OBI) ELISAs. AMH, testosterone (T) and gonadotrophins were also measured.

Results: Serum InhB was 164.8±65.7 pg/mL (mean ±SD) in the 0-2 yr group; then decreased to 77.1±40.2 pg/mL between 2 and 9 yr. InhB was always above the assay’s detection limit. During puberty, peak levels were attained at Tanner stage II (TII) (195.1±70.2) with no significant changes thereafter: TII: 198±64.9, TIV: 195.4±53.9 and TV: 222.9±69.7. Testicular volume and inhB positively correlated (r=0.64, p<0.001). A good correlation between results from Gen II ELISA and the previously used Oxford Bio-Innovation (OBI) method was found: r=0.81, p<0.0001. Seven of 11 boys with CMPHD had InhB below -2 SDS, in coincidence with AMH, T and gonadotrophins below reference values, indicating congenital hypogonadism.

Conclusions: Gen II ELISA showed similar ontogenic changes in serum InhB to those described with the OBI assay. Low InhB appears to be a helpful tool for the diagnosis of hypogonadism in newborns and infants with CMPHD.

P2-d3-669 Gonads and Gynaecology 2

Precocious testicular endocrine dysfunction in adolescents with cystic fibrosis (CF)

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Background: Delayed puberty is usually described in adolescents with cystic fibrosis (CF); though, hormonal assessment seems to be normal at the end of puberty. Nevertheless, adult men with CF have low testosterone level, associated with infertility, secondary to congenital bilateral absence of the vasa deferens and abnormal morphology of the spermatozooids.

Objective and hypotheses: To describe the testicular endocrine function in adolescents with CF.

Methods: Among 29 CF male patients, we proceeded in a clinical and biochemical evaluation of growth and puberty by evaluating testosterone, anti-müllerian hormone (AMH), inhibin B (INHB), FSH and LH levels, performed during the annual oral glucose tolerance test (from 10 years old). Pulmonary function was assessed by the mean of all forced expiratory volume in 1 second (FEV1) recorded during the year before endocrine evaluation. Nutritional status was assessed by determination of body mass index (BMI) at the time of endocrine evaluation.

Results: Age at peak height velocity was available for 17 patients and was 14.0± 1.7 years, which is compatible with a normal puberty development. Testosterone levels rose regularly through Tanner stages, and LH levels were in the normal range excepted for one patient. Mean InhB level was -1.63 +/- 1.37 SDS (p<0.0001) and 21/50 assays were lower than -2 SDS. Mean AMH level was -1.31 +/- 0.75 SDS (p<0.0001) and 43/45 assays were lower than 0 SDS. FSH levels were above the normal range in 17/35 assays. INHB SDS was highly negatively correlated with FSH level (r²=0.318, p=0.0004). FEV1 didn’t influence neither INHB SDS (r²=0.001, p=0.83) nor AMH SDS (r²=0.006, p=0.61). BMI didn’t influence neither INHB SDS (r²=0.031, p=0.234) nor AMH SDS (r²=0.008, p=0.578).

Conclusions: Leydig cells function seems to be preserved in CF adolescents. We highlighted precocious alterations in Sertoli cells function, which are not influenced by pulmonary function or by nutritional status. Impact of these anomalies on spermatogenesis remains to be assessed.

P2-d3-667 Gonads and Gynaecology 2

Circulating anti-müllerian hormone and inhibin B in boys during early puberty and in men with idiopathic hypo-gonadotropic hypogonadism

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Aims: To investigate (i) longitudinal changes in circulating anti-müllerian hormone (AMH) and inhibin B levels in boys during early puberty; and (ii) the impact of deficient gonadotropin secretion on AMH levels in men with idiopathic hypogonadotropic hypogonadism (IIH).

Methods: Serum AMH, gonadotropin and sex steroid levels were measured in 14 prepubertal boys with idiopathic short stature (ISS) who had been followed-up for 3 years, and in 20 patients with IIH.

Results: In healthy boys with ISS, serum AMH levels decreased before a significant increase in testis volume had occurred, and displayed reciprocal changes with serum inhibin B (r=-0.77, p<0.001). The decline in AMH occurred already when serum T levels were below 1 nM. Patients with IIH displayed AMH levels that were lower than those observed in prepubertal boys. AMH SDS (r²=0.008, p=0.578).

Conclusions: In boys, the pubertal decline in AMH starts before the clinical onset of puberty. The data on patients with IIH suggests impaired development of the Sertoli cell population.

P2-d3-668 Gonads and Gynaecology 2

Uterine malformations and mutation of HNF1 β gene: about one case

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Objective and hypotheses: Uterine malformations affects 1 / 5000 women is a main cause of amenorrhea. The association with micropolycystic kidney should suggest a diabetes maturity onset diabetes of the young 5 (MODY5).

Methods: We report the case of Marina, who consulted at age 14yrs 1 / 2, for pelvic and intense cyclic pain associated with primary amenorrhea. There was no personal or familial story (no diabetes), her mother was set at 13 years. She measured 1.65 m, normal BMI at 19.8 kg/m², she has a complete pubertal development that began at age 11 years. On the gynecological examination, the hymen was permeable, the vaginal length was 5 cm, the cervix is not visualized. The renal function was slightly altered. The pelvic ultrasound noted 2 hemibody uterine 55 x 30 mm with hematic retention and normal ovaries.

Results: Pelvic MRI confirmed the presence of 2 uterine horns, more voluminous at left and the cervical agenesis. Given this association, the molecular biology HNF1 β gene (hepatocyte nuclear factor β) has identified a nonsense mutation p.Ser379X in patient but not in the 2 parents. Treatment with LHRH analogues (Decapeptyl 3mg per month) allows regression of pain. Six months later, the treatment was stopped, a conservative surgery with the opening of the vagina and the Anastomosis with the left uterine horn has restored the rules. A renal and metabolic monitoring was explained to the patient and to the family because in this genetic background, she is exposed to a renal failure.

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and an MODY diabetes. At present blood glucose and glycated hemoglobin are normal, renal function is stable.

Conclusions: HNF1β mutation is well known to nephrologists we must not forget that the gynecological examination is essential in the context of associated malformations.

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A new case of Bardet-Biedl syndrome associated with vaginal atresia and uterus hypoplasia

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Background: Bardet-Biedl syndrome is an autosomal recessive disorder characterized by retinal dystrophy, digital malformations, obesity, mental retardation, hypogonadism (described mainly in males) and renal anomalies. Genital abnormalities in females with Bardet-Biedl syndrome have been rarely reported, including hypoplasia of uterus, ovaries, and fallopian tubes, uterine duplicities, vaginal atresia and septate vagina. Most of these anomalies were missed in the childhood.

Case: A 15 year-old female with Bardet-Biedl syndrome was presented to our clinic due to evaluation of primary amenorrhea. The pubertal status was stage 4 according to Tanner staging. Pelvic ultrasonography showed uterus hypoplasia and normal ovaries. Genitogram revealed vaginal atresia. Reconstruction surgery was planned.

Conclusion: This patient was reported to emphasize the possibility of association of genital anomalies in females with Bardet-Biedl syndrome. Early systematic evaluation of patients with this syndrome for genital anomalies will prevent late diagnosis and possible complications.

P2-d3-671 Gonads and Gynaecology 2

Endocrine profile, BMD evaluation, estroprogestinic treatment in the follow up of girls with congenital coagulopathies

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Background: Menarche is a crucial event in the life of adolescents affected by coagulopathies, with a risk of a severe blood loss if not adequately and promptly treated since menarche.

Objective and hypotheses: A multidisciplinary approach, including haematologist, paediatric endocrinologist, gynaecologist is the best model for the management of these adolescents.

Methods: We followed 16 girls(13 ± 1.2 years) with coagulopathies (9 Von Willebrand disease(VWD), 3 inherited platelet dysfunction, 1 Haemophilia A: an extremely rare homozygous mutation in a female; 2 VII factor deficiency, 1 congenital afibrinogenemia) admitted for a metrorrhagia event related to menarche; we evaluated growth (SDS for stature, weight, growth velocity, bone age), pubertal stage, endocrine assess (FSH, LH, PRL, E2), pelvic scan (uterine and ovary morphology and volume; endometrial thickness), haemoglobin, coagulation, coagulation factors concentration, platelet function and aggregation. FSH, LH, PRL, E2, TSH, FT3, FT4, bone age were normal for age. To prevent severe menstrual bleeding the patients received: type I VWD: DDAVP; type II or III: VW and VIII factors (tranexamic acid in all); congenital afibrinogenemia: fibrinogen; Haemophilia A and factor VII deficiency: factor VIII and VII respectively. In girls with concluded PHV and bone age ≥14 years, estroprogestinic treatment (E2: 0.03mg-chlormadinone acetate: 2mg) was added.

Results: We observed a significant reduction of menstrual bleeding and a significant reduction in the doses of the specific factors. All the patients were evaluated by DEXA to precociously evidence a reduction in bone mineral density (BMD). BMD values were in the normal range for age and sex, also in patients treated with DDAVP and E2. However our patients received DDAVP for few days/month and E2 from 3 years.

Conclusions: We stress the role of endocrine follow up in patients with severe coagulopathies. The correct age to start estroprogestinic therapy must be evaluated by the endocrinologist, to prevent a poor growth prognosis and osteopenia.

P2-d3-672 Gonads and Gynaecology 2

Glucocorticoid resistance (GR) is a novel reason for polycystic ovarian syndrome

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Background: PCOS is a heterogeneous group of diseases presenting with ovarian and/or adrenal hyperandrogenism. Although insulin resistance at the level of the ovaries seems to be the main cause of PCOS, other causes have been attributed to the cause of PCOS. There have only been a few reports of glucocorticoid resistance(GR) and hypersensitivity causing PCOS. We present 10 subjects with PCOS who had in addition to elevated androgens, fluctuating elevations of ACTH and/or cortisol levels.

Objective and hypotheses: To study glucocorticoid sensitivity in patients with PCOS.

Methods: We evaluated 10 patients with PCOS(7 overweight, 3 lean) and 15 healthy controls with normal ACTH and cortisol. ACTH stimulation testing normal. 21 hydroxylase mutations were excluded in all patients. F-Dex binding assays were used to evaluate differential binding to the glucocorticoid receptor versus control. DNA was extracted and the glucocorticoid receptor gene(NR3C1), FKBP4 and FKBP5(molecules in glucocorticoid receptor complex) were amplified using PCR and sequence analysis was performed.

Results: F-Dex binding studies in all patients were positive demonstrating 10-50% decrease in binding.

Conclusions: GR has not been shown to be a frequent cause of PCOS. However, screening of our patients with PCOS with fluctuating elevated ACTH and/or cortisol showed 10 patients with decreased F-Dex binding, demonstrating that GR can be a cause of PCOS in these patients.
Background: Prolactin level may increase due to various reasons such as physiologic conditions (e.g. exercise, lactation), stimulation of nipples, hypotalamic-pituiter stalk damage (e.g. trauma, tumor), prolactinoma or drugs. However, contact dermatitis is not a well-known cause of hyperprolactinemia. We here report an adolescent girl presenting with galactorrhea caused by contact dermatitis.

Case report: A 15-year-old female patient applied to our hospital with a chief complaint of whitish flow from her breasts. Also, she suffered from crusts and itching around her nipples bilaterally. She was referred to our department because of hyperprolactinemia. Her serum prolactin level was 41.4 ng/ml (normal range: 5-20). The patient’s medical story revealed that she had had pruritus on her breasts for three months and her nipple discharge had begun for the last two weeks. We also learned that she wore small sized and tightly hugging nylon brassieres. Her menstrual cycles were regular. She denied taking any medication. Physical examination was unremarkable except for bilaterally galactorrhea and dermatitis around breast areolae. A topical steroid ointment was given and she was recommended not to wear bras for a short period and to change them to comfort bras made of cotton. One month later, contact dermatitis recovered, her complaints disappeared, and serum prolactin level was normalized (14.4 ng/ml).

Conclusions: In our case subject, prolonged tactile stimulation to nipples due to itching caused by contact dermatitis resulted in galactorrhea together with hyperprolactinemia before meticulous investigation of its etiology.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at Presentation</th>
<th>ACTH</th>
<th>Cortisol</th>
<th>NR3C1</th>
<th>FKB4</th>
<th>FKB5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17y</td>
<td>59</td>
<td>29.2</td>
<td>Pending</td>
<td>Pending</td>
<td>Pending</td>
</tr>
<tr>
<td>2</td>
<td>16y</td>
<td>18</td>
<td>25.2</td>
<td>Pending</td>
<td>Pending</td>
<td>Pending</td>
</tr>
<tr>
<td>3</td>
<td>14y</td>
<td>39</td>
<td>22.2</td>
<td>Pending</td>
<td>Pending</td>
<td>Pending</td>
</tr>
<tr>
<td>4</td>
<td>15y</td>
<td>168</td>
<td>16.9</td>
<td>E2E/R23K</td>
<td>Negative</td>
<td>Pending</td>
</tr>
<tr>
<td>5</td>
<td>14y</td>
<td>13</td>
<td>8.99</td>
<td>Negative</td>
<td>C6130G</td>
<td>Pending</td>
</tr>
<tr>
<td>6</td>
<td>15y</td>
<td>11</td>
<td>16.3</td>
<td>Pending</td>
<td>Pending</td>
<td>Pending</td>
</tr>
<tr>
<td>7</td>
<td>16y</td>
<td>60</td>
<td>30.5</td>
<td>Negative</td>
<td>C6130G</td>
<td>Pending</td>
</tr>
<tr>
<td>8</td>
<td>16y</td>
<td>39</td>
<td>11.5</td>
<td>N768N</td>
<td>Negative</td>
<td>Pending</td>
</tr>
<tr>
<td>9</td>
<td>16y</td>
<td>13</td>
<td>12.4</td>
<td>Pending</td>
<td>Pending</td>
<td>Pending</td>
</tr>
<tr>
<td>10</td>
<td>17y</td>
<td>20</td>
<td>9.3</td>
<td>Pending</td>
<td>Pending</td>
<td>Pending</td>
</tr>
</tbody>
</table>

Table 1: baseline data of patients before initiating of testosterone treatment

<table>
<thead>
<tr>
<th>Treatment center</th>
<th>A</th>
<th>B</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>114</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Age at onset [years]</td>
<td>14.2 ± 1.3</td>
<td>13.5 ± 1.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Height at onset of treatment [cm]</td>
<td>187.8 ± 7.3</td>
<td>185.5 ± 5.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Bone age at onset of treatment [years]</td>
<td>13.8 ± 0.8</td>
<td>13.6 ± 0.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Predicted height at onset of treatment [cm]</td>
<td>205.2 ± 5.2</td>
<td>205.6 ± 3.8</td>
<td>n.s.</td>
</tr>
<tr>
<td>Testosterone dose</td>
<td>500 mg every 2 weeks i.m.</td>
<td>250 mg every 2 weeks i.m.</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of treatment [months]</td>
<td>14.2 ± 4.0</td>
<td>11.3 ± 2.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total dose of testosterone [mg]</td>
<td>14.246 ± 3.986</td>
<td>5.638 ± 1.101</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height velocity during treatment [cm/year]</td>
<td>6.2 ± 3.1</td>
<td>7.3 ± 4.2</td>
<td>0.118</td>
</tr>
<tr>
<td>Height at end of treatment [cm]</td>
<td>195.1 ± 5.0</td>
<td>192.4 ± 4.4</td>
<td>0.002</td>
</tr>
<tr>
<td>Bone age at end of treatment [years]</td>
<td>16.9 ± 0.5</td>
<td>15.9 ± 0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Predicted height at end of treatment [cm]</td>
<td>197.7 ± 5.3</td>
<td>196.2 ± 4.6</td>
<td>0.005</td>
</tr>
<tr>
<td>Delta bone age / delta chronological age</td>
<td>2.7 ± 0.8</td>
<td>2.5 ± 1.0</td>
<td>0.293</td>
</tr>
<tr>
<td>Reduction of height based on predicted height at end of treatment [cm]</td>
<td>7.6 ± 5.0</td>
<td>7.9 ± 4.8</td>
<td>0.306</td>
</tr>
</tbody>
</table>

In all patients of treatment center B and in 55 (48%) patients of center A height data were available at least 1 year after end of treatment. The difference between height at end of treatment >1 year and predicted height at end of treatment was 0.8 ±1.7 (p<0.001) in center A and 0.1 ±2.2 (p=0.733) in center B.

Conclusions: The lower testosterone dose application was as effective as the higher testosterone dose for reducing height.
P2-d1-675 Growth 1

Study on the deficiency of SHOX gene and the correlation with x-ray skeleton deformity of ISS
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Background: The human SHOX gene (short stature homeobox-containing gene) is one of the major genes contributing to longitudinal growth. Heterozygote mutations or deletions of the SHOX gene causing haplosufficiency have been reported in some individuals with idiopathic short stature (ISS) and in many patients with Leri-Weil-dyschondrosteosis (LWD), an osteochondrodysplasia with mesomelic short stature and Madelung deformity of the wrist. The preceding survey showed that the short arm or short leg and Madelung deformity are in the SHOX deficiency; therefore, our research concluded 6 indicators of skeleton changes in X-Ray of left forearm and wrist, which could be used to picking out the patients with SHOX gene deficiency from ISS.

Objective: To study the deficiency of SHOX gene from ISS and to find the relationship between genotypes and skeleton alteration in X-Ray.

Patients and methods: The authors tested for variations in gene SHOX and the pseudoautosomal region (PAR1) of the sex chromosomes in 354 individuals with ISS and compared with 200 normal height controls, using microsatellites and direct sequencing.

Results: 3 mutations and 32 deletions were found; the prevalence of SHOX deficiency in patients with ISS was 9.9%. There are some indicators were significantly different between SHOX gene deficiency group and the normal group, such as the high vertical radius (3.70±1.08mm; P <0.05), inside the radius angle of the distal ulna and radius (140.69±9.05°; P <0.01), height between the distal ulna and radius (8.68±1.80mm; P <0.05). We also found the skeleton changes in girls were more serious than males.

Conclusions: Patients with SHOX mutations and deletions present a broad phenotypic variability, while certain correlations between genotypes and corresponding skeleton deformity in X-ray had been found, so that these should be used for selecting ISS children to undergo SHOX deficiency molecular studies.

P2-d1-676 Growth 1

Vitamin D receptor (VDR) gene polymorphisms in Greek children with idiopathic short stature
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Background: Idiopathic Short Stature (ISS) is defined as height more than 2SD below the mean for a given population, with no identifiable disorder present. Genetics studies, mostly concerning the GH-IGF-1 axis, have tried to shed light into the aetiology of this highly heritable trait. However, abnormalities in this axis account for only a minority of ISS cases. Recently, a few studies have provided evidence of an apparent association of ISS with Vitamin D receptor (VDR) gene polymorphisms.

Objective: To investigate the association of the VDR gene FokI, ApaI and TaqI polymorphisms with ISS in Greek children.

Methods: The VDR gene polymorphisms was accomplished through established PCR-RFLP methods. Fisher’s test was used to compare genotype and allele frequency distributions between ISS children and controls.

Results: No statistically significant deviations from the Hardy-Weinberg equilibrium were observed, with respect to any VDR polymorphism, in either group of children. A marginally statistically significant difference (genotypes, P=0.036; alleles, P=0.05) was observed with respect to the VDR Fokl polymorphism, as a result of the complete absence of F alleles among ISS children in our population. No statistically significant difference was found with respect to the other VDR polymorphisms.

Conclusions: Our results are in agreement with a small number of earlier studies, suggesting that the transcriptionally more active allele of the VDR Fokl polymorphism (F allele) is over transmitted to ISS children. The mechanism behind this effect remains to be elucidated.

P2-d1-677 Growth 1

Association between anthropometry, glucosensitivity and body composition at the age of 10 years in children born with extremely low birth weight (ELBW)
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Background: Preterm are at risk of suffering from the metabolic syndrome later in life.

Objectives: Do anthropometric parameters at birth and during early infancy predict fat distribution and metabolic state in 9.5 year-old ELBW children?

Patients: A total of 39 (17 male) healthy children (mean 9.5 years; range: 7.9-11.9) of normal development were recruited. All were born with a birth weight (BW) <1000g (BW-SDS: -0.75 +/-0.2, birth length-SDS 0.39 +/-0.3).

All but 8 (6 male) were prepubertal.

Methods: Auxiological data were gathered retrospectively from measurements at birth and during regular pediatric medical checkups as well as at 2 follow-up exams (mean age: 5.7 and 9.5 years) in our hospital. At the present survey a laboratory test was conducted and body composition (BC) was analysed per dual-energy x-ray absorption (DXA).

Results: BW-SDS correlated significantly with BMI, triceps skinfold thickness (TSF) and lean-body-mass. There was no correlation between birth length or gestational age and BW. BMI-SDS at 0.5 yrs and at the following exams correlated highly significant with almost all parameters of BC at 9.5 years.

HOMA-index correlated significantly with BC. The correlation between HDL-cholesterol and abdominal fat mass was significantly negative. No correlation existed between other parameters of glucosensitivity, insulin-like growth factors, total or LDL-cholesterol and BC. By differentiating into subgroups we found that the significant correlations shown above could be ascertainment in particular in females and prepubertal children.

Conclusions: Considering birth parameters, only BW affects BC in 9.5 year-old prepubertal children. BMI achieved at 6 months of age seems to have an impact on BC later on. As expected total fat mass correlated significantly positive with HOMA-index. Low levels of HDL-cholesterol indicated an unfavourable fat distribution.
P2-d1-678 Growth 1

Using genetic markers to improve the prediction of year 1 growth response to growth hormone (GH) in girls with Turner syndrome (TS): the PREDICT follow-up study

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Background: The PREDICT follow-up study investigates relationships among conventional biomarkers, genetic polymorphisms and long-term auxological changes in GH treatment-naïve prepubertal girls with TS during GH therapy.

Objective: To assess the contribution of genetic markers associated with Y1 growth response to GH in girls with TS to a predictive model for individualistic treatment based on auxological parameters and serum biomarkers.

Methods: Prediction analysis of height velocity (HV) after Y1 of GH therapy was performed. Linear modelling was conducted in 4 steps: Model 1 included auxological data only (age [years], weight [SD], distance from mother’s height [SD], GH dose [IU/kg/week], number of injections [6 or 7]); Model 2 added genetic markers (from a list of 4 identified by genetic screening of candidate growth-related genes, with the addition of karyotype 45X); Model 3 added GH-related serum biomarkers (from a pre-defined list of 14 identified as potentially correlated with HV at Y1); Model 4 added both genetic markers and biomarkers. Goodness of fit was assessed by R2 of response variability. The R2 increased to 57% when adding a selection of baseline biomarkers. Karyotype 45X estimate was significant in genetic and combined models. Genetic markers largely contributed to goodness of fit and the precision of the model was retained.

Conclusion: In addition to auxological data, genetic and serum biomarkers contribute to prediction of HV after 1 year of GH therapy in GH-naïve girls with TS. However, due to the limited sample size here, further confirmatory research is needed.

P2-d1-680 Growth 1

Assessment of pituitary function after traumatic brain injury in childhood

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Background: Traumatic brain injury (TBI) is one of the causes of hypopituitarism. Several studies in adults have demonstrated a 30-70% occurrence of pituitary dysfunction following a moderate to severe TBI. The extent of this potential complication is unknown in paediatric patients.

Objective and hypotheses: The aim of this study is to evaluate the prevalence of pituitary dysfunction following TBI and to investigate the relationship between TBI severity and endocrine involvement.

Methods: Prospective study in children admitted to the Paediatric Intensive Care Unit (PICU) of a tertiary care hospital because of TBI from 2004 to 2009. The severity of TBI was assessed with the Glasgow Coma Scale (GCS), clinical evaluation and image findings. A clinical exploration was carried out and basal hormone levels were determined (free T4, TSH, prolactin, cortisol, ACTH, estradiol or testosterone, LH, FSH, IGF 1 and IGF BP3), as well as serum ions levels and urine and serum osmolality.

Results:

• 36 patients were included: average age at admission 3.8±3.7 years and 61.1% males. Falls were the leading cause of brain trauma (61.1%). 63.9% were mild TBI, 16.7% moderate and 19.4% severe TBI. 25% of children developed an epidural hematoma, 19.5% intracerebral haemorrhages or contusion and 8.3% subarachnoid haemorrhages.
• No abnormalities were found in the endocrine exploration. The average height SDS was -0.21±0.9 and the average weight SDS 0.12±1.2. Secondary adrenal insufficiency was suspected in two patients and IGF 1 levels were in the lower normal range in four patients. These six children are currently being followed-up. No relationship was found between the presence of hormone alteration and the severity of TBI.

Conclusions: Endocrine disorders are not a common finding in this study. The pituitary-adrenal axis has been the only one involved so far, in contrast with what has previously been reported. In these children the TBI was mild, frontoparietal-located and with subarachnoid haemorrhage in the CT.
A novel SHOX gene mutation in inherited short stature
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Background: Mutations of the SHOX gene in the pseudo autosomal region 1 (PAR1) of the X and Y chromosomes are an important cause of idiopathic short stature (ISS). In the presence of characteristic clinical features such as disproportionate short stature, cubitus valgus, mesomelia, Madelung deformity, muscular hypertrophy and structural abnormalities on hand radiographs patients should be genetically evaluated for SHOX haploinsufficiency.

Objective: To identify genetic background of ISS in a familial case.

Case: We describe a case of a 13,5 year old girl who was referred due to familial short stature. Her physical exam revealed the following australological data: height 142,5 cm (< P 3, - 3,01 SDS), weight 40,5 kg (P 20), BMI 20,1 kg/m2 (P 75) and arm span 136,5 cm. Her bone age was delayed by 2,6 years. Her estimated adult height was 146 cm vs. her projected target height of 156,5 cm. Clinically she presented with mesomelia, coarse features, high palate and cubitus valgus. Her Tanner stages were appropriate for age (B3, P3, A2). Her history, lumbar radiography and laboratory findings excluded other known causes of growth impairment.

Results: Multiplex Ligation-dependent Probe Amplification (MLPA) of the SHOX gene region was performed but no deletion was found. Via sequencing analysis a heterozygous single base pair insertion was detected within the 3’ untranslated region of exon 6a of the SHOX gene (c*2044_2045insT). This mutation has not yet been described previously in association with disproportionate ISS.

To confirm the association with ISS we performed a sequencing analysis in the mother of the patient whose height was 150 cm and who was shown to have the same insertion.

Conclusions: We identified a new pathogenic SHOX gene mutation associated with familial short stature. SHOX haploinsufficiency is caused by deletions in the majority of the cases. Only 25% of the patients with SHOX syndrome display a point mutation. If no large SHOX gene deletion can be identified in patients with typical symptoms, sequencing of the whole gene should be performed.

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Genetic characterisation of primary growth hormone insensitivity (GHI) presenting as growth failure
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Background: GHI is a genetic condition in which patients present with growth failure due to primary IGF-I deficiency caused by a defect in the GH-IGF-I axis.

Objective and hypotheses: Genotype-phenotype characterization of GHI. Patients in this study were growth hormone insensitive (GHI), defined as postnatal short stature (< -2 SDS) associated with normal or high GH levels and low basal IGF-I levels. GHR, IGFALS and STAT5B were analysed by direct sequencing.

Results: Mutations were identified in genes of the GH-IGF-I axis in 60/70 patients (Table). A STAT5B mutation was responsible in 2 siblings, IGFALS changes caused 6 other cases but the majority of defects identified were in GHR (n=52,18 mutations, 5 of which were novel). Most GHR mutations were autosomal recessive, missense or nonsense changes in extracellular domain coding exons (n=25), but 15 cases were caused by pseudoexon activation.

Other unusual cases included a homozygous deletion of 22bp in the intracellular domain in two siblings, the first polypyrinid tract mutation and a dominant negative mode of inheritance in a family with a mild short stature phenotype. Both height and IGF-I SDS values were lower in subjects with missence/ nonsense GHR mutations (p=0,05) than in subjects with splice site GHR mutations including the pseudoexon defect.

Conclusions: Sequencing of candidate genes was informative in the investigation of a significant proportion of patients with GHI. Most cases were caused by mutations in GHR but defects in other genes of the GH-IGF-I axis such as STAT5B and IGFALS are being increasingly recognised.

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The relationship between bone age and stature: implications for the pediatrician
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Background: It is a common belief that a delayed bone age (BA) in a child with short stature is a sign that this child will achieve a final height on a higher growth centile than its presenting centile and that an advanced BA in a child with short stature is a sign that this child will achieve a final height on a higher growth centile than its presenting centile.

Objective and hypotheses: This presentation is intended to test this hypothesis and present the results in a way that gives the practitioner an intuitive insight into the relationship between BA and stature.

Poster Presentations
Methods: 231 normal children from the First Zurich Longitudinal Study (1ZLS) were followed from age 5 until cessation of growth with annual X-rays of the left hand. Children were classified as tall (height >1 SDS) and advanced (BA >1 SDS) or short (height <-1 SDS) and delayed (BA < -1 SDS) at the age of 7 years in girls and 9 years in boys.

Results: There is a good correlation between height SDS and BA SDS throughout childhood (mean r² = 0.39 range 0.35 to 0.45 for boys at age bins 8 to 14, mean r² = 0.27 range 0.20 to 0.30 for girls at age bins 7 to 13). Irrespective of their height, children enter puberty at the same BA, which is attained earlier in tall children and later in short children. The longer period of growth in the short children until start of puberty contributes to improving their final height, but much of this effect is lost again because shorter children grow more slowly during puberty.

Conclusions: Normal tall children have advanced BA and normal short children have delayed BA and pathologies should be searched for when this is not the case. Short children to end up as normal-short adults and tall children to end up as normal-tall adults. This rule is only altered when bone age SDS deviates from height SDS (i.e. when BA deviates from “height-age”).

P2-d2-686 Growth 2
Body mass index does not affect spontaneous nocturnal GH secretion in children with short stature
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Background: Obesity is characterized by reduced spontaneous as well as stimulated GH secretion. An inverse relationship has been shown between body mass index (BMI) and peak growth hormone (PGH) response to stimulation in children with short stature and normal BMI.

Objective and hypotheses: The aim of this study was to evaluate the effect of BMI on spontaneous nocturnal GH secretion in children with short stature.

Methods: This was a retrospective study in 35 short children (age 5-17.2; bone age 2.6-13.3; 14M and 21F; 28prep and 7pub; mean±SD height-SDS –2.23±0.74) who underwent nocturnal GH secretion studies in the last 6 years. Spontaneous nocturnal GH secretion was assessed with use of blood samples taken every 30 minutes for 12 h (from 20.00 to 08.00). IGF-I was measured in all patients and peak growth hormone was calculated.

Results: Mean BMI-SDS in the entire cohort was -0.86±0.92 (range -1.95 to -0.05). Three patients had a nocturnal PGH <10µg/L and 32 patients had a PGH >10µg/L. All patients had mean GH concentration (MGHC) >7µg/L. In univariate regression analysis nor PGH (r=-0.26, P=0.13) or MGHC (r=0.22, P=0.21) were correlated with BMI-SDS. PGH and MGHC were also not correlated in children with BMI-SDS <0 (n=29) and those with BMI-SDS 0 to +2 (16.37±4.29 and 6.19±1.58µg/L, r²=0.02).

Conclusions: In this cohort of short children with normal BMI-SDS, BMI has no significant impact on nocturnal spontaneous GH secretion. These findings suggest that evaluation of the spontaneous nocturnal PGH might be more accurate than stimulation testing in the diagnostic work-up of children with suspected GHD.

P2-d2-687 Growth 2
The headless way to auxology
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Background: The head is a disturbing factor in auxology, where its contribution changes from much in infancy to less thereafter. In terms of height, the skull is a flat bone whose growth reflects brain growth and is largely independent of the hormonal control of growth. In weight and BMI, the head is lighter than other tissues and varies with head pathology.

Hypothesis: Headless auxology will unveil borderline problems of growth and body composition.

Objective: To assess the head contribution to auxology and establish reference nomograms in prepubertal children for a modified headless height, weight and BMI.

Methods: This prospective observational cohort study included 153 boys and 157 girls age 2-9, with weight, height and BMI within 2SD of the mean. Headless height was obtained from bottom to protuberance occipitalis externa. Head weight was estimated from volume assessment, assuming an ellipsoid shape, and calculated from 3 head circumferences, verified to accuracy of 0.1%.

Results: In 157 girls age 2-9, headless height SDS increased from 0.89 to 0.93 (157 girls age 2-9), and in boys from 0.88 to 0.91. The BMI headless/standard ratio increased in girls from 0.89 to 0.91 (age 2 to 9), and in boys from 0.88 to 0.91. The headless BMI/standard ratio remained constant at 1.06-1.08 for boys and girls, reflecting the head’s smaller specific gravity. In 1 children with obesity (cutoff >30 kg/m2), the headless BMI increased to 111-113% as compared to 107% in controls, and in 3 children with short stature (<3rd percentile), the headless height remained unchanged at 89-91% in short stature and controls.

Conclusions: Headless auxology improves the power of anthropometry in understanding growth and adiposity. Obesity becomes more apparent by headless auxology.
Background: Androgens and their conversion to estrogens by aromatase have a major role in the pubertal growth but there is little knowledge of the details of the relationship between testosterone levels and the phases of the pubertal growth.

Objective: To study 24 h profiles of serum testosterone in boys admitted for short or tall stature or participating as health subjects at Queen Silvia Children’s Hospital in relation to their growth.

Methods: Inclusion criteria to the study were birth weight and length above -2 SDS, gestational age 37-42 weeks, prepubertal length and weight within ±3 SDS, normal 24 h growth hormone (GH) profile and no GH treatment. Assent was obtained from the boys and informed consent from parents for future analysis of the data. This resulted in 26 boys and 41 profiles of 24 h serum testosterone. Serum testosterone concentrations were determined in duplicate by a modified radioimmunoassay (Spectria testosterone; Orion diagnostica, Espoo, Finland). Lower assay sensitivity was 0.03 nmol/L. A 6th grade polynomial was fitted to each child’s growth data and growth velocity and age of peak height velocity (PHV) was calculated.

Results: A positive correlation between morning testosterone and increase in growth velocity was found (r=0.57). In a simple Effect-max model the 50% of increase in growth velocity from prepubertal growth to PHV was observed at a morning testosterone level of 2.8±0.9 nmol/mL. All boys (n=9) with morning testosterone levels above 10 nmol/L had reached above 96% of their pubertal growth capacity up to PHV. The morning testosterone median of the 6 boys who were investigated at PHV ±3 months was 11.4 nmol/L (6.5-12.6).

Conclusions: 1) Morning testosterone levels of 1.9-3.7 nmol/L are associated with a 50% of increase in growth velocity from prepubertal growth to PHV in healthy boys. 2) Morning testosterone levels above 10 nmol/L are seen close to PHV.

P2-d2-689 Growth 2

Phenotypic characterization of patients with deletions in the 3′-flanking SHOX region
Monique Lossevåg1; Sandra Broekman1; Caroline de Wit2; Marloes Bes1; Vincent Jannasch1; Egbert Bakker1; Jan Maarten Wit2; Sarina Kant1
Leiden University Medical Centre, LDGA, Dept. of Clinical Genetics, Leiden, Netherlands; Leiden University Medical Centre, Dept. of Clinical Genetics, Leiden, Netherlands; Leiden University Medical Centre, Dept. of Pediatrics, Leiden, Netherlands

Background: The SHOX gene is located on the short arm of the X-chromosome in the pseudoautosomal (PAR) 1 region and escapes X-inactivation thus showing a pseudoautosomal pattern of inheritance. Leri-Weill dyschondrosteosis is caused by haploinsufficiency of the SHOX gene in 60-70%, and in 15% by deletions of a putative enhancer sequence in the 3′-flanking region. The precise localization of the enhancer sequence is unknown.

Objective and hypotheses: This study aims to obtain insight in the genotype-phenotype correlation of deletions in the 3′-flanking SHOX region and point out the regulatory sequences in this region.

Methods: We collected clinical data from patients and their relatives with different deletions in the 3′-PAR region, detected by the MRC-Holland MLPA kit (P018-D). PAR probes were numbered 1-12 where nr 1 is SALSA probe 5642-LO5096.

Results: Twelve individuals carried a large deletion starting in PAR1 and extending to PAR9 or to the flanking CSF2RA probe while 4 individuals had a PAR3-CSF2RA deletion. Thirty-two individuals carried a smaller deletion of 3 probes (PAR4-6), just 5′ to the previously described common deletion interval. Median height SDS, sitting height/height ratio SDS and the presence of Madelung deformity in patients with PAR4-6 deletions were -1.8, +1.4, and 67%, in comparison to -2.4, +1.9 and 42% in patients with larger deletions. The index patients had a median height SDS of -2.7, shorter than their affected parents (-2.0), but disproportion and the presence of Madelung deformity were similar.

Conclusions: Variability of the phenotype in the whole group of patients was remarkable. We conclude that the critical interval of the enhancer region may be larger than previously suggested.
Conclusions: Children with FAS demonstrated growth failure for Ht, Wt and OFC compared to CDC norms. However, growth failure was not seen in children with ARND or pFAS. In fact, children with ARND and pFAS were heavier than the normal population. Based upon these results, growth failure does not appear to impact children with ARND or pFAS.

Objective: Our aim was to study satisfaction, associated side effects and psychological well-being in adult tall women who were treated with high-dose estrogen during adolescence.

Methods: Questionnaires including 2 reminders were mailed to 174 treated and 218 untreated patients, all being referred for tall stature during their adolescent years. Areas covered included treatment satisfaction, side-effects and psychological well-being assessed with a validated general health questionnaire (GHQ-12). The overall response rate was 47.4 % (55.1 % in treated and 41.3 % in untreated patients).

Results: The average adult height was almost identical in the two groups, 181.7 cm in treated and 181.2 cm in untreated patients. Among treated patients, 91.2 % (73/80 patients) expressed satisfaction with the given therapy usually motivated by the fact that height reduction was achieved. In contrast, 8.8 % (7/80) of treated patients reported dissatisfaction. The given reasons for this were that the expected reduction of adult height was not achieved, worries for long term side-effects and not longer experiencing tall stature as a problem. Side-effects were reported in 65.5 % while 34.4 % reported no side effects from the treatment. The most common side-effects were nausea (34/87), weight gain (22/87) and headache (9/87). Serious side-effects were reported by two patients (deep venous thrombosis and major depression). The overall psychological well-being was assessed and compared to that of the control group. The given reasons for this were that the expected reduction of adult height was not achieved, worries for long term side-effects and not longer experiencing tall stature as a problem.

Conclusions: Children with FAS demonstrated growth failure for Ht, Wt and OFC compared to CDC norms. However, growth failure was not seen in children with ARND or pFAS. In fact, children with ARND and pFAS were heavier than the normal population. Based upon these results, growth failure does not appear to impact children with ARND or pFAS.

Aims: The aim of this investigation was to evaluate the influence of one year growth hormone (GH) therapy in children with growth hormone deficiency on dental and skeletal maturity and to compare the results to the ones of healthy children.

Materials and methods: The investigation was carried out on 26 subjects. The peridontal health status of all subjects were evaluated by plaque index (PI) and gingival index (GI).

Main outcome measures: The findings dental and skeletal maturity at baseline and one year later of the groups were expressed as scores. The scores were statistically investigated.

Results: The mean dental age in the study group was 08.05 ± 1.95 years, compared to their healthy control 11.60 ± 1.42 years at the baseline (p=0.001). The mean dental age in the study group was 10.68 ± 0.91 years, compared to their healthy control 11.64 ± 1.22 years (p<0.005).

Conclusions: When comparing the mean difference between dental maturity at baseline and one year later, in the children with growth hormone deficiency there was shown an acceleration in dental maturity, whereas in control group the acceleration was less pronounced. As indicated, however, dental development of children with growth hormone deficiency was characteristically less affected than either somatic growth or skeletal maturation.

Objective and hypotheses: The aim of this study was to identify possible defects in GH-IGF-1 axis. We studied IGF-1, IGFBP-3 levels and IGF-1 gene polymorphisms. Genotype distribution of IGF-1 gene rs35767 polymorphism was 92.2%, 7.8%, 0% in ISS and 96.3%, 3.7%, 0% in controls. There were no significant differences in height SDS, IGF-1 and IGFBP-3 levels for the two different IGF-1 gene polymorphism groups studied.

Methods: 128 (70M,58F) ISS patient with a mean age of 11.8±3.6 years and 138 (72M,66F) age and sex matched control children (mean age 11.8±3.1 years) were included in this study. IGF-1 and IGFBP-3 levels were measured by IRMA. IGF-1 gene polymorphisms were determined by quantitative real-time PCR.

Results: Mean IGF-1 SDS level was significantly lower in ISS (-1.32±1.44) than in controls (-0.61±1.64) who had similar BMI. There was no significant difference in IGFBP-3 SDS levels and genotype distribution of polymorphisms. Genotype distribution of IGF-1 gene rs35767 polymorphism was 8.6%, 33.6%, 57.8% (wild type, heterozygous, homozygous) in ISS and 3%, 36%, 61% in controls; rs17032362 polymorphism was 92.2%, 7.8%, 0% in ISS and 96.3%, 3.7%, 0% in controls. There were no significant differences in height SDS, IGF-1 and IGFBP-3 levels for the two different IGF-1 gene polymorphism groups studied.

Conclusions: IGF-1 SDS was significantly low in ISS indicating to an underlying defect in GH-IGF-1 axis. However, there were no significant differences between the ISS and control group with respect to the polymorphisms studied.
Background: Marshall syndrome is a syndrome with short stature, skeletal dysplasia, facial dysmorphology, myopia, hearing difficulties and other minor signs. The genetic mutations are located on chromosome 6 at the COL11A1 gene. Mean final height for people with MS is about 3 SDS for both sexes.

Objective and hypotheses: There were no reports of any successful growth treatment in MS before these three children started on such therapy. These children all had short stature and the typical major signs of the syndrome. They have all been treated with hGH with normal dosages to near final height, and the growth data are presented to final height. Genetic data and preliminary growth data were earlier presented at ESPH in 2000 and 2004.

Method: They have all been treated with hGH dosages within normal or slightly increased ranges to near final height.

Results: Patient 1 hGH-treated for 9 years, H-SDS at start -1.8, FH 182.4 cm, H-SDS +0.3, a total gain of + 2.1 SDS. H-SDS at start of puberty -1.1. Patient 2 hGH-treated for 5 1/2y, H-SDS at start -1.6, FH 171.8 cm, H-SDS -1.2, a total gain of +0.4 SDS. H-SDS at start of puberty -0.8. Patient 3 hGH-treated for 9 1/2 y, H-SDS at start -4.7, FH 150.7 cm, H-SDS -2.7, a total gain of + 2.0 SDS. H-SDS at start of puberty -2.3. Thus the main increase in H-SDS was achieved before puberty for pat 2 & 3 after which they grew less well during puberty and lost relative height, opposite to pat 1 who gained most in puberty.

Conclusions: Growth hormone therapy in MS is efficient in increasing final height, but most of the effect seem to be achieved before start of puberty.
Haploinsufficiency of SHOX gene in 69 short children with and without Madelung deformity: auxologic, antropometric and dismorphological evaluation

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Background: SHOX gene belongs to the family of genes associated with short stature. The haploinsufficiency of SHOX (SHOX-D) in many cases is recognized in Leri-Weill Dyschondrosteosis (LWD), defined by short stature (ST) mesomelia, Madelung deformity (MD) and with the frequent presence of other dysmorphological defects. The short stature in Turner syndrome (TS) is considered largely a result of SHOX-D. The advantage of the growth achieved by GH therapy in TS suggested also this treatment in short children with normal GH secretion, but with SHOX-D.

Objectives: 1) To assess in short children the frequency of SHOX-D and the presence also isolated of antropometric and dismorphological signs related to the absence or presence of SHOX-D in addition to short stature.

Patients: 69 children with short stature, including 18 pre-selected for the presence of MD in addition to short stature.

Methods: All patients were examined by molecular analysis of the SHOX gene and by a detailed auxologic, anthropometric and dismorphological assessment.

Results: SHOX-D was present in 12/69 (17.4%). The auxologic, anthropometric and dismorphological aspects in relation to the absence or presence of SHOX-D are given in tables A, B, C, respectively.

Methods: Patients of both genders treated with Omnitrope will be enrolled and data collected at intervals according to clinical practice.

Results: As of January 2011, 786 patients had been enrolled in the “PATRO children” study in Europe. Demographic data for these patients can be seen below.

Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>438 (56.2%)</td>
</tr>
<tr>
<td>Chronological age / bone age (years)</td>
<td>8.97 (SD 3.60) / 7.48 (SD 3.70)</td>
</tr>
<tr>
<td>Height Standard Deviation Scores</td>
<td>-3.3 (SD 1.15)</td>
</tr>
</tbody>
</table>

Diagnosis at presentation

- Growth hormone deficiency
- Small for gestational age
- Turner Syndrome
- Prader-Willi Syndrome
- Chronic renal insufficiency
- Other

Country of origin

- Germany 441 (56.0%)
- France 187 (25.0%)
- Italy 52 (6.6%)
- Poland 52 (6.6%)
- Sweden 22 (2.8%)
- Austria 13 (1.7%)
- Romania 10 (1.3%)

Naïve / pretreated patients 635 (83.3%) / 130 (17%)

Patients have been treated with Omnitrope for 0–54 months and overall exposure is 928 patient years. 49 adverse reactions (including 4 cases of glucose metabolism disorders and 7 cases of hypothyroidism) and 1 serious adverse reaction (increased intracranial pressure) have been reported. No patient developed anti-rhGH antibodies.

Conclusions: The ‘PATRO children’ outcome database has been initiated to provide on an ongoing basis important safety data on the use of rhGH in infants, children and adolescents.

P2-d3-700 Growth 3

Effect of Helicobacter pylori infection on ghrelin and leptin concentrations in children with idiopathic short stature

Renata Stawerka; Marzena Kolasa-Kicinska; Joanna Smyczynska; Etiwna Czkwianiec; Andrzej Lewinski; Maciej Hilczer
1Medical University of Lodz, Department of Pediatric Endocrinology, Lodz, Poland; 2Polish Mother’s Memorial Hospital - Research Institute, 3Department of Gastroenterology and Pediatrics, Lodz, Poland; 3Medical University of Lodz, Department of Digestive Tract Diseases, Lodz, Poland; 4Medical University of Lodz, Department of Endocrinology and Metabolism Diseases, Lodz, Poland

Background: Recently, a lot of controversial data concerning influence of Helicobacter pylori (HP) infection on serum concentrations of ghrelin and leptin were presented.

Objective and hypotheses: The aim of the study was to assess ghrelin and leptin serum concentrations in children with idiopathic short stature (ISS) with and without HP infection.

Methods: Sixty-one children (25 girls and 36 boys) aged 5.03 – 14.5 years (mean ± SD: 9.87±3.12 years) with ISS below -2.0 SD were studied. Based on urease test and histopathology during gastroscopy, the children were divided into HP(+) group (15 children) and HP(-) group (46 children). In each child, the body height (expressed as HSDS) and body weight (expressed by BMI SDS for height age) were assessed and ghrelin and leptin concentrations were measured.

Results: The ghrelin serum concentration was significantly lower in HP(+) children with 4.74 ±4.79 vs 5.96 ±8.58 ng/ml, p<0.05) In children with HP(+), there was no correlation between ghrelin levels and both patients age (r=-0.14, p<0.05) and BMI SDS for height age (r=0.14, p<0.05), while such correlations were observed in children with HP(-): r=-0.54, p<0.05 and r=-0.43, p<0.05, respectively.
Conclusions: These results provide evidence that HP infection in short children is responsible for lower serum ghrelin concentrations. Moreover in HP(+) children, ghrelin secretion is independent on child’s age and nutritional status. It seems that leptin concentrations is not changed in HP(+) children with short stature.

P2-d3-701 Growth 3
Longitudinal study in normal children up to 28 years
Antonio de Arribae; Carmen Ruedae; José Ignacio Peralesb; José Ignacio Labarta; Esteban Mayayo; Beatrix Fugaa; Angel Ferrándeza
aMiguel Servet Hospital, Pediatrics Endocrinology, Zaragoza, Spain; bAndrea Prader Center, Pediatrics Endocrinology, Zaragoza, Spain

Background: Longitudinal studies show population trends. They are used as a guide for the assessment of patients. Most studies end when the population reached an adult height, but it is interesting to analyze the development of the population during adulthood.

Objective and hypotheses: 1. To continue the Andrea Prader Longitudinal Study begun in 1980, analyzing patients at 28 years old. 2. To draw percentile graphs of waist circumference and body mass index (BMI) until 28 years old. We studied patients from birth to 18 years old annually, and at 28 years of age.

Methods: We include data from 42 men and 45 women. We collected anthropometric data (weight, height, BMI, head circumference, chest circumference, waist circumference, arm circumference, chest circumference, triceps skinfold, subscapular skinfold). These anthropometric data have been always measured by the same observer.

Results: We present two tables for men and women with waist circumference percentiles from 3 to 28 years. There are also two tables with BMI percentiles from birth to 28 years for both men and women. There is an increment in waist circumference and BMI in males from 18 to 28 years of age. In females, this increment is only observed in the higher percentiles above percentile 50.

Conclusions: Although most longitudinal studies end when they reach adult height, in our study, we observed that some anthropometric measurements change subsequently. We have observed an increment in waist circumference and BMI from the 18 to 28 years. Studies about nutritional habits and physical activity are needed in order to assess these changes.

P2-d3-702 Growth 3
Carotid intima-media thickness diverges by age 3 between children born appropriate- versus small-for-gestational-age (AGA vs SGA)
Giorgia Sebastianib; Marta Díazb; Cristina Durinc; Ariel Lopez-Bermejoc; Abel Lopez-Bermejoc; Francis De Zegherd; Lourdes Ibañezd
aSant Joan de Déu Hospital, Pediatric Endocrinology, Barcelona, Spain; bFigueres Hospital, Pediatric, Figueres, Spain; cTrueta Hospital, Pediatric Endocrinology, Girona, Spain; dUniversity of Leuven, Pediatric Endocrinology, Leuven, Belgium

Background: SGA children, especially those with early and rapid catch-up of weight, are at increased risk for developing insulin resistance and other features of the metabolic syndrome by late childhood. Carotid intima-media thickness (IMT) and abdominal fat partitioning (subcutaneous vs visceral) are markers of cardiometabolic risk.

Objective and hypotheses: To assess the endocrine-metabolic profile and cardiometabolic risk markers in term AGA vs SGA children at age 3 yr.

Methods: Study Population Twenty-nine children aged 3 (AGA, n=18; SGA with spontaneous catch-up growth, n=11). Outcomes: Circulating glucose, insulin and IGF-I in fasting state; body composition (by DXA); carotid IMT; subcutaneous fat (subxiphoid and supraumbilical), pre-peritoneal fat (subxi-phoid) and visceral fat (between aorta and musculus rectus) by ultrasound.

Results: All outcomes were comparable between AGA and SGA children, except for a minor reduction of lean mass (P=0.003) and a minor elevation of IGF-I (P=0.03) in SGA children, and for a major increment of carotid IMT (P=0.0001) in SGA children.

Conclusions: Carotid IMT appears to be a marker diverging early between AGA and catch-up SGA children.

P2-d3-703 Growth 3
Does nutrient intake have an influence on growth response to growth hormone (GH) replacement, in children with growth hormone deficiency (GHD)?
Lamperea Fofollo; Maria Katsozapi; Alexandra Padapadpouloou; Andrianni Vazaiou; Ioanna Themelii; Lela Starmogiannou
P and A Kryiakou Children’s Hospital, 1st Department of Pediatrics, Athens, Greece

Background: Children with GHD receiving GH treatment show a broad response.

Objective and hypotheses: To evaluate whether nutrient intake interferes with growth response in GHD children receiving GH treatment.

Methods: Forty one GHD children [mean (SD) age 9.95 (3.18) years; height SDS -1.8 (1.1); 22 boys] who were under treatment with GH for a median duration of 1.9 years (range 0.3-6.9) were studied.

A 4-day diet assessment was performed and was analysed using the Science Technology Diet 200A Advanced Edition Software. Weight, height, Body mass index (BMI), BMIz-score, height velocity (HV), HVSDS, the year before GH treatment, one year after and at the time of examination were assessed.

Children were classified as high responders to GH treatment if their first year growth velocity was >75th CE and intermediate/poor responders if growth velocity was <75th CE. Both groups were comparable in age, duration of GH treatment and pubertal status. IGF-I and lipid profile were measured.

Results: Thirty four children [mean (SD) age (years) 10.0 (3.4); 26 prepubertal, 21 boys] were high responders [median (range) HVSDS 3.3 (0.4-10.0)]. Eight patients [mean (SD) age (years) 10.1 (3.5); 6 prepubertal, 2 boys] were intermediate/low responders [median (range) HVSDS 1.1 (-0.8-3.1)]. BMI was comparable between the two groups.

No differences were found between the two groups in energy or macronutrient intake. However, vitamin D intake was higher in high responders compared to intermediate/poor responders: median (range) % of daily recommended allowances (RDA) for vitamin D 66.9 (8.07-155.9) vs 43.2% (11.3-57.3) respectively; p=0.004.

No differences were found in other micronutrients or elements. IGF-I and lipid profile were comparable between the two groups.

Conclusions: This pilot study shows that vitamin D intake may be important in children with GHD, in order to achieve a good growth response to GH treatment.
**P2-d3-704 Growth 4**

**Oral clonidine test in the diagnosis of growth hormone deficiency in children**

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Hamad Medical Corporation, Pediatrics, Doha, Qatar

**Background:** Clonidine, a specific alpha adrenergic receptor stimulant it increases serum Growth Hormone (GH) concentration in children through stimulation of Growth Hormone-Releasing Hormone (GH-RH) release, is one of the most frequently used tests, and represent a very useful screening measure for the detection of Growth Hormone Deficiency (GHD), but the duration of the test is not uniform and can vary from 120-180 minutes or more depending on the institutions.

**Objective:** The aim of our study was to standardize the duration of the oral clonidine test.

We retrospectively studied the GH response to the oral clonidine test in 116 children (78 males & 38 females) aged 10.29±3.7 years, consecutively referred between January 2003 and December 2008. The clonidine stimulation test was started after an overnight fast, after an abase line blood sample (0min) clonidine tablet (0.15mg/m²) given by oral route and blood samples for GH measurement were drawn every 30min to 120min.

We defined the GH peak after the clonidine test in two ways; (1) as a maximum value reached after any stimulus; (2) the first time in which GH value is possible to reduce the time of clonidine test to 90 min and limit the blood samples to 3 collected at 30, 60, and 90 min to reduce cost, patient discomfort, parent staying time and save medical personnel time.

**Results:**

<table>
<thead>
<tr>
<th></th>
<th>GHD (n= 42)</th>
<th>ISS (n= 74)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>7.1±3.4</td>
<td>10.7±3.6</td>
<td>NS</td>
</tr>
<tr>
<td>Sex,M/F</td>
<td>31/11</td>
<td>47/27</td>
<td>NS</td>
</tr>
<tr>
<td>Height, SDS</td>
<td>-2.4±0.7</td>
<td>-2.1±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>GH basal, ng/ml</td>
<td>2.4±1.3</td>
<td>3.5±5.3</td>
<td>NS</td>
</tr>
<tr>
<td>GH peak, ng/ml</td>
<td>6.45±2.6</td>
<td>17.4±6.4</td>
<td>S</td>
</tr>
</tbody>
</table>

Baseline characteristic of the patients.

<table>
<thead>
<tr>
<th></th>
<th>30 min</th>
<th>60 min</th>
<th>90 min</th>
<th>120 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>GHD</td>
<td>2</td>
<td>22</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>ISS</td>
<td>2</td>
<td>58</td>
<td>13</td>
<td>1</td>
</tr>
</tbody>
</table>

Frequency distribution of GH peak during the test in GHD and Idiopathic Short Stature (ISS).

<table>
<thead>
<tr>
<th></th>
<th>&lt;90 min</th>
<th>&gt;90 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects%</td>
<td>97.4</td>
<td>2.6</td>
</tr>
<tr>
<td>ISS%</td>
<td>98.6</td>
<td>1.4</td>
</tr>
<tr>
<td>GHD%</td>
<td>96</td>
<td>4</td>
</tr>
</tbody>
</table>

Percentage of GH peaking during clonidine in all subjects and in ISS and GH children before and after 90 min.

<table>
<thead>
<tr>
<th></th>
<th>30min</th>
<th>60 min</th>
<th>90 min</th>
<th>120 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>12</td>
<td>51</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Percentage</td>
<td>16.1%</td>
<td>72.8</td>
<td>8.5%</td>
<td>1.4%</td>
</tr>
</tbody>
</table>

First GH values higher than 10 ng/ml in ISS children.

<table>
<thead>
<tr>
<th></th>
<th>&lt;90min</th>
<th>&gt;90min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage</td>
<td>98.6</td>
<td>1.4</td>
</tr>
</tbody>
</table>

First GH values higher than 10 ng/ml in ISS children.

**Conclusions:** Our data show that the biggest frequency of GH peak occurs within the first 90 min, both when considering the first value of 10 ng/ml and when considering the maximum GH value reached during the test. So it is possible to reduce the time of clonidine test to 90 min and limit the blood samples to 3 collected at 30, 60, and 90 min to reduce cost, patient discomfort, parent staying time and save medical personnel time.

50th Annual Meeting of the ESPE

**P2-d3-705 Growth 4**

**Waist circumference and waist-for-height ratio in Norwegian children. Reference values and population-based cut-off levels**

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**Background:** Abdominal obesity is considered a substantial risk factor for the metabolic syndrome in children as well as in adults. Waist circumference and waist-for-height ratio is used as an indirect measure of central obesity.

**Objectives:** To establish reference values for waist circumference and waist-for-height ratio of Norwegian children, suggest population-based cut-offs for overweight and obesity, and to compare Norwegian data with those from other European countries.

**Material and methods:** The data were collected in 2003-6 as part of a cross-sectional study, including 5725 children 4-18 years of age. Reference curves were fitted with the LMS method; appropriate cut-offs were selected using Receiver Operating Characteristics analysis.

**Results:** Reference values for waist circumference and waist-for-height ratio are presented. Mean waist circumference increased with age for both genders. Boys had a higher waist circumference at almost all ages. Mean waist-for-height ratio decreased until early adolescents, thereafter increased slightly towards adult age. There was a strong positive correlation between waist circumference and BMI (r=0.907, p<0.01), and a moderate positive correlation between waist-for-height ratio and BMI (r=0.397, p<0.019). A waist circumference cut off value of 1.0 SDS (85th percentile) gave a sensitivity of 76% and a specificity of 95% to detect overweight. A cut-off value of 1.6 SDS (95th percentile) gave a sensitivity of 90% and a specificity of 96% to detect obesity. Compared to newer data on waist circumference from other European countries, Norwegian children had a lower WC, although less prominent in the older age groups.

**Conclusion:** This study presents reference values of waist circumference and waist-for-height ratio of Norwegian children 4-18 years of age. The 85th and 95th percentile of waist circumference are proposed as appropriate cut-offs for central overweight and obesity. The waist circumference of Norwegian children seems to be in the lower range compared to other European countries.

**P2-d3-706 Growth 4**

**Increased head circumference-to-height ratio is an early and common feature in NF1 patients in infancy**

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**Background:** The diagnosis of neurofibromatosis 1 (NF1) is made on individuals who meet two of the seven clinical criteria set by National Institute of Health in 1987. These criteria are sensitive and specific in adults with NF1. However, their diagnostic accuracy is not equally good in young children, since their frequency increase by age. Inclusion of other criteria sensitive and specific in pediatric patients have been suggested.

**Objective and hypotheses:** To evaluate growth in NF1 patients. We hypothesized that a distinct growth feature, elevated head circumference-to-height ratio (HCHR) is an early feature in NF1 patients and therefore potentially useful in diagnostics.

**Population and methods:** Retrospective analyses of growth data and health records of pediatric NF1 patients (n= 86, 44 boys, 42 girls) visiting two university hospital outpatient clinics between 1.1.1996-1.6.2010. Current Finnish growth references of healthy infants were used for comparison. HCHR was studied from birth to 7 years of age.

**Results:** The median age at diagnosis was 3.6 years. At the diagnosis, the 3 most frequent criteria for NF1 were café au lait macules (96.3%), 1st degree relative with NF1 (41.5%) and axillar or inguinal freckles (23.2%). At the di-
agosis, HCHR SDS exceeded 2.0 or 1.6 in 29.5% and 39.7% of the patients (specificity 98% and 95%). HCHR was elevated (over 2.0 or 1.6 SDS) in NFI patients already at the age of one (20.8% and 31.9%) and at least once during the 1st year of life (over 2.0 SDS) in 33.3% of the patients.

Conclusions: Elevated HCHR is an early and common feature for NFI in children below 7 years and it is strongly suggestive for NFI when the disease is suspected but yet not fulfilling the NIH criteria.

Background: In girls with central precocious puberty (CPP), treatment with GnRH agonist (GnRHa) effectively enhances adult height. In some patients, growth velocity (GV) decreases below the age-appropriate normal range during GnRHa treatment.

Objective and hypotheses: The purpose of this study was to investigate clinical and laboratory factors related to changes of GV during GnRHa treatment in girls with CPP.

Methods: We analyzed clinical and laboratory data of 49 girls (aged 7.8±0.5 years) with idiopathic CPP who were treated with GnRHa. GV, height standard deviation score (SDS), hormonal parameters, pubertal stage, chronological age and bone age (BA) were evaluated.

Results: GV during the first year of GnRHa treatment was 5.9±1.0 cm/yr and decreased significantly to 5.4±1.1 cm/yr during the second year of treatment (P<0.005). GV during the third year (5.0±1.0 cm/yr) was not different from GV during the second year. During the second year of treatment, 36.7% and 8.2% of the girls had a GV <5 cm/yr and <4 cm/yr, respectively. Girls with more advanced pubertal stage (> breast Tanner stage II) showed higher risk of GV <5 cm/yr (52.2% vs 23.1%, odds ratio [OR], 3.6; P<0.035). In multivariate logistic regression analysis, advanced BA (OR, 16.3; 95% confidence interval [CI], 2.1-124.1) and low height SDS for BA at start of treatment (OR, 0.032; 95% CI, 0.003-0.38) were associated with decreased GV during the second year of GnRHa treatment.

Conclusions: These data suggest that some decrease in GV during the second year of GnRHa treatment is associated with advanced BA and low height SDS for BA.

Background: Deletions spanning or surrounding the SHOX gene account for a significant proportion of patients with idiopathic short stature and allied disorders, such as Leri-Weill dyschondrosteosis. Short stature due to SHOX deficiency is considered as a new indication for GH therapy, despite limited experience on efficacy and safety.

Objective and hypotheses: To describe the clinical and molecular findings in SHOX deficient patients starting GH therapy in Belgium and to analyze the 1st year growth response to a standardized dose of GH in prepubertal patients.

Methods: 22 Caucasian short patients (10 males) with SHOX deficiency, documented by FISH or MLPA analysis, were retrieved from the GH registry of the BSGPE. Anthropometric data were expressed as z-scores for age using Flemish population references (Reefmans 2009).

Results: Thirteen had a deletion of the SHOX gene, 5 showed a deletion downstream in the PAR1 region and 4 had point mutations of the SHOX gene. Six patients showed a Madelung deformity and 2 had strikingly short legs. Fourteen patients had a familial history of SHOX, and 8 were siblings (4 families). Mean ± SD birth weight SDS (1.3±1.2 SDS) and mid-parental height (-1.0±0.9 SDS) were below the mean for the reference population. GH treatment (47±7 µg/kg/day) was started at an age of 9.7±2.4 yr. Mean standing height was -3.0±0.6 SDS and BMI was 0.1±0.9 SDS at start of GH. During the 1st year of GH treatment, height velocity (HV) in the 17 prepubertal patients increased from 5.0±0.9 to 8.5±1.4 (p<0.001), resulting in an increase of height SDS of 0.6 ±0.2. No serious adverse events were reported.

Conclusions: GH at a dose of 30 µg/kg/day promotes during the 1st year a significant increase of the HV. Since SHOX deficient patients in contrast to Turner girls have a normal timing of puberty, long-term studies will be required to determine whether the first year height gain will translate ultimately in a greater final height without adverse events.

Methods: Growth factors evaluation in Babinga Pygmy from childhood to adulthood

Babinga Pygmies (8: 4 females and 52 males, age 1-70 years) and 93 sympatric African Bantu farmers (46 females and 47 males, age 3.5-81 years) living in South East Cameroon to evaluate the role of the mediators of the GH/IGF-I axis in Pygmy stunted growth.

Methods: For each subject body weight and height were measured and blood samples were collected for measuring IGF-I, IGF-II, ALS, GH and GHBP circulating levels. Height and BMI were expressed as standard deviation score (SDS), using the standards by Tanner and Whitehouse. Serum GH and IGF-I concentrations were measured by an automatic chemiluminescent assay. Circulating levels of GHBP were measured by a commercially available ELISA kit, IGF-II by IRMA assay and ALS by RIA assay.

Results: No signs of malnutrition were observed among Pygmies and Bantu following standard clinical examination. The heights of Babinga Pygmies of different ages were significantly reduced compared to Bantu (Pygmies: -2.96±1.14 SDS, Bantu: -0.55±1.09 SDS, p=0.0001). Pygmy showed significantly decreased levels of IGF-I (Pygmies: -2.50±1.76 SDS, Bantu: -1.08±1.66 SDS, p=0.0001), GHBP (Pygmy: 298.6±146.8 pmol/L, Bantu: 676.4±637.6 pmol/L, p=0.021) and ALS (Pygmy: 26.3±6.72 µg/ml, Bantu: 33.5±8.18 µg/ml, p=0.008) compared to Bantu. On the contrary, GH and IGF-II levels were comparable between the two groups of subjects.

Conclusions: In conclusion, we found reduced levels of IGF-I, GHBP and ALS in Pygmies from childhood to adulthood compared to African Bantu, suggesting that these factors may have a role in determining their short stature.
P2-d3-710 Growth 4

Abstract withdrawn.

P2-d3-711 Growth 4

**CNS dysfunction during GH treatment**

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**Background:** Little is known about negative side effects on CNS during growth hormone (GH) therapy.

**Objective and hypotheses:** Here we describe CNS dysfunction in 2 boys with GH therapy.

**Methods:** The boys were taken care at our hospital and received standard diagnostic and therapy.

**Results:** Pat. 1 was 5 cm below 3rd perc. at age of 2y. He had a partial GH deficiency and a central hypothyroidism. On MRI scan, Pituitary was slightly reduced in size. On GH and thyroxin, he reached the 25th percentile (TH) within 2y. At the age of 6y, the patient became increasingly unconcentrated. In the evening he was restless and hardly fell asleep. He woke up at the night and stood trembling beside the parents bed. EEG, both awake and during sleep and a new MRI were normal. Discontinuation of GH stopped the phenomena. In 1 of 3 restart periods the phenomena reappeared. GH therapy was stopped. The problems resolved apart from a tremblemind 1 ½ y later during an upper airway infection. Patient 2 was a SGA baby. He had a low normal GH secretion and a mild primary hypothyroidism. GH therapy due to SGA and thyroxin therapy was introduced at the age of 6½y. He crossed 3rd percentile after 6 months. At the same time, the parents reported concentration problems, which could be handled. At the age of 10y, the patient became increasingly unconcentrated and restless and aggressive in the evening. School performance decreased rapidly. He woke up several times during the night spoke in a confused way. EEG and MRI were normal apart from a slightly reduced pituitary. Immediately after stopping GH therapy, all symptoms resolved. School performance improved and remained stable since then.

**Conclusions:** The observations show remarkable changes in sleep, activity and behaviour in close association to GH therapy. They developed long time after the onset of GH therapy and resolved after discontinuation of GH therapy. Thus, we have consider negative side effects of GH therapy on CNS function besides the well described positive effects.

P2-d3-712 Growth 4

**Can growth hormone (GH) secretory status predict the result of two-year growth hormone treatment?**

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**Background:** In short children GH peak release after GH provocative stimuli is currently used to evaluate GH secretory status and to decide on GH therapy.

**Objective and hypotheses:** To evaluate whether there is a difference in growth in a 2 y GH response between children with severe or moderate GH deficiency.

**Methods:** 97 GHD children (27 girls, 70 boys) were included. The children underwent 2 different GH release stimuli: insulin-induced hypoglycaemia and L-dopamine tests. Children were classified as: severe GH deficient (SIGH) (GH peaks <5 ng/ml after both stimuli; n = 47) and moderate (MGHD) (GH peaks <10 ng/ml, but one or both between 5 and 10 ng/ml; n = 40). There was no significant difference in age, height(H), height-SDS(HtSDS), midparental height, predicted height(PH), bone age(BA), sex or Tanner status between the two groups at the initiation of therapy. Height, HtSDS, height velocity(HV), height velocity SDS, BA, height gain, heightSDS gain, distance of height SDS to mid-parental height, distance of height SDS to predicted height, GH/kg/day, at 6 months, 1 and 2 years were evaluated.

**Results:** Children with MGHD had smaller distance of height SDS to mid-parental height at 2 but not at 1 year (mean [SD] 0.225 [2.58] vs -0.74 [1.49], p=0.045, and a tendency of higher BA gain at 1 year (1.2 [1.09] vs 0.82[0.58] p=0.081. No other differences were found in the rest variables. Children with the highest HtSDS gain at 1 year were those with the lowest BA (p=0.054), the highest velocity (p=0.0005) and velocity SDS (p=0.0005) at 1 year.

**Conclusions:** GH release stimuli seem to be of little help for predicting the result of GH replacement. Further studies and follow up until adult height are needed to decide whether GH stimuli can help predicting the result of GH treatment.

P2-d3-713 Growth 4

**Heterozygous mutation of CBL gene in Noonan-like syndrome**

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**Background:** CBL is a tumor suppressor gene that is mutated in myeloid malignancies and encodes a multipotent adaptor protein with E3 ubiquitin ligase activity, implicated in the RAS signaling voice that is affected in a group of clinically related developmental disorders characterized by facial dimorphisms, short stature, congenital cardiopathy, chyrotendoscopic phenomena reappeared. GH therapy was stopped. The problems resolved apart from 1 trembling episode 1 ½ y later during an upper airway infection. Patient 2 was a SGA baby. He had a low normal GH secretion and a mild primary hypothyroidism. GH therapy due to SGA and thyroxin therapy was introduced at the age of 6½y. He crossed 3rd percentile after 6 months. At the same time, the parents reported concentration problems, which could be handled. At the age of 10y, the patient became increasingly unconcentrated and restless and aggressive in the evening. School performance decreased rapidly. He woke up several times during the night spoke in a confused way. EEG and MRI were normal apart from a slightly reduced pituitary. Immediately after stopping GH therapy, all symptoms resolved. School performance improved and remained stable since then.

**Conclusions:** The observations show remarkable changes in sleep, activity and behaviour in close association to GH therapy. They developed long time after the onset of GH therapy and resolved after discontinuation of GH therapy. Thus, we have consider negative side effects of GH therapy on CNS function besides the well described positive effects.

P2-d3-714 Hypoglycaemia 1

**Developmental outcomes in children with congenital hyperinsulinism**

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**Background:** Congenital hyperinsulinism (CHI) is a group of genetic disorders resulting in impaired regulation of insulin secretion from the β-cells of the pancreas. Its prevalence is 1:50,000 births. Patients with CHI are at risk for developing neurodevelopmental difficulties due to infantile hypoglycemia. These include developmental delay, motor, coordination and speech problems and even severe mental retardation.

**Objective and hypotheses:** The aim of this study is to describe the implications of CHI on child cognitive and adaptive development.

**Methods:** The study group included 14 children aged 1-9 years, diagnosed with CHI and treated by drug therapy only (octreotide and/or diazoxide). Each participant underwent a physical and neurological examination and a battery of standardized cognitive and behavioral tests. Cognitive development was assessed by Bayley (BSID III) or Kaufman (K-ABC), depending on the child’s age. Child adaptive functioning and behavior were assessed by Vineland (VABS). Behavioral/emotional problems were assessed using the Achenbach (CBCL) parent questionnaire.

**Results:** The cognitive achievements of most of the study group (12 of 14) were around the normal average. Only 2 children showed cognitive achieve-
neonates with HH. Paradoxical serum GH and cortisol counter regulatory hormonal responses in resistance. Further studies are required to understand the mechanism/s of the serum IGF-1 levels are relatively low, demonstrating a degree of GH re-

are markedly elevated whilst the serum cortisol counter regulatory hormonal 

caremia was 12μg/L (±1.69). The data on serum IGF-1 was available in 8 
during the fast was 2.1mmol/L (SEM±0.13) and the mean insulin level was 

Results: 

Conclusions: 

Hypoglycaemia 1

Paradoxical serum growth hormone and cortisol counter-regulatory hormonal responses in neonates with hyperinsulinaemic 

Hypoglycaemia

Background: Hyperinsulinaemic hypoglycaemia (HH) is the most common cause of severe and persistent hypoglycemia in the neonatal period. It has been shown that the neonates with HH fail to generate adequate serum cortisol counter regulatory response to symptomatic hypoglycemia. However the role played by the various other counter regulatory hormones like growth hormone (GH), epinephrine and glucagon is not clear.

Objectives: To assess the serum growth hormone (GH), Insulin like Growth Factor 1 (IGF-1) and cortisol responses to HH in neonates undergoing diagnostic fasting studies.

Population and methods: Data was retrospectively collected on full term neonates who presented with severe and persistent hypoglycemia and were confirmed to have HH. Neonates born with Intra-uterine growth retardation or with associated syndromes, or those on medical therapy (diazoxide and octreotide) were excluded.

Results: 22 neonates with HH (mean gestational age: 38 weeks and mean weight: 4kg) were included in the study. The mean age at the time of diag-

nostic fasting studies.

P2-d3-717 Hypoglycaemia 1

Transient congenital hyperinsulinism caused by a novel maternally inherited mutation in the ABCC8 gene

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Background: A male newborn was referred to our center due to severe hypoglycemia, requiring up to 21 mg/kg/min of i.v. glucose. The mother’s family history revealed several members presenting insulin-dependent diabetes mellitus.

Objective and hypotheses: To identify genotype and phenotype of an individual with congenital hyperinsulinism (CH) and his family.

Methods: Clinical and laboratory work up as well as molecular analysis of leukocyte DNA were done.

Results: The patient was born at 34+5 weeks of gestation as second twin to a 2G3P healthy mother, after an urgent caesarean section. Birth weight: 2150 gr. (0 SDS). He had a moderate asphyxia (APGAR score 0 45 81, pH 6.9) needing non-invasive ventilatory support. Physical examination was normal except for a left preauricular tag. Repeated hypoglycemic episodes (<2.4 mmol/L, with unsuppressed insulin levels during hypoglycemia (> 25 μU/mL) and high carbohydrate requirements to main-

tain normoglycemia (> 15 mg/kg/min), while growth hormone (47.5 mcg/L) and cortisol (464 nmol/L) levels during hypoglycemia were adequately el-

vat normoglyceamia (> 15 mg/kg/min), while growth hormone (47.5 mcg/L) and cortisol (464 nmol/L) levels during hypoglycemia were adequately el-

vated confirmed the diagnosis of CH.

Treatment with Diazoxide (5 mg/kg/d) promptly resolved the hypoglycemias. Further studies are required to understand the mechanism/s of the paradoxical serum GH and cortisol counter regulatory hormonal responses in neonates with HH.

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Hypoglycaemia 1

P2-d3-715

Day Hour Glucose (mg/dL) Insulin (mIU/L) Cortisol (μg/dL) Epinephrine Glucagon (ng/mL) HGH (ng/mL)

1 06:00 81 3.3 17 47 N/A 1.8

12:00 74 1.4 9 50 46 1.06

18:00 64 1.3 14 132 52 0.61

21:00 52 0.57 10 N/A N/A N/A

after a 20 cc of 50% dextrose

120 5.43

Time (minutes) HGH (ng/mL)

basal 0.38

30 5.07

60 3.40

90 4.15

120 5.43

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Poster Presentations
Novel and known mutations of ABCC8 causing congenital hyperinsulinism in Vietnam

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Background: Potassium channels in the plasma membrane of the pancreatic beta cells are critical in maintaining glucose homeostasis by responding to ATP and coupling metabolic changes to insulin secretion. These channels consist of subunits denoted the sulfonylurea receptor SUR1 and the inwardly rectifying ion channel Kir6.2, which are encoded by the genes ABCC8 and KCNJ11, respectively. Activating mutations in the subunit genes can result in monogenic diabetes, whereas inactivating mutations are the most common cause of congenital hyperinsulinism of infancy (CHI).

Aims: The aim of the study was to identify mutations of ABCC8 and KCNJ11 in Vietnamese patients with CHI.

Subjects: Eleven Vietnamese probands with CHI were analyzed for alterations in ABCC8 and KCNJ11.

Methods: All exons of KCNJ11 and ABCC8 genes were amplified from genomic DNA and directly sequenced. In patients with detected mutations, the parental origin of each mutation was determined.

Results: Six probands had mutations in the ABCC8 gene. Three patients were homozygous or compound heterozygous for the mutations, indicating diffuse pancreatic disease. Their blood glucose levels were normal after nearly total pancreatectomy by laparotomy. In three patients, heterozygous and paternally inherited mutations were found, suggesting focal disease. Altogether, 4 different ABCC8 mutations including two novel alterations (F686I, G1379S) were identified. The same heterozygous, novel ABCC8 mutation Q444H was seen in 4 unrelated families, causing medically resistant patients, Table 1. Ten (83%) of the mutations were found in the KATP-channel genes ABCC8 and KCNJ11. The same heterozygous, novel ABCC8 mutation Q444H was seen in 4 unrelated families, causing medically resistant focal form in 3 patients and diazoxide responsive form in 1. GCK mutations were medical responsive, and resistant, respectively. There were no mutation carriers among children with spontaneously recovery. Further genetic investigations are pending.

Table 1. Genotype-phenotype correlation in patients with mutations detected

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>ABCC8</th>
<th>KCNJ11</th>
<th>GCK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutations found in medically responsive cases</td>
<td>R74L hetz</td>
<td>Q444H hetz</td>
<td>A96T homoz</td>
</tr>
<tr>
<td>Mutations found in medically resistant cases of focal forms</td>
<td>Q444H hetz, paternal</td>
<td>Q444H hetz, R411P hetz, paternal</td>
<td>R136AAsX5 hetz, de novo</td>
</tr>
<tr>
<td>Mutations found in medically resistant cases of diffuse forms</td>
<td>R98X hetz, delF1387 hetz, de novo</td>
<td>-</td>
<td>Y241C hetz</td>
</tr>
</tbody>
</table>

Hetz – heterozygous; homoz – homozygous

Conclusion: A genetic cause was detected in 23%, and 53%, of children with mild, and severe CHI, respectively, in Vietnam. The ABCC8 mutation Q444H was prevalent and found in both medical responsive and resistant patient. Further genetic investigations are pending.
Hypoglycaemia 1

Low glycaemic index foods reduce mild hypoglycemia episodes in children and adolescents with type 1 Diabetes

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Background: The metabolic influence of food glycaemic index (GI) on the management of type 1 Diabetes is still controversial, although there are some evidences of improvement of metabolic control, and reduction of post-prandial glucose excursion with low-glycaemic index diet.

Objective and hypotheses: The objective of this study was to evaluate the incidence of MH in relationship to GI of meals consumed.

Research design and methods: 82 type 1 diabetic patients, aged 14.1±6.1, disease duration 6.5±4.3 years, were enrolled in the study. All patients were treated with multiple injection regime consisting of a basal dose of long-acting insulin and three or four doses of short-acting insulin. Median HbA1C values were: 7.3±0.9. Patients were asked to complete a 15-days food diary where noted the frequency use of both high and low glycaemic index (HGI and LGI) foods and to use a logbook to register every hypoglycemia episode as indicated by a home BG monitor and by symptoms. Mild hypoglycemia (MH) was defined as BG <50 mg/dL (<2.77 mmol/L) and <70 mg/dL (<3.88 mmol/L) with or without symptoms.

Results: During the study period we recorded a lower number of MH episodes in patients who consumed LGI cereals for breakfast daily, as well as in patients with a high fiber, LGI, legumes rich diet. The percentage of patients who recorded at least four MH episodes was 26.1, in the group that avoided LGI cereal daily vs 65.2 in the group that did not. Similar results were recorded considering LGI legumes (29.7% vs 70.35%) p= 0.03 and p= 0.01 respectively.

Conclusion: Although logic suggests that LGI diet should positively affect postprandial glucose excursion, few studies have focused the attention on this influence on hypoglycemia episodes. Our findings suggests that LGI diet could help to minimize MH in patients, contributing to better quality of life.

P2-d3-722 Hypoglycaemia 1

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, oculogyratic crises and autonomic features. Prognosis is poor and available treatment options like dopamine agonists, vitamin B6, monoamine oxidase inhibitors and atroponine only have marginal therapeutic effect.

Objective and hypotheses: We describe a five year old boy with AADC-deficiency confirmed by mutation analysis. He showed a severe neurologic clinical picture and no improvement was found under several dopamine agonists, high doses of vitamin B6 and an atropine agonist. 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 diagnosed as having epilepsy. The pathogenesis of hypoglycaemia in these patients is unknown. I hypothesise that the potent dopamine agonists in these patients can give rise to hypoblycaemia 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 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.

Conclusions: Dopamine agonists can give rise to episodes of hypoglycaemia in patients with AADC-deficiency by acting on overactive receptors in the central nervous system (hypophyse) and the beta cells.

P2-d3-723 Perinatal and Neonatal Endocrinology 1

Clitoral and penile sizes in healthy newborn babies in Ibadan, Nigeria

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Background: Standards of penile and clitoral lengths are useful for diagnosis of genital abnormalities. Micropenis could be the only sign in pituitary/ hypothalamic dysfunction while clitorometry may reflect abnormalities of neonatal and maternal origin. Ambiguous genitalia if missed at birth could be fatal especially in cases of congenital adrenal hyperplasia. There are no African reports on normal reference ranges of both penile and clitoral sizes. This study aimed to generate key information that did not exist on the size of external genitalia of newborn babies in Nigeria.

Objective and hypotheses: To establish the normal reference values for penile and clitoral sizes in Nigerian infants and to compare with standards from other ethnic populations.

Methods: A total number of 515 healthy newborn babies delivered at gestational age more than 37 weeks were included in the study. After collecting some of their demographic data (sex, age, mode of delivery), clitoral and penile lengths were measured.

Results: Fifteen children (45%) had a mutation: 11 in ABCC8 and 4 in KCNJ11. Seven were new mutations. Seven patients showed a recessive mutation: 5 of them were unresponsive to medical treatment and underwent total pancreatectomy for Di-HI, 1 patient presented compound heterozygous mutation with a wilder phenotype. Eight patients had an heterozygous mutation: 2 patients had a paternal inherited mutation with a severe form of CHI unresponsive to medical treatment and underwent surgery for Fo-HI; the other patients showed a milder form of CHI with a good response to medical treatment and 4 of them had a clinical remission and stopped therapy.

Conclusions: The first molecular and clinical analysis of Italian patients with CHI confirms what previous studies have shown in other populations.
Neonatal diabetes (DNN) is rare (1/400,000 newborns). It has two main clinical forms: a transient form (TNDM) and a permanent form (PNDM). We report six cases of neonatal diabetes, collected at the service of Diabetology Pediatric Children’s Hospital of Rabat. These two cases of Wolcott-Rallison syndrome diagnosed respectively on the association of parental consanguinity, neonatal diabetes, a skeletal dysplasia with osteoporosis in one case and liver failure in the second case. A case of transient neonatal diabetes. A fourth case with consanguineous parents and two siblings died in the neonatal period with hyperglycemia, the latter two cases presented early diabetes, with a fatal outcome in a case involving an array of severe stunting and generalized atopic eczema. The genetic study was performed in all cases. She confirmed the presence of the mutation in EIF2AK3 Wolcott Rallison syndrome, the presence of a mutation in a transient diabetes in the third case, a newly described mutation in the gene for insulin in the fourth case, and no mutation was found in the fifth case. For the sixth case, IPEX syndrome was confirmed by genetic mutation FOX P3; The management was based on insulin therapy. We emphasized the diagnostic and therapeutic difficulties of neonatal diabetes and the need to complete the etiological by a genetic study to confirm or deny the permanent or transient diabetes, which could facilitate the therapeutic management.

**Background:** Low birth weight and length for gestational age are associated with a high risk of short stature and metabolic syndrome in adulthood. The mechanisms linking prenatal growth to adult stature and metabolic syndrome have not been entirely clarified yet.

**Objective and hypotheses:** The aim of our study was to evaluate the relationship between standardized anthropometric measures at birth and IGF-I, IGF-II, insulin, adiponectin, and non-esterified fatty acids (NEFA) cord blood levels.

**Methods:** We included 250 newborns from the northwest of Italy, treated at the newborn unit of the “Gaslini” Children’s Hospital. Background and anthropometric measures were collected. The main objective was to evaluate the relationship between standardized anthropometric measures at birth and IGF-I, IGF-II, insulin, adiponectin, and non-esterified fatty acids (NEFA) cord blood levels.

**Results:** Anthropometric parameters were calculated according to standard Italian tables. Insulin values were treated as categorical, since in several cases the results were below the laboratory detection cut-off. Mean birth weight was 3214.23±488.99 gr, mean length 49.82±2.17 cm. Females had higher mean IGF-I (p=0.04), and were more likely to have insulin levels either <2 µU/ml or >4.5µU/ml (p=0.04) compared to males. Weight and length SDScore (SDS) were higher in subjects with higher insulin levels (p=0.002). A moderate correlation was found between weight and IGF-II (r=0.354). Multiple regression analysis showed that insulin and IGF-II combined together accounted for 16.7% of birth weight variability. An increase in IGF-II predicted the postnatal growth, and suggests that gender differences should be taken into consideration when evaluating prenatal growth.
**P2-d3-727** Perinatal and Neonatal Endocrinology 1

**Early postnatal growth and metabolic profile differences in very low birth weight (VLBW) preterm (PT) infants born small for gestational age (SGA) or appropriate for gestational age (AGA) independent of nutritional intake**

Maria Isabel Hernandez1; Veronica Peñal1; Katherine Roesel1; Mirna Garcia1; Teresa Salazar1; Gabriel Cavada1; German Iñiguez1; Veronica Merico1

**Background:** Low birth weight is associated with metabolic risk. Early infancy weight gain is a key factor. Objective: To evaluate whether early patterns of infancy anthropometry and metabolic hormonal profile differs in VLBW PT born SGA or AGA.

**Methods:** We recruited 87 VLBW PT, 48 AGA, 55 females. Mean BW -1.36±1.06 SDS, birth length -0.8±0.8 SDS, 29 weeks GA. Complete anthropometry weekly nutritional registry and blood sampling for glycemia, Insulin, IGF-I, IGF-II and leptin determination obtained at 72 hrs, 15, 28, 60 days (d), 0, 1, 3, 6 and 12 months (m) corrected age (CA=40 weeks GA). Statistics: SPSS 17.0.

**Results:** During in-hospital differences in patterns of weight and length increase. No differences in nutrition (total calories and nutrients) were observed. A steady increase in tricipital skin fold of 0.25 mm/week was observed similarly in all subjects. A 28% of SGA had length ~25 SDS by 3 m CA vs. none of the AGA (p<0.001). Only in SGA IGF-I decreases at 15d and recovers by 60d (p<0.02). Glycemias differ by age (SGA):0,1,3,6 and 12 months (m) corrected age (CA=40 weeks GA). Statistics: SPSS 17.0.

**Conclusions:** In all VLBW PT whereas weight SDS increase is lower in those born SGA. With higher levels in AGA subjects. A higher IGF-I and lower IGF-II were found in the left lobe of thyroid and hemithyroidectomy was performed. All parathyroid glands were not enlarged, histology showed normal parathyroid tissue. No decrease in calcium and PTH levels were seen after the surgery and during 2 yrs of follow up unless short periods after bisphosphonate administration. Sestamibi Scan was performed three times and did not reveal any additional parathyroid glands.

**P2-d3-728** Perinatal and Neonatal Endocrinology 1

**Incidence and risk factors for rib fractures in ex-preterm infants**

Angela Lucas-Herald1; Helen McDevitt2; Sandra Butler3; Jean Herbsom1; S. Faisal Ahmed1

**Background:** Neonatal severe hyperparathyroidism (NSHPT) is a rare disease caused by homozygous inactivating mutations of CaSR gene. Total parathyroidectomy was curative in most published cases of NSHPT.

**Aims:** To identify the prevalence and characteristics of rib fractures in ex-preterm infants. **Methods:** A total of 1780 infants with a gestational age<37 weeks were identified and followed up to the age of 1 year. Posterior rib fractures, previously suggestive of non-accidental injury, were noted in 27 infants. The greatest number of rib fractures noted in an individual infant was 6. Anatomically, the highest rib affected was the 4th rib. All other rib fractures were lower, most commonly the 7th rib (15/36, 27%). Out of 26, 24(92%) of the rib fractures were posterior, 11 (20%) were lateral and 1(2%) was anterior. The precise location of the rib fractures was not reported in 20 (36%) of the fractures. Typical risk factors that were identified included conjugated hyperbilirubinemia, use of diuretics, total parenteral nutrition and low calcium and/or phosphate levels in 11(41%), 12(44%), 11(41%) and 3(11%) cases, respectively. Non-accidental injury was considered likely in only 1 case(4%).

**Conclusions:** Rib fractures are present in 1.5% of ex-preterm infants up to the age of 1 year. Posterior rib fractures, previously suggestive of non-accidental injury are not uncommon in these infants.

**P2-d3-729** Perinatal and Neonatal Endocrinology 1

**A 5-year old boy with neonatal severe hyperparathyroidism and homozygous CaSR mutation: failed total parathyrectomy**

Elizaveta Orlova1; Maria Kureva1; Maria Melikyan1; Valentina Peterkova2; Henrik Christensen1

1Endocrinological Research Center, Institute of Paediatric Endocrinology, Moscow, Russian Federation; 2Odense University Hospital, Paediatrics, Odense, Denmark

**Background:** Neonatal severe hyperparathyroidism (NSHPT) is a rare disease caused by homozygous inactivating mutations of CaSR gene. Total parathyroidectomy was curative in most published cases of NSHPT.

**Aims:** To identify the prevalence and characteristics of rib fractures in ex-preterm infants. **Methods:** A total of 1780 infants with a gestational age<37 weeks were identified and followed up to the age of 1 year. Posterior rib fractures, previously suggestive of non-accidental injury, were noted in 27 infants. The greatest number of rib fractures noted in an individual infant was 6. Anatomically, the highest rib affected was the 4th rib. All other rib fractures were lower, most commonly the 7th rib (15/36, 27%). Out of 26, 24(92%) of the rib fractures were posterior, 11 (20%) were lateral and 1(2%) was anterior. The precise location of the rib fractures was not reported in 20 (36%) of the fractures. Typical risk factors that were identified included conjugated hyperbilirubinemia, use of diuretics, total parenteral nutrition and low calcium and/or phosphate levels in 11(41%), 12(44%), 11(41%) and 3(11%) cases, respectively. Non-accidental injury was considered likely in only 1 case(4%).

**Conclusions:** Rib fractures are present in 1.5% of ex-preterm infants up to the age of 1 year. Posterior rib fractures, previously suggestive of non-accidental injury are not uncommon in these infants.

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**Table: CaSR gene analysis**

<table>
<thead>
<tr>
<th></th>
<th>Boy</th>
<th>Mother</th>
<th>Father</th>
</tr>
</thead>
<tbody>
<tr>
<td>s-total calcium (mmol/l)</td>
<td>4.5</td>
<td>2.8</td>
<td>N/A</td>
</tr>
<tr>
<td>s-ionized calcium (mmol/l)</td>
<td>2.5</td>
<td>1.38</td>
<td>N/A</td>
</tr>
<tr>
<td>s-phosphorous (mmol/l)</td>
<td>1.03</td>
<td>0.86</td>
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</tr>
<tr>
<td>u-calcium/creatinine</td>
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<td>0.209</td>
<td>N/A</td>
</tr>
<tr>
<td>s-PTH (9-74 pg/l)</td>
<td>199</td>
<td>45.9</td>
<td>N/A</td>
</tr>
</tbody>
</table>

He had dramatically delayed psychomotor and physical development: Height -3.2 SD, weight -6.4 SD, could not hold his head up, neither sit, stand and eat solid food. He had severe constipation, normal renal function with no signs of kidney stones, no bone deformities and no fractures with radiological signs of osteopenia. Molecular analysis of CASR gene revealed homozygosity for p.Arg220Trp mutation. Ibondronate 1 mg i/v and Zolendronate 4mg i/v led to no, and, transient serum calcium decrease, respectively. The patient underwent surgery: three parathyroid glands were removed and the fourth was left for potential need of additional parathyroid gland surgery. He did not have neither feeding problems or vomiting, nor bone fractures or deformities. Severe hypercalcemia (total Ca was 5 mmol/l, ionized Ca was 3.05 mmol/l) with suppressed level of phosphorus (1.0 mmol/l) was revealed at 6 month. When admitted to our clinic at 3 yrs, severe NSHPT was still present, Table 1.
Circulating cytokines influence fetal growth in pregnant women with rheumatoid arthritis (RA)

Florentien D.O. De Steenwinkel; Yael A. De Man; Yolanda B. De Rijke; Johanna M.W. Hazes; Anita Hokken-Koelega; Radboud J.E.M. Dolhain

Objective: High levels of circulating cytokines are a hallmark of RA. Methods: Current study is embedded in the PARA study; a prospective study on RA and pregnancy. 134 pregnant RA patients were enrolled in first trimester and 34 were added in second. We analysed the maternal RA disease activity (DAS28) and the cytokine levels of IL-10 and IL-6 in first and third trimester of pregnancy in relation with the bwsds. Results: Strong correlations were found between DAS28 and IL-10, IL-6. Patients with detectable IL-10 showed a higher DAS28 than patients without IL-10. The difference in bwsds of IL-10 positive and negative patients was determined after matching for DAS28, parity and prednisone use. First trimester: mean (SD)bwsds in the IL-10 positive group (n=12) was significantly higher (0.02 (SD 0.7), p=0.02) than in the IL-10 negative group (n=24): 0.15 (SD 0.7). No such differences were found in third trimester. To determine the additional effect of IL-6 to DAS28 on bwsds, we stratified all patients on the median IL-6 and DAS28 levels resulting in 4 groups. In first trimester, if the DAS28 was high the bwsds was significantly lower when IL-6 was also high. In the high and low IL-6 groups bwsds was -0.19 (SD 1.12) and 0.36 (SD 0.93), resp. No such association was found in third trimester. Conclusion: Fetal growth in pregnant women with RA is influenced by circulating cytokines in the first trimester. Elevated IL-10 seems to protect against the negative influence of DAS28 on birth weight, whereas IL-6 amplifies the negative influence of DAS28 in this trimester. In third trimester there is no influence of these cytokines suggesting an early critical window in the first trimester only.

Congenital Combined Pituitary Hormone Deficiency (CPHD), dysmorphic features; severe developmental delay, seizure disorder, blindness and neurogenic bladder: a new disorder

Angham Al Mutairi; Abdelhammed Albargany; Abderhamn Suwaid; Fowzan Alkuraya; Emma Webb; Daniel Kelberman; Mehrul Dattani

Background: Combined Pituitary Hormone deficiency (CPHD) is usually characterized by variable hypopituitarism and may be associated with syndromic features. To date, mutations in a number of developmental genes (POU1FT1, PROP1, LHX3, LHX4, SOX2, SOX3, OTX2 and HESX1) have been implicated in the aetiology of hypopituitarism in humans, but only a small proportion of cases are accounted for by genetic mutations,and the aetiology remains unknown in the majority of cases of congenital CPHD. Objective: We report a cohort of 6 patients from a highly consangunous pedigree with a novel and highly distinct phenotype comprising femailal panhypopituitarism, including central DI, and a number of unusual features. Methods: Here we will describe the phenotype, biochemical and neuroradiological characterization of the pedigree. Results: Five girls and one boy were affected with the disorder; all patients have the same facial dysmorphic features with a normal karyotype; All patients had an early neonatal presentation with a sepsis-like picture, collapse due to ACTH deficiency, and polypuria due to central DI requiring DDAVP therapy. Five patients developed central hypothyroidism at a few weeks of age. All patients are blind (cortical), severely developmentally delayed with spasticity, hyperreflexia, and with recurrent seizures. All patients had multiple urinary tract infections; and the presence of a neurogenic bladder was confirmed in all patients (n=5) in whom had the urodynamics tests were performed. Renal ultrasound was abnormal in all; MRI of the hypothalamo-pituitary region was abnormal in all tested (n=5) Mutation analysis was performed in 4 patients and failed to reveal a mutation in any of the genes known to be implicated in hypopituitarism. Conclusions: We describe a pedigree with a novel CPHD phenotype including central DI. Anterior and posterior pituitary deficit was associated with severe developmental delay, a seizure disorder, blindness, neurogenic bladder and dysmorphic features. This new syndrome is likely to represent a novel genetic aetiology.
traumatic period (2–14 days, T0) and in 3, 6 a 12 months after the injury (T3, T6 to T12). Dynamics tests were performed in patients with abnormalities in clinical examination and/or laboratory results. MRI was made in T12.

Results: The median of age in time of an injury was 11.3 (0.5-18.7) years. Twenty-three patients had GCS ≤ 8/15. In T0 diabetes insipidus (DI) was occurred in 12 patients and a SIADH in 4 patients, hormonal changes simulated a central hypothyroidism in 45% of patients and a hypogonadotropic hypogonadism (HH) in 25% of adolescents. Combined pituitary hormones deficiency was found in 2 boys and DI in one patient in T3. A precocious puberty and a GHD were found in two boys in T6. In T12 a new endocrine dysfunction was diagnosed in five patients (2 had a GHD, 2 had a HH and in one patient with a GHD a central hypothyroidism was confirmed). An empty sella has been found on MRI in two patients. Patients with GCS ≤8 had hormonal dysfunction more often (6/23) compared to those with a medium trauma (3/35) and also they had more often DI or SIADH in T0. The occurrence of early endocrine dysfunction significantly correlated with severity of injury (p<0.05), but did not serve as an indicator of development of late hormonal dysfunction (p=0.5).

Conclusions: Within a year from an injury hormonal disorder has occurred in 15.5% of patients. Risk factors include severity of TBI, abnormalities in the brain-imaging techniques and DI or SIADH in acute posttraumatic phase.

P2-d1-735 Pituitary 1

Central diabetes insipidus in infants

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Birmingham Children's Hospital, Endocrinology, Birmingham, United Kingdom

Background: Central Diabetes Insipidus (CDI) is rare in infants, with case reports alone previously documented in the literature.

Objective and hypotheses: We describe our experience of CDI in infants < 1 year at a tertiary paediatric endocrine unit.

Methods: We characterised the clinical features of infants diagnosed with CDI between April 1992 and February 2011 by retrospective case notes review.

Results: There were 19 children, 10 (52%) male. Median age at diagnosis was 24 days (range 5 – 300). 8 (42%) were preterm (<37 weeks gestation). Whilst hyponatraemia was identified in some during initial investigations for presenting problems such as poor weight gain (3/19), seizures (3/19) or jaundice (1/19), in others (11/19) it was discovered incidentally, during routine blood tests on preterm babies or investigation of a metabolic problem. The final underlying diagnosis was: Septo-optic dysplasia (SOD) (n=7), isolated CDI (n=5), chromosomal abnormalities (n=3), microcephaly with infantile spasms (n=1), pilomyxoid astrocytoma (n=1), panhypopituitarism (n=1) and Ohtahara syndrome (n=1). Three of five infants with isolated CDI were born very premature (<30 weeks gestation). Eleven infants (including all with SOD and panhypopituitarism) had other pituitary hormone deficiencies; of these, 9 had associated TSH and ACTH deficiency, 1 ACTH deficiency and 1 TSH, ACTH and GH deficiency. The median (range) plasma sodium, osmolality and urine osmolality before diagnosis were 156 mmol/l (145 - 175), 320 mosmol/kg (300 – 345) and 112 mosmol/kg (66-322) respectively. Desmopressin (DDAVP) therapy was administered intranasally (i.n.) in 8 infants and orally (p.o.) in the remainder, with median (range) initial doses being 0.64 mcg/kg/day (0.2 – 1.7) and 2 mcg/kg/day (0.26 – 18.5) for i.n. and p.o. routes respectively.

Conclusions: Cranial Diabetes Insipidus (CDI) is a rare but important diagnosis in infants with persistent hyponatraemia. Presentation, clinical features, biochemistry and initial DDAVP doses are very variable.
P2-d1-736 Pituitary 1

Brain Magnetic Resonance Imaging (MRI) phenotypes correlate with pituitary, ophthalmic and neurologic defects in patients with midline defects and/or suspected Septo Optic Dysplasia

Anna E.M. Allegretti; Natascia Di Iorgi; Flavia Napoli; Annalisa Calcaigno; Enrica Bertelli; Irene Olivieri; Giovanna Pala; Maria Savina Severino; Andrea Rossi; Mohamad Maghniew

1IRCCS, Giannina Gaslini, Pediatrics Department of Pediatrics, Genoa, Italy; 2IRCCS, Giannina Gaslini, Pediatric Neuroendocrinology, Genoa, Italy

Background: The diagnosis of septo-optic dysplasia (SOD) is assessed when two or more of these features are present: optic nerve hypoplasia (ONH), pituitary hormone abnormalities, midline brain defects-agenesis of septum pel- lucidum (SP) and/or corpus callosum (CC). Brain MRI has a central role in diagnosis, although the relation between MRI imaging and clinical features is controversial. In addition, Diffusion Tensor Imaging (DTI) has not been used in SOD definition yet.

Objective and hypotheses: Our aim was to evaluate the relation between MRI/DTI phenotypes and clinical findings in SOD.

Methods: 17 patients with clinical SOD or with incidental MRI findings of midline brain defects (age 1-18 years) underwent conventional MRI, DTI (7 patients) and hormonal investigations.

Results: 3 subsets of patients were identified based on MRI/DTI findings of: SP, CC, ONH, ectopic posterior pituitary (EPP), anterior pituitary hypoplasia (APH) and pituitary stalk (PS). Group A (n=2): complete or partial absence of the SP, normal CC, normal fornices tracts. Other MRI features were: ONH in 6 patients, EPP in 1, PS abnormalities in 3 and APH in 4 patients; Group B (n=4): normal SP, complete or partial agenesis of CC, abnormalities of fornices tracts. ONH was present in 2 patients, EPP in 1, PS abnormalities in 2 and APH in all patients; Group C (n=4): normal SP, normal CC, normal fornices tracts. ONH, EPP, PS abnormalities and APH in all patients.

Combined pituitary hormone deficiency (CPHD) was present in 6/17 patients. Only 1 patient in group A and 1 in group B presented CPHD, both associated with ONH, EPP, PS abnormalities and APH. In group C all patients presented CPHD in association with ONH, EPP, PS abnormalities and APH.

Conclusions: Our findings confirm that individuals with ONH, in particular when associated to EPP, are at high risk for endocrine abnormalities. In contrast to previous findings complete or partial absence of the SP is not associated with hypopituitarism in our cohort.

P2-d1-737 Pituitary 1

A case of 10-year-old girl with intact hypothalamic-pituitary functions after radical resection of craniopharyngioma

Elena Iluy; Natalya Strebookova; Evira Kuznetsova; Valentina Petekrakova

Endocrinology Research Centre, Institute of Pediatric Endocrinology, Moscow, Russian Federation

Introduction: Craniopharyngioma are rare embryonic malformations of the sellar area with low-grade histological malignancy. Most patients (85-95%) suffer from multiple deficits of hypothalamic-pituitary functions, ranging to panhypopituitarism.

Case report: We present the case of 10-years-old girl after complete transcranial resection of extraventricular craniopharyngioma and following a full safety of hypothalamic-pituitary function. A 7.8-year-old girl presented a two-month history of headache, nausea and vomiting. Biometrical parameters: the height was 135 cm (1.94 SDS) and weight was 29 kg (0.01 SDS). Bone age was 7.5 years. The visual fields were impaired (bitemporal hemianopsia). MRI demonstrated tumor located below the third ventricular floor (suprasellar extraventricular craniopharyngioma). Biochemical data: TSH, FT4, cortisol, prolactin and IGF-1 were within normal ranges for age. Complete transcranial resection was performed. After surgery, a transient polyuria was well controlled by DDA VP, taken only for a month. Visual acuity improved postoperatively. During 2 years’ follow-up, hypothalamic-pituitary functions remained unchanged and adult MRI showed no signs of relapse (partial empty sella). The girl grew spontaneously, achieving the growth velocity of 5.0 cm during the first and 7.0 cm during the second post-operative year. At the age of 10 years, her height was 147 cm (1.66 SDS) and weight was 38 kg (0.89 SDS). Bone age was 10 years. Serum IGF-1 level was 364 ng/ml (ref. 55-399 ng/ml). Basal adrenal and thyroid function were normal.

Conclusion: We describe a girl after radical resection of craniopharyngioma and following full safety of hypothalamic-pituitary functions that occurs only in exceptional cases.

P2-d1-738 Pituitary 1

New phenotype in the familial DICER1 tumour syndrome: pituitary blastoma presenting at age 9 months

Stefanie Wildi-Rumke; Mohamed-Amin Bahubeshi; Anne-Sophie Carré; Louis Crevier; Yves Robitaille; Bernd Scheithauer; Kovacs Kalman; William Foulkes; Cherri Deal

1CHU-Sté-Justine/Université de Montréal, Endocrine Service, Dept. Pediatrics, Montréal, QC, Canada; 2McGill University, Human Genetics and Oncology, Montréal, QC, Canada; 3CHU-Sainte Justine/Université de Montréal, Oncology Service, Dep. Pediatrics, Montréal, QC, Canada; 4CHU-Sté-Justine/Université de Montréal, Neurosurgery, Montréal, QC, Canada; 5CHU-Sté-Justine/Université de Montréal, Pathology, Montréal, QC, Canada; 6Mayo Clinic, Pathology, Rochester, MN, United States; 7St Michael’s Hospital, Pathology, Toronto, ON, Canada

Background: DICER1 is an RNase endonuclease important for production of microRNAs which regulate multiple protein-coding genes. It has been linked to several tumours particularly pleuropulmonary blastoma (PPB), cystic nephroma, ovarian Sertoli-Leydig cell tumours and to familial multinodular goiters. We enlarge the endocrine phenotype to include pituitary blastoma.

Case: This 9-month old male French Canadian boy was first seen after an ophthalmology consult for strabismus led to the diagnosis of a 16 x 30 x 23 mm sellar and suprasellar tumour. His growth was normal. Family history revealed a PPB and cystic nephroma in a male second cousin. Physical examination of this well-looking baby was significant for R proptosis. Bone age was 6-9 m.

Baseline endocrine evaluation detected elevated serum AFP (174 ug/L) and central hypothryoidism. Following partial tumour resection, the patient developed discrete signs of Cushong syndrome, confirmed by endocrine testing. Tumour pathology was consistent with a pituitary blastoma, revealing primitive Rathke-type epithelium, brisk mitotic activity, small folliculo-stellate cells and larger secretory cells immunoreactive for ACTH, beta-endorphin and O- ANCG.

Conclusion: This is the second reported case of pituitary blastoma in infancy, we suspect that other cases previously labelled as pitutary ACTH-producing adenoma in very young infants may be part of a larger DICER1 familial cancer syndrome. Incomplete penetrance of the various tumours are likely due to modifying loci, such as that described in our patient.
thyroidism (T4=9.70, TSH=0.21), a low cortisol and an IGF-1 of 25. Examination was unremarkable with no evidence of pigmentation. The triad of low sodium, low TSH and cortisol was felt to be due to hypopituitarism and he was commenced on thyroxine and hydrocortisone. Synacthen test was done prior to the start of treatment and showed a normal cortisol of 661 (ACTH 23), following which his steroid replacement was stopped. He gradually improved and was discharged on thyroxine 2 weeks later. His thyroxine was discontinued post recovery from the illness and repeat TSHs have been normal.

Discussion and conclusion: This young boy had a presumed viral illness causing profound lethargy resulting in a prolonged hospitalisation with abnormal biochemistry suggesting a partial hypopituitarism (low TSH, IGF-1 & random cortisol). In retrospect, given, his normal synacthen and recovery of thyroid function and improved height velocity, the possibility of sick euthyroid or transient central hypothyroidism which has previously been seen in failure to thrive is more likely. Interestingly, only about 10% of hospitalized patients with sick euthyroid present with low TSH with T3 followed by T4 abnormalities seen much more commonly.

### P2-d3-740 Pituitary 1

**Familial hypogonadotropic hypogonadism**

**Nadia Charfi**1; **Mouna Mnif**1; **Mahdi Kamoun**1; **Basma Ben Naceur**1; **Mouna Elleuch**1; **Nabila Rekik**1; **Hassen Kamoun**1; **Mouna Belghith**1

1Hedi Chaker Hospital, Endocrinology Department, Sfax, Tunisia; 2Hedi Chaker Hospital, Pediatric Department, Sfax, Tunisia; 3Faculty of Medicine, Department of Human Molecular Genetics, Sfax, Tunisia

**Background:** Congenital hypogonadotropic hypogonadism is a relatively rare heterogeneous disorder, with prevalence estimated at nearly 1 / 10000. Most cases are sporadic but there are also familial forms.

**Objective and hypotheses:** The aims of this study were to describe clinical, biological and therapeutic characteristics of familial hypogonadotropic hypogonadism.

**Methods:** We report 5 patients belonging to two different families who were followed for hypogonadotropic hypogonadism.

**Results:** The first case was a 17 years old girl who was presented for an isolated delayed puberty. Hormonal investigations confirmed the central hypogonadism with integrity of other pituitary axis. Magnetic resonance imaging (MRI) pituitary was normal and the karyotype was 46 XX. Her brother, aged of 15 years was also presented for delayed puberty without anosmia. Hormon al investigations revealed isolated gonadotropin insufficiency. MRI pituitary was normal. The second family included three brothers, aged respectively of 15, 16 and 23 years operated all for cryptorchidism. Parental consanguinity was noted. Clinical exam showed micropenis without dysmorphic syndrome in all cases, anosmia in 2 cases, gynecomastia in 2 cases and macroskelia in 1 case. Hormonal investigations revealed isolated central hypogonadism. MRI pituitary showed pituitary hypoplasia without signs of adenoma in two cases and pituitary microadenoma in the second brother. These three patients were treated by androgen therapy with pubertal progress. During follow-up, the first patient of the first family developed alacrima, achalasia and adrenal deficiency. Mutation analysis identified a novel homozygous mutation within intron 14 (IVS14+1(G) →A), consisted with Allgrove syndrome. Intron 14 (IVS14+1(G) →A), consisted with Allgrove syndrome. Intron 14 (IVS14+1(G) →A), consisted with Allgrove syndrome.

**Conclusions:** Diagnosis of congenital hypogonadotropic hypogonadism is generally easy when the etiological diagnosis provide a research area based mainly on genetic studies, especially in familial forms.

### P2-d3-741 Programming/Epigenetics 1

**IGF2 gene methylation in obese children born small for gestational age (SGA)**

**Alice Liguori**1; **Antonella Puglianiello**1; **Daniela Germani**1; **Claudia Bufani**2; **Danilo Fintini**2; **Marco Cappa**2; **Fabrizio Barbetti**2; **Stefano Ciamparini**2

1Tor Vergata University, Dept. Public Health and Cell Biology, Rome, Italy; 2Bambino Gesù Children’s Hospital, Endocrinology Unit, Rome, Italy; 3Bambino Gesù Children’s Hospital, Cardiorespiratory and Sport Medicine Unit, Rome, Italy; 4Bambino Gesù Children’s Hospital and Tor Vergata University, Laboratory of Monogenic Diabetes and Department of Laboratory Medicine, Rome, Italy

**Background:** An adverse intrauterine environment may affect both growth and development, permanently programming endocrine and metabolic functions. The epigenetic modification of genes involved in the control of key metabolic pathways is one of the mechanisms of programming. Periconceptional exposure to famine was associated with lower methylation of the IGF2 gene 6 decades later. The reduced methylation of IGF2 may represent the consequence of intrauterine exposure to deficient methyl donors supply.

**Objective and hypotheses:** We asked whether obese children born SGA show alterations in the degree of methylation of the IGF2 gene.

**Methods:** We investigated IGF2-DMR gene methylation in 8 obese SGA (4M/4F, birth weight ≤ 2 SDS, at term; BMI-2 SDS), age 11.6 ± 1.7 yrs and 22 obese AGA (7M/15F, birth weight between 25th and 75th centile, at term). The two groups were closely matched for age, BMI and pubertal stage. Metabolic parameters, blood pressure, and body composition were assessed. Mann-Whitney non-parametric U-test was used to identify any differences between the groups.

**Results:** No significant difference in the degree of IGF2 gene methylation was found. 4 subjects in the whole study cohort, 3 AGA and 1 SGA, showed more than 90% of unmethylation. No significant differences in age, birth weight, gestational age, current BMI and pubertal stage were observed between the group with high degree of IGF2 unmethylation (N=4) and subjects with intermediate degree of methylation (N=25). The group with IGF2 gene unmethylation showed significantly higher levels of adiponectin 23.2 ± 4.8 vs 12.0 ± 4.7 mcg/ml, p<0.005), and lower although not significant concentrations of triglycerides (p=0.057). No differences in metabolic and body composition parameters were found.

**Conclusions:** Our findings suggest that the degree of IGF2 methylation may be associated with metabolic status in obese children. Further studies are needed to confirm these preliminary results.

### P2-d3-742 Programming/Epigenetics 1

**Effects of prenatal exposure to modern pesticides on birth weight, growth and body composition in childhood; interactions with maternal smoking and PON1 gene- polymorphisms**

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**Background:** Endocrine disrupting chemicals in the environment such as pesticides are suspected to play a role in the pathogenesis of obesity.

**Objective and hypotheses:** Aim was to assess possible long-term effects of prenatal exposure to currently used pesticides on children’s growth.

**Methods:** In a prospective study of 247 children born by women working in greenhouses in early pregnancy, 168 were categorized as prenatally exposed to pesticides. At three months (n=203) and at 6 to11 years of age (n=177) the children underwent a clinical examination and blood sampling for analysis of gene polymorphisms of Paraoxonase1 (PON1); a HDL-associated antioxidative enzyme that hydrolyzes some pesticides. Body fat percentages at age 6 to11 years were calculated from skin fold measurements. Pesticide related effects on IGF2 gene methylation were explored.

**Results:** At 6 months of age, the exposed group had higher body fat percentage in boys than the non-exposed group (p=0.029) and the exposed group had lower systemic IGF2 methylation (N=25) compared to the non-exposed group (p=0.02), and lower although not significant reductions in triglycerides (p=0.057). No differences in metabolic and body composition parameters were found.

**Conclusions:** Our findings suggest that the degree of IGF2 methylation may be associated with metabolic status in obese children. Further studies are needed to confirm these preliminary results.
were tested by linear multiple regression analysis, adjusting for relevant con-
founders.

Results: Birth weight and weight for gestational age were 4.1% lower in the
exposed children (p<0.02). Exposed children had significantly higher (0.55 SD) ΔBMI Z-score from birth to school age (p=0.018) and a non-significant
tendency to larger skin folds and higher body fat percentage compared to unexposed.
If prenatally exposed to both pesticides and maternal smoking
the sum of four skin folds was 46.9% (95% CE: 8.1; 99.5, p=0.015) and body fat percentage 29.1% higher (95% CE: 3.0; 61.4), p=0.028). Among children with the PON1 192QR/RR genotype (n=61), prenatally pesticide exposed had
significantly lower birth weight, higher BMI-z-scores, and body fat percent-
age than unexposed.

Conclusion: Maternal exposure to combinations of modern, non-persistent
pesticides during early pregnancy may affect growth, both prenatally and
postnatally. We found a biphasic effect with lower weight at birth, followed by
an increased body fat accumulation from birth to school age, which was
potentiated by maternal smoking during pregnancy and. Children with PON1
192QR/RR genotype were especially vulnerable to the exposure.

Background: SGA infants are exposed to late metabolic complications.
Catch-up growth is regarded as a risk factor. However, the definition of
SGA does not distinguish between those with severe fetal growth restriction
(SFGR) and innate “small size babies”.

Objective: To test for anthropometrics and hormonal profile at 2 years of age
in SGA without SFGR.

Methods: 54 SGA children (BW < 10th percentile) were prospectively followed
from mid-gestation up to 2 years of age and compared with 50 AGA
(Appropriate for Gestational Age) children. Fetal growth velocity (FGV) was
measured from 4 standardized ultrasound measurements (22-36th week of
GA). Percentage of body fat (FM) was derived from skin fold measurements.

Results: FGV was not significantly different between SGA and AGA
(-0.21±0.26 vs. -0.14±0.35 percentile/day: p=0.22). SGA, were thinner at birth
(BMI -1.66 ±1 ± vs. -0.90 ±1 - z-score: p<0.0001) and all through the follow-up
4 months 0.12 ± 1.35 ± vs. 0.53 ±1 : p=0.08 ; 1 year -0.67±0.94
vs. -0.11±1 : p=0.0045; at 2 years -0.94±1.12 ± vs. -0.36±1.07 
(p=0.007) with lower percent fat (birth 5.2±4 vs. 9.4±3.8 %: p=0.0001; 1 year 17.7±5.3 vs. 19.1±4 .%: p<0.09 ; 2 years 18±4.6 vs. 20.3±4.2 %: p=0.009). No signifi-
cant difference in HOMA-IR was observed (at birth 0.57±1.1 vs. 1.31±1.83;
p=0.24 ; 1 year 0.83±1.04 vs. 1.34±1.37: p=0.12 ; 2 years 0.85±1.16
vs. 1.27±1.18: p=0.16). Interestingly, parents of SGAs were significantly thin
compared to AGAs (BMI 24.2 ± 2 ± vs. 26.1 ± 5, 1 kg/m2: p=0.03 ; maternal BMI 23 ± 4 ± vs. 24.8 ± 5, 7 p=0.08).

Conclusions: SGA children with no SFGR and born to rather small parents
do not show excessive fat or insulin resistance at 2 years of age, despite an
earlier (0-4th month) and moderate catch-up growth. Assessing fetal growth
restriction at birth with an accessible surrogate would be helpful to distin-
guish between innate “small size babies” and those who previously faced fetal
growth restriction.

Background: Familial aggregation of cardiovascular risk factor profile and
metabolic syndrome is described in the literature. The aim of this paper was
to look for different intrafamilial associations for cardiovascular risk factors.

Methods: During the eight-year follow-up of the Ulm Birth Cohort Study,
prepubertal children aged 8.3 ± 0.2 years and their parents were examined in
the University Hospital of Ulm. We analysed serum levels in fasting blood
samples of: apoA, apoB, hsCRP, IL-6, adiponectin (adipo), insulin and glucose
(FBG). The 15th and the 85th group percentile were used to define decreased
and increased blood levels. Data of 303 trios (child, mother and father) were
used to test for intrafamilial associations (correlation and regression analy-
sis).

Results: For FBG, insulin and HOMA-IR significant correlations were found
between the offspring and the mother but not between the offspring and the fa-
thet (r=0.21, p=0.05 vs. r=0.27, p=0.001 vs. r=0.30, p=0.001). ApoB levels
of the mother and the child showed the highest intrafamilial correlation (r=0.37,
p=0.001). Adipo levels of the mother and child have a correlation of 0.33
(p<0.0001). Paternal correlation with apoB and adipo levels of the child was
lower (r=0.24, p=0.05 vs. r=0.23, p=0.001). If a mother has an increased
HOMA-IR the relative risk (OR) of a child getting elevated HOMA-IR will
increase 2.8 fold (p=0.05). A lower maternal adipo level is associated with an
increased OR of a child getting decreased adipo levels (OR: 2.3, p<0.0001).
The OR of a child getting elevated adipo levels will increase 4.5 fold if the
mother has elevated apoB levels (p<0.0001).

Conclusions: Interestingly there is a stronger intrafamilial correlation for
insulin, FBG, HOMA-IR, adipo and apoB levels between mother and child
in comparison to father and child. Intrauterine programming of the child’s
decendence and metabolic system by the mother is suspected.
Background: Both preterm birth and small birth size for gestational age (SGA) have been associated with increased risk for developing cardiovascular diseases (CVD), but controversies still exist.

Objective and hypotheses: We aimed to investigate the effect of preterm birth on several parameters of vascular health status. We hypothesized that preterm birth is associated with increased risk for CVD in young adulthood, independent of small birth size.

Methods: In 406 young adults of the PROGRAM/PREMS study, aged 18-24 yr, the influence of preterm birth (gestational age <36 weeks) on systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure, blood pressure variability, heart rate, Pulse Wave Velocity (PWV), and carotid Intima Media Thickness (cIMT) was analyzed. These parameters were also analyzed in subgroups: young adults born small for gestational age with short stature (SGA-S) or normal stature, born either preterm or term, and young adults born appropriate for gestational age with normal stature (AGA), born either preterm or term.

Results: Unadjusted parameters of vascular health of subjects born preterm compared to subjects born at term are shown in Table 1. In the total group, the continuous variable gestational age was inversely associated with SBP via an increased heart rate, inversely associated with pulse pressure and blood pressure variability, and positively associated with DBP, also after adjustment for confounders. There was no effect of gestational age on PWV and cIMT, a marker of atherosclerosis. Of all the vascular health parameters measured, higher pulse pressure affected cIMT the most.

Conclusions: Our results show that young adults born preterm have a less favorable vascular health status than those born at term, independent of birth size.

Table 1 Unadjusted vascular health parameters of subjects born preterm versus those born at term

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preterm (n=163)</th>
<th>Term (n=243)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>112.3(8.0)*</td>
<td>110.0(9.0)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>63.3(5.3)#</td>
<td>66.1(5.9)</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>48.9(6.2)#</td>
<td>43.8(5.8)</td>
</tr>
<tr>
<td>Coefficient of Variation, Systolic blood pressure</td>
<td>5.17(1.8)*</td>
<td>4.77(2.7)</td>
</tr>
<tr>
<td>Coefficient of Variation, Diastolic blood pressure</td>
<td>9.77(3.2)#</td>
<td>7.98(3.7)</td>
</tr>
<tr>
<td>Heart rate (beats/minute)</td>
<td>70(1.9)#</td>
<td>65(0.9)</td>
</tr>
<tr>
<td>PWV (m/sec)</td>
<td>7.60(1.0)</td>
<td>7.59(0.9)</td>
</tr>
<tr>
<td>cIMT (mm)</td>
<td>0.52(0.1)</td>
<td>0.52(0.05)</td>
</tr>
</tbody>
</table>

Values are given as mean (sd).
* p<0.01 compared to term.
# p<0.001 compared to term.

P2-d3-746 Programming/Epigenetics 1

Aggressive adrenarche in Silver-Russell Syndrome compromises final height despite GH treatment

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Background: Silver-Russell Syndrome (SRS) is characterized by the association of severe intra-uterine growth retardation (IUGR) to macrocephaly, characteristic dysmorphic features and feeding difficulties. In young age, bone age (BA) is usually delayed. In over 50% cases, SRS is due to IGFl/H19 11p15 loss of methylation (LOM). Because of poor catch-up growth and short final heights, SRS patients often undergo early and prolonged growth hormone (GH) therapy. However, in our experience, final height is not always improved by GH.

Objective and hypotheses: Aggressive adrenarche seems to be responsible for rapid BA maturation and compromise final height in some SRS patients. We therefore aim to show evidences for this assumption.

Methods: We describe 6 SRS patients with IGFl/H19 11p15 LOM.

Results: All patients (4 boys and 2 girls) demonstrated severe IUGR (birth weight: -4.3 to -2.8 SDS; birth length: -7.5 to -3 SDS). Three patients were treated with GH since the age of 2 and 3 years respectively, two patients were treated after the age of 8 years and 1 patient was not treated. Five patients caught up with their BA delay before the age of 8 years and adrenarche occurred between 3 and 8 years of age. In all cases, SDHEA and IGF-1 levels were higher than the upper limit for age. Despite GH administration and treatments aiming to slow down BA maturation (Cyproterone Acetate and/or LRH analogs), final height or final height prognosis were compromised (final height: 137cm in a boy and 143cm in a girl; final height prognosis: 149 to 160cm in 3 boys, and 147cm in a girl).

Conclusions: Adrenarche in SRS patients can cause rapid BA maturation, thus compromising final height despite prolonged GH therapy. The aggressive character of adrenarche remains unexplained. Variations in body composition, insulin-resistance and high IGF-1 levels may play a role in the onset of adrenarche in these SRS patients.
Severity of intra-uterine growth retardation predicts generalized hormone resistance and severity of metabolic consequences

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Background: Epigenetic programming results in foetal and post-natal growth restriction, later diabetes mellitus and metabolic syndrome. We hypothesize that severity of growth restriction may predict future metabolic consequences.

Methods: We present a case series of 4 children with severe IUGR. Cases 1 and 2 had 11p15 methylation defects at the H19 locus. Cases 3 and 4 had IMAGe syndrome.

Results: Case 1 was a boy born at 34 weeks gestation at 1.16 kg. Undescended testes were surgically treated. Response to growth hormone was poor. He had early puberty. At age 13 he had height 147cm, adult genitalia but 2ml testes, fused epiphyses, BMI 90th centile, cystic acne, acanthosis nigricans, BP151/97, hepatic steatosis, type 2 diabetes mellitus, cholesterol 6.9mmol/L, triglyceride16.1mmol/L and gonadal impairment with LH 15.9 IU/L, FSH 27.2 IU/L. Case 2 had IUGR with full term birth weight 1.4 kg, poor growth, early puberty, reduced final height and early onset metabolic syndrome with central adiposity, hyperlipidaemia, impaired glucose tolerance and compromised gonadal function with raised LH, FSH by age 43 years. Case 3 was diagnosed with IMAGe syndrome at birth with typical dysmorphism, IUGR (Birth Weight 1.2kg at 37 weeks), adrenal insufficiency with later onset metaphyseal dysplasia. She developed overt metabolic syndrome at age 2 due to well meaning over-nutrition, with central obesity, hypertension and hyperlipidaemia, settling with dietary restriction. Growth failure was treated with growth hormone, with poor response. Case 4 was diagnosed at age 7 with facial dysmorphism, metaphyseal dysplasia, adrenal insufficiency, growth failure with poor GH response. By age 15 he had type 2 diabetes mellitus, mixed hyperlipidaemia, central obesity, hepatic steatosis and gonadal failure.

Conclusion: These cases highlight the serious nature and spectrum of IUGR consequences. IUGR may be a model for more generalized hormone resistance, the severity and multiplicity of which is dependent on severity of growth restriction.

Association of pre-pregnancy weight and body mass index at 18 months and 4 years

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Background: Prevalence of childhood obesity is a serious public health concern. Maternal overweight and gestational weight gain (GWG) could influence early overweight.

Objective: To analyze association of pre-pregnancy weight and GWG with birth weight, body mass index (BMI) at 18 months and at 4 years and adiposity.

Methods: 482 pregnant mothers recruited between 2004-2007 and their children from the Asturias cohort of the INMA (Environment and Childhood) project, a population-based birth cohort study conducted in Spain. The research protocol was approved by the Ethics and Research Committee. We analyzed maternal BMI, GWG, birth weight, BMI at 18 months and at 4 years and the sum of subscapular, triceps, abdominal and suprailiac skinfold thicknesses at 4 years. Statistical analyses were conducted.

Results: 17 mothers were underweight (BMI less than 18.5 kg/m2), 319 normal (65.8%;BMI 18.5-24.9 kg/m2), overweight 108 (22.3%; BMI 25-29.9 kg/m2) and 41 obese (8.5%;BMI equal or more than 30 kg/m2). GWG was as recommended in 166 pregnant mothers, low 115 and high 192 (39.6%). Birth weight standardized for 40 weeks was 3372 gr ±397.4, BMI at 18 months, BMI at 4 years was found. Childhood obesity prevention must be started from pregnancy and infancy.

Precocious puberty and gelastic seizures in an infant due to hypothalamic hamartoma type VI treated with endoscopic disconnection: case report

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Background: Hypothalamic hamartomas (HH) are rare congenital lesions of the tuber cinereum presenting with the classic triad of gelastic epilepsy, central precocious puberty and developmental delay.

Case report: A 9-month old boy was referred for evaluation of pubic hair. His past medical history was uneventful. No parental consanguinity and family history of sexual precocity could be found. Developmental milestones were normal. At the admission, height was 75.5 cm (90-97p), weight 12 kg (>90p) and head circumference (50-75p). Bone age was 18 months. He had epileptic seizures 40-50 times a day since 2 months of age. He had acne on the cheeks and forehead. Penis size was 7.x8 cm (<90p) and pubic hair was Tanner III. Testicular volumes were 3 ml. Hormonal investigation had shown that a predominate pubertal LH response to the GnRH stimulation test (peak LH 3.9 and FSH 4.16). Abdominal and scrotal ultrasound examinations were normal. The severity and multiplicity of which is dependent on severity of growth restriction.

Conclusions: High prevalence of overweight or obesity pre-pregnancy was detected. Correlation between BMI at 18 months and adiposity and BMI at 4 years was found. Childhood obesity prevention must be started from pregnancy and infancy.
normal. Cranial MRI revealed a 36x24 mm, non-enhancing lesion at the tuber cinereum, filling the third ventricle and attached to its left wall, evaluated as a hypothalamic hamartoma type VI according to Regis classification. Leuprolide acetate was given monthly. EEG showed epileptiform activity and gelastic seizures were resistant to five different antiepileptic drugs. The hamartoma was disconnected from its pedicle and biopsied via neuroendoscopic approach from right frontal burr hole. Post-operative course was uneventful. Histological examination revealed mature neuronal and glial tissue. GnRH analog treatment was stopped one month after the operation. GnRH stimulation test which was performed at post-operative 6 th months showed prepubertal response. MRI had shown regression of HH (25x20 mm). Frequency and duration of seizures were decreased by approximately %90. Last EEG was normal while the patient was on two antiepileptic drugs.

Conclusion: Neuroendoscopic disconnection of the hypothalamic hamartoma is an effective and minimally invasive treatment option for intractable epilepsy and precocious puberty.

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P2-d1-752 Puberty and Neuroendocrinology

Assessment of gonadotropin suppression in girls treated with GnRH analogue for central precocious puberty; validity of single luteinizing hormone measurement after leuprolide acetate injection

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Background: Intravenous GnRH stimulation test has often been used as a gold standard test in the diagnosis of central precocious puberty (CPP) as well as in the assessment of pubertal suppression during gonadotropin releasing hormone analog (GnRHa) therapy in patients with CPP. However, this test is time consuming, costly and uncomfortable for patients. Therefore, other reliable methods that could be easily performed are needed for diagnosis and for evaluation of gonadotropin suppression during therapy.

Objective: We aimed to analyze the validity of single LH sample 90 minutes after GnRHa administration in the evaluation of gonadotropin suppression during CPP therapy. We also aimed to determine a cut off level for LH showing adequate suppression.

Patients and methods: One hundred and forty two patients with CPP were included in this study. In this group peak LH level during iv GnRH stimulation test after the third dose of GnRHa was compared with LH level 90 minutes after injection of the 3rd dose of GnRHa.

Results: There was a positive correlation between LH level after GnRHa injection and peak LH during standard iv GnRH stimulation test (r=0.83;p<0.0001). An LH value of 2.5 mIU/ml or less 90 minutes after GnRHa injection was considered to be the cut off for determination of pubertal suppression (sensitivity and specificity was 100% and 88% respectively). In 117 patients gonadotropin suppression was present according to both GnRHa and iv GnRHa tests. In 25 patients gonadotropin suppression was not found in the GnRHa test. However 16 of them were suppressed according to the iv GnRHa test. Conclusion: Single LH determination 90 minutes after GnRHa administration using a cut-off level of 2.5 mIU/ml reflects pubertal suppression with a high sensitivity and specificity. However, this test may fail to show pubertal suppression in some cases, those patients who appear to be inadequately suppressed should be reassessed using standard iv GnRH stimulation test for optimal dose adjustment.

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P2-d1-753 Puberty and Neuroendocrinology

Reproductive phenotype in patients with anosmic (aHH) or normosmic (nHH) hypogonadotropic hypogonadism

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Background: Congenital hypogonadotropic hypogonadism (HH) is characterized by an absolute/relative deficiency of GnRH often associated with anosomias which suggest a non-gonadal phenotype.

Objective and hypotheses: To compare the reproductive phenotype in women (WH) and men (MH) with aHH (aWH and aMH) and nHH (nWH and nMH) and the correlation with genetic defects of the gonadal axis.

Methods: 68 patients under treatment for delayed puberty or HH were recruited. A complete health evaluation, smell test and DNA screening for genetic defects were performed. Statistics: SPSS 17.0 Significant p <0.05.

Results: 27 MH and 41 WH. Pubertal development: in MH gonadarche occurred at 15.0 ± 2.7 yrs and pubarche at 13.5 ± 1.9 yrs whereas in WH age of thelarche was 14.7 ± 3.8 yrs, pubarche 14.3 ± 3.5 yrs and menarche 16.2 ± 3.7 yrs, 59% had induced menarche at 18.7 ± 4.2 yrs. A 55.6% of MH and 17.1% of WH are anosmic (p 0.005). In aMH 56% had micropros, 69% cryptorchidism and 81% absence of puberty, vs. 50%, 62% and 25% in nMH, respectively. A 25% of aWH had spontaneous menarche vs. 54% of aWH. Genetic results: In 47.8% of MH mutations were identified. There were 5 with monogenic disease (FGFR1, KISSIR, KAL1), and 6 with digenic mutations (TAC3R, KAL1, PROK2, FGFR1, KISSIR). There were 6/31 WH (19.4%) with mutations: one with digenic mutations (GNRHR/PROKR2), 4 were heterogeneous for FGFR1 and other for TAC3R. A 43% of aMH and 40% of aWH had identified mutations vs. 63% of nMH and 17% nWH.

Conclusions: Reproductive phenotype in patients with aHH is more severe than nHH. Attention to phenotype/anosmia may induce an early suspicion. Normosmia does not exclude the presence of genetic defects in the gonadal axis, mainly in men.

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P2-d1-754 Puberty and Neuroendocrinology

Preliminary experience with a V2-receptor antagonist in a boy with chronic syndrome of inappropriate antidiuretic hormone secretion (SIADH)

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Background: Treatment of SIADH remains challenging in children with brain tumors and after neurosurgery. Recently an orally administered selective antagonist of the vasopressin V2 receptor (Tolvaptan) has been approved for treatment of SIADH in adults.

Objective and hypotheses: We describe treatment with a V2-receptor antagonist of a 12-year old boy with chronic, symptomatic SIADH as a result of an inoperable pilocytic astrocytoma, which was resistant to conventional treatment and located in the diencephalon enclosing the optic chiasm.

Results: Clinical course: SIADH evolved in the 12-year old boy with a progression of an inoperable pilocytic astrocytoma. Fluid restriction up to 800 ml/m2/day and conventional diuretic therapy did not normalize the serum hyponatremia and hypoosmolality. His weight was 70.7 kg (1.91 SDS) and he complained about headaches, nausea, general muscle tremor, and fatigue, which was not attributable to the tumor. Lowest serum sodium was 125 mmol/l and serum osmolality as low as 251 mosm/kg H2O with an urine osmolality of 757 mosm/kg H2O. Treatment with Tolvaptan 15 mg (low adult dose) increased serum sodium to 132 mmol/l, serum osmolality to 268 mosm/kg H2O and diuresis to 400 ml/h within 4 hours; maximal urine output was 41 l. The aquaretic effect of Tolvaptan 15 mg once daily sustained over 4 weeks and serum sodium ranged from 134 to 138 mmol/l and serum osmolality from 266 to 274 mosm/kg H2O while he lost 8 kg of weight and the headaches and nausea resolved. We plan to continue treatment with this V2 receptor antagonist until radiation will be initiated, which may reverse SIADH.

Conclusions: This orally administered, selective V2 receptor antagonist increased serum sodium concentrations and serum osmolality in a 12 years old boy with symptomatic, chronic SIADH due to a pilocytic astrocytoma and mellowed his clinical symptoms without the need of titrating the dose and without adverse events.
Urinary gonadotrophins: a useful non-invasive marker of activation of the hypothalamic-pituitary-gonadal (HPG) axis

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1Royal Hospital for Sick Children, Bone and Endocrine Research Group, Glasgow, United Kingdom; 2Royal Hospital for Sick Children, Department of Biochemistry, Glasgow, United Kingdom

Methods: Pubertal status was performed by children and parents using self-assessment charts and then classified as pre-pubertal (Tanner 1); early-pubertal (Tanner 2-3); late pubertal (Tanner 4-5). A single non-timed urine specimen was collected. Luteinising hormone (LH) and follicle stimulating hormone (FSH) were measured using a two-step chemiluminescent microparticle immunoassay (CMIA). The detection limits of the assays were FSH, 0.05 IU/L and LH, 0.07 IU/L. Creatinine excretion, measured using a kinetic assay, was quantified as 0.35mmol/L, was used to correct data.

Results:

<table>
<thead>
<tr>
<th>Age, years</th>
<th>LH, Creatinine</th>
<th>LH, FSH, Creatinine</th>
<th>Med</th>
<th>Range</th>
<th>Med</th>
<th>Range</th>
<th>Med</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-pubertal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Girls (n=14)</td>
<td>9.3</td>
<td>5.5-12.8</td>
<td>0.02</td>
<td>0.01-0.04</td>
<td>0.29</td>
<td>0.10-0.1</td>
<td>0.04</td>
<td>0.02-0.12</td>
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<tr>
<td>Boys (n=15)</td>
<td>7.8</td>
<td>6.1-13.3</td>
<td>0.01</td>
<td>0.01-0.19</td>
<td>0.17</td>
<td>0.01-1.00</td>
<td>0.10</td>
<td>0.01-0.46</td>
</tr>
<tr>
<td>Early-pubertal</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Girls (n=21)</td>
<td>12.3</td>
<td>10.0-15.1</td>
<td>0.06</td>
<td>0.01-0.98</td>
<td>0.49a</td>
<td>0.02-3.63</td>
<td>0.15</td>
<td>0.00-0.95</td>
</tr>
<tr>
<td>Boys (n=14)</td>
<td>12.4</td>
<td>10.0-16.9</td>
<td>0.10a</td>
<td>0.01-0.28</td>
<td>0.22c</td>
<td>0.11-0.68</td>
<td>0.33</td>
<td>0.02-1.43</td>
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<tr>
<td>Late-pubertal</td>
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<tr>
<td>Girls (n=20)</td>
<td>15.6</td>
<td>13.5-17.2</td>
<td>0.12b</td>
<td>0.01-1.06</td>
<td>0.48b</td>
<td>0.16-2.56</td>
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<td>0.03-1.05</td>
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<tr>
<td>Boys (n=16)</td>
<td>16.2</td>
<td>13.0-18.0</td>
<td>0.12b</td>
<td>0.01-0.26</td>
<td>0.20c</td>
<td>0.03-0.48</td>
<td>0.47bc</td>
<td>0.04-1.77</td>
</tr>
</tbody>
</table>

A difference between same sex pre-pubertal and early-pubertal groups (p<0.05) b difference between pre-pubertal and late-pubertal groups (p<0.05) c difference between boys and girls of same pubertal group (p<0.05).

Conclusions: Urinary gonadotrophins, as measured by a CMIA can differentiate between physically pre-pubertal and pubertal children. However, some pre-pubertal children have biochemical signs of HPG activation and the value of the urinary gonadotrophin assay for investigating central causes of hypogonadism needs to be re-visited.

The relationship between pubertal development and iron chelation regimen in young patients with beta thalassemia major

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Background: Beta thalassemia (TM) major is a haematological disorder frequently associated with pubertal development abnormalities, mainly due to iron overload. Although the introduction of the intensive chelation regimens

in the last decades in the management of beta TM patients dramatically improved the complications associated with iron overload, recent studies continue to report a high prevalence of puberty disorders.

Objective and hypotheses: We aimed to study the relationship between pubertal abnormalities and iron chelation regimen in young betathalassemic patients.

Methods: We performed a cross-sectional study on 65 patients with transfusion-dependent beta-thalassemia major (33 female/32 male, mean age 16.3±3.9 yrs) treated with nightly subcutaneous deferoxamine. Data regarding haematological disease were available from medical records.

Results: We found that 44.6% (29/65) of the patients had delayed and 18.5% (12/65) arrested puberty. When compared with patients with normal pubertal development those with pubertal abnormalities were significantly older at start of iron chelation (12.3±1.4 yrs vs 6.6±2.2 yrs, p=0.005), were less compliant with deferoxamine treatment (17% vs 64%, p<0.0001) and had begun less frequently early chelation (<10 yrs) (9.75% vs 87.5%, p<0.01). Moreover patient with pubertal delay had higher mean ferritin levels (3375±1937 vs 2341±1314, p<0.05) and higher prepubertal ferritin levels comparing with patients with normal pubertal progression, without any significant differences in pubertal ferritin values between groups. No association was found between puberty abnormalities and mean haemoglobin, age at diagnosis of beta TM or age at start of transfusions.

Conclusions: Our results suggest that early chelation and good compliance with chelator treatment have a positive impact on pubertal development, probably mediated by reduced iron load, especially in prepubertal period.
**P2-d1-758 Puberty and Neuroendocrinology 1**

**Analysis of Kallmann syndrome genes in a paediatric and adolescent cohort with HH**

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**Background:** The genetic aetiology of hypogonadotropic hypogonadism (HH) is complex. To date several genes have been implicated; FGFR1, FGFR8, KAL1, PROKR2 and PROK2 are the most commonly described in pedigrees with both isolated HH and Kallmann syndrome (KS). **Objective:** We aimed to identify mutations in genes associated with KS in a paediatric and adolescent HH cohort. **Population and methods:** DNA samples from 33 children and adolescents with HH (28 males) were directly sequenced for mutations in the following genes: KAL1, FGFR1, FGFR8, PROKR2, PROK2. Four patients had KS. Other associated features such as cleft lip/palate, sensorineural deafness and microphthalmia were present in 2, 3 and 1 patients respectively. One patient with KS also had Tetralogy of Fallot. Familial HH was present in 3 pedigrees. **Results:** One maternally inherited mutation in the FGFR1 gene (G687R) was identified in a 15-year-old male with HH. His mother also suffered from HH and had received fertility treatment with GnRH. The rest of his pituitary function was normal. A mutation in KAL1 gene (R423X) was found in a 17-year-old male with familial KS (two maternal half-brothers affected, samples not available) who carried an additional maternally inherited pericentric inversion in chromosome 8 (p23.3;q11.23). His mother was unaffected. Both mutations have been previously described in KS. **Conclusions:** Two familial mutations in FGFR1 and KAL1 were detected in a population of 33 paediatric and adolescent patients with HH. The patient’s phenotype with the KAL1 mutation (R423X) is unlikely to be affected by the chromosomal aberration encompassing the GnRH1 gene locus since his mother is phenotypically unaffected. Our data suggest a low incidence of mutations in known genes associated with KS in our cohort of paediatric and adolescent patients, suggesting the role of other genes.

**P2-d1-759 Puberty and Neuroendocrinology 1**

**Prokineticin 2 receptor gene mutation in patients with isolated hypogonadotropic hypogonadism**

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**Background:** Mutations in the gene of the prokineticin 2 receptor (PROKR2) are among the most recent anomalies described in congenital isolated hypogonadotropic hypogonadism with or without anosmia. **Objective and hypotheses:** To search for the PROKR2 gene mutation in patients with congenital isolated hypogonadotropic hypogonadism and to specify their phenotypes. **Methods:** This is a study of 16 patients (11 men and 5 women) with congenital isolated hypogonadotropic hypogonadism. Among these patients, six had anosmia. The mean age was 19 years. Each patient had a family screening, a clinical examination, hormonal assays, MRI hypothalamic-pituitary imaging and genetic study. **Results:** We found two PROKR2 mutations: P290S in a homozygous state in a patient with Kallmann’s syndrome, and a new mutation in a heterozygous state in a patient and his mother who had no anosmia. This new mutation is not autosomal dominant, because the mother carrying the mutation has no sign of hypogonadotropic hypogonadism. The mode of autosomal recessive transmission in this case is not possible because, in this situation, the patient should have two alleles carrying the mutation in PROKR2 to exhibit hypogonadotropic hypogonadism. The more probably mode of transmission is digenic or oligogenic, another gene or other genes responsible for hypogonadism is or are mutated. This or those genes are involved in hypogonadotropic hypogonadism without anosmia (GnRH, GPR54, GnRH1, or TAC3 TACR3) because our patient had no anosmia. SNP (single nucleotide polymorphism) variations of PROKR2 were found in five patients with different phenotypes. **Conclusions:** The discovery of genes involved in isolated hypogonadotropic hypogonadism led to a better understanding of the normal development of the gonadotrop axis and describes new modes of transmission in this disease (digenic or oligogenic).

**P2-d2-760 Puberty and Neuroendocrinology 1**

**Isochromosome Yp in a boy with hypogonadotropic hypogonadism, gynaecomastia and short stature**

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**Background:** Micro-deletions of the long arm of the Y chromosome are associated with spermatogenic failure and infertility. In addition, it has been suggested that the Y long arm contains genes that control height. Among structural rearrangements, the isochromosome of Yp (iYp) appears to be the most uncommon. In the literature no data regarding the course of puberty in boys affected by iYp is described. **Case report:** We describe a 13 years old boy with monolateral gynaecomastias who was referred to our center. His auxological parameters were: height 151.4 cm (M SDS), weight 65.8 kg (+3 SDS) and bone age of 14 years. Genital development was stage 1. Baseline luteinizing hormone (LH) and follicle stimulating hormone (FSH) values were in the prepubertal range and testosterone (T) response to HCG stimulation test showed modest rise. Caryotype was 46 X i(Yp) with the FISH analysis confirming the presence of double SRY. No mutations in KAL1 gene was found. The pituitary MRI scan was normal with no abnormalities of olfactory system. At 15 years his parameters were height of 158 cm (+1.8 SDS) weight of 63 Kg (+0.8 SDS) and a bone age of 16 years. His final height (FH) was ~ 2.8 SDS to Target Height (TH) (177 cm; +1 SDS). Genital prepubertal development. Basal and stimulated levels of LH, FSH and T were prepubertal. Baseline inhibin B value was 44 pg/mL. **Secondary sex characteristics were attained by exogenous testosterone one enanthate (TE) replacement.** **Conclusion:** We described the course of puberty in an adolescent with iYp, a rare genetic abnormality associated with male infertility. Our patient showed gynaecomastia, HH and short stature. Usually, male hypogonadism presenting during the period of bone growth will result in increased body height caused by retardation of androgen-induced closure of epiphyses. Our case support the existence of a Y-linked growth gene because the FH was significantly smaller than TH. Our case report of pertinent HH in a patient with iYp may contribute to our understanding of patho-physiology of hypothalamic-pituitary-gonadai axis.

**P2-d2-761 Puberty and Neuroendocrinology 2**

**Etiology and clinical characteristics of 80 boys presenting with isosexual precocious puberty**

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**Background:** Precocious puberty is less common in boys. Unlike girls, precocious puberty in boys has many different causes, careful examination is necessary before a diagnosis of idiopathic precocious puberty is made. While data on precocious puberty in girls are abundant, data on male precocious puberty are limited. **Objective and hypotheses:** To review the etiology and clinical characteristics of boys presenting with isosexual precocious puberty. **Methods:** Eighty boys presenting with isosexual precocious puberty over 22 years period at a pediatric endocrine center were reviewed. **Results:** Of the 80 boys referred for isosexual precocity, 57(71.25%) were GnRH-dependent precocious puberty (central precocious puberty, CPP) and 23(28.75%) were GnRH-independent precocious puberty (peripheral precocious puberty, PPP). The most common diagnosis in CPP was idiopathic precocious puberty(ICPP, 31/57), hypothalamic hamartoma(7/57) and secondary CPP with congenital adrenal hyperplasia(CAH, 7/57) in order. And the two most common diagnosis in PPP was lCG-secreting germ cell tumor(12/23) and congenital adrenal hyperplasia (CAH, 9/23). Boys diagnosed

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with isosexual precocious puberty with different underlying cause present with different clinical characteristics.

**Conclusions:** As we reported that most of male isosexual precious puberty have underlying organic disease, it is very important to identify the cause especially the life-threatening condition like hCG-secreting germ cell tumor in a precocious boy.

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**P2-d2-762** Puberty and Neuroendocrinology 2

**Puberty gynaecomastia is more related with insulin resistance rather than ghrelin**

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**Background:** Previously it has been shown that leptin hormone might be involved in the pathogenesis of pubertal gynaecomastia, but ghrelin and pubertal gynaecomastia relation didn’t studied. So this is the first clinical trial that subjected ghrelin and pubertal gynaecomastia relation.

**Objectives:** In this study we aimed to show the relations between pubertal gynaecomastia with plasma ghrelin levels and insulin resistance.

**Methods:** For the study 54 nonobese pubertal boys diagnosed pubertal gynaecomastia, aged 11 to 17 years and as the control group, 50 age and pubertal stage matched normal boys were selected. Fasting plasma ghrelin levels were measured by ELISA method. Besides ghrelin, routine hormonal parameters including thyroid hormones, prolactine, total and free testosterone, estradiol, luteinizing hormone, follicle stimulating hormone, prolactin and dehydroepiandrosterone sulfate levels were studied. Oral glucose tolerance test was done and HOMA-IR index of each participant was calculated to show insulin resistance.

**Results:** No significant difference existed in plasma ghrelin levels of the boys with pubertal gynaecomastia and boys in control group (340.25±122.31 pg/ml and 325.66±162.55 pg/ml, p>0.05). Boys with pubertal gynaecomastia had higher HOMA-IR values compared to control group, which showed that they were more insulin resistant than controls (HOMA-IR values 2.1±1.35 versus 1.6±0.9, p<0.05). There was no significant difference for other hormonal parameters between boys with pubertal gynaecomastia and controls.

**Conclusions:** Ghrelin levels didn’t relate to pubertal gynaecomastia, adversely insulin resistance seemed to be related to it. Insulin resistance might play a role in pubertal gynaecomastia.

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**P2-d2-764** Puberty and Neuroendocrinology 2

**Estrogen gene analysis in girls with central precocious puberty**

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**Background:** Precocious puberty is characterized by early activation of the puberal biological axis, exposure to exogenous sex steroid hormones, and the presence of endogenous sex steroids caused by various factors. Estrogen is the final key factor to start onset of puberty. The raised sensitivity of estrogen receptor, which may be caused by ESR1 mutation or polymorphism, has been mentioned for interpreting the etiology of precocious puberty. However, currently there is a limited amount of data available regarding ESR1 gene mutations or polymorphisms. The aim of this study is to identify ESR1 gene mutations or polymorphisms in girls with central precocious puberty (CPP).

**Methods:** 154 Korean girls with CPP were included in this study and 55 healthy Korean female adults as the control group. All coding exons and exon-intron boundaries of the ESR1 gene were sequenced. The relationship between identified sequence variations and CPP was evaluated via the comparison of allele frequencies between the two groups.

**Results:** 10 polymorphisms were identified in the ESR1 gene. Among the 10 polymorphisms in this study, 7 polymorphisms have been previously reported, whereas the other three were novel polymorphisms. Two of three novel polymorphisms, p. Gly145Ser in exon1 and p. Arg555His in exon8 were only identified in patient group. Although two novel nonsynonymous polymorphisms were found in patient group, further supporting clinical evidences were not found.

**Conclusions:** The polymorphism scanning and typing of ESR1 uncovered several potentially meaningful polymorphisms, but the conclusion was not solid and further studies are necessary for function validation of these polymorphisms.

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**P2-d2-765** Puberty and Neuroendocrinology 2

**Clinical course of isolated premature thelarche in girls with onset under 2 years of age**

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**Background:** Premature thelarche (PT) refers to isolated breast development under 8 years of age without presence of clinical and laboratory findings consistent with precocious puberty.

**Objective:** In our study, we investigated the clinical course in girls with confirmed diagnosis of PT with an onset below 2 years of age and we aimed to find out whether these girls had a benign clinical course as has usually been suggested.

**Methods:** Clinical and laboratory findings of 61 girls with PT (median age at initial evaluation 19 months) were evaluated at initial presentation and at follow-up, with a median duration of 34 months (range 12-151 months).

**Results:** Children with PT were divided into two groups as classical PT (n=44,
72.1%) and atypical PT (n=17, 27.9%) according to advancement of bone age (BA) and increased height velocity (HV). BA SDS and HV SDS were significantly higher in girls with atypical PT than the classical ones (0.7±1.4 vs -2.1±4.9; p<0.035; 1.2±2.8 vs -0.2±1.4; p<0.0003; respectively) by definition. Pelvic ultrasonography findings, basal serum estradiol, GnRH stimulated LH, FSH levels and LH/FSH ratios were similar in both groups. However, basal serum LH (L/H) at a cut-off level of 0.3 IU/L was found to be a significant risk coefficient among girls with premature puberty. Three of the girls with atypical PT were diagnosed as precocious puberty, and 14 as thelarche variants.

Conclusion: PT with onset under 2 years of age may not have a benign course in a significant proportion of the girls. Diagnostic management and follow-up of each girl should be individualized independent of age at onset of the thelarche.

P2-d2-766 Puberty and Neuroendocrinology 2

Precocious puberty in a girl with a major brain structural anomaly
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Introduction: Precocious puberty can be of idiopathic or organic origin, and is mostly due the hypothalamic hamartoma, septo-optic dysplasia or arachnoid cyst. Structural anomalies of the brain such as congenital meningeal anomalies, ectopic or bifid pituitary, etc, have rarely been described as a cause for premature sexual development. Several syndromic disorders (Kabuki, Alstrom, Williams) are also associated with premature sexual development.

Materials and methods: We present a girl with severe mental retardation, ataxia, facial dysmorphism and precocious puberty. This was a firstborn child in a family with no remarkable family history. Failure to thrive was noticed in early infancy. Facial dysmorphism and multiple birth defects were consistent with acrocallosal syndrome. MRI showed cerebellar and vermis hypoplasia, dilated ventricles, and hypoplastic and bifid pituitary. The onset of puberty was at the age of 5 years with breast development. Her height and weight were at the 50%. Bone age was 12 years. GnRH test showed increased level of LH of 15.4 mU/mL. Other pituitary hormones were normal. She has been treated with GnRH agonist for several years when there was reduction of pubertal signs and height velocity.

Discussion: Several studies showed that pituitary–mostly minor abnormalities are responsible for 10% of all cases with precocious puberty. However there is no evidence that such extensive brain lesion in this case could cause premature sexual development. Also there is no association between acrocallosal syndrome and precocious puberty described so far. It has been proposed that the cause is disturbance in neuronal organization along gonadotropic axis. The hypothalamic–hypophyseal axis is a probable case when pituitary brain defects can cause premature development. Genetic background for this regulation is complex and remains to be elucidated.

P2-d2-767 Puberty and Neuroendocrinology 2

Body mass index increase precedes breast development in internationally adopted girls with early/precocious puberty
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Introduction: A recent study performed in Spain has reported that internationally adopted girls have an increased risk of early/precocious puberty as compared to girls born in Spain. Although the underlying cause is unknown, it has been suggested that genetic and psychosocial factors, as well as nutritional changes could precipitate maturation in these girls.

Subjects and methods: In this retrospective study, we report the growth course in adopted girls (n=18) with precocious/early puberty, followed in the International Adoption Clinic since their arrival in Spain. Weight-for-age, height-for-age and body mass index (BMI) Z-scores (SDS) since arrival and annually thereafter until puberty were analyzed.

Results: Age at arrival was 4.9±2.4 year (mean±SD); 55% of the girls were from Asian ancestry. Weight and height SDS on arrival were -0.99±0.85 and -0.78±1.2, respectively, and age at diagnosis of puberty (Tanner stage 2, B2) was 7.3 yr (range 5.2 to 8.9). BMI SDS upon arrival was -0.7±0.9, and increased steadily over the next two years (end of first year, -0.12±0.8 at 2 yr, -0.08±0.7 at onset of B2, -0.14±0.6). The mean BMI SDS increase from arrival to the onset of B2 was +0.8±0.9. At diagnosis of puberty, 33% of the girls had a BMI SDS exceeding the mean population values by at least +0.5. Thirteen girls (72% of the total population) were treated with GnRH agonists. Of those, six patients completed puberty after 35±5.0 mo, and menarche occurred at 10.4±1.05 yr.

Conclusions:
• In internationally adopted girls, weight, height and BMI upon arrival are below the population mean.
• Early and marked gains in weight and in BMI are common after adoption.
• Prior to the development of B2, the girls increased their BMI by nearly +1 SD.
• Routine auxological follow-up and nutritional recommendations after arrival may be useful to prevent rapid weight gain in these patients.

P2-d2-768 Puberty and Neuroendocrinology 2

Changes in serum levels of hormones and neurotransmitters during sleep in girls with precocious puberty
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Objective and hypotheses: Aims of this study are to determine whether sleep patterns, hormones and neurotransmitters in sleep that are responsible of pubertal development, are different among aged matched girls with precocious puberty and premature telarche and non-pubertal girls.

Methods: Thirty nine girls with breast development were underwent full anthropometric, hormonal (basal FSH, LH, estradiol), radiologic (pelvic ultrasonography and bone age). Depending on the results of Gonadotropins-Releasing Hormone (GnRH) test 22 patient, as premature telarche, and the rests, as precocious puberty, were evaluated. Nineteen age-matched, non-pubertal girls, were included as control group. Polysomnography was carried out to all patients. Levels of hormones and neurotransmitters were assessed during REM period.

Results: There was no difference regarding anthropometric parameters among three groups (p>0.05). Basal FSH, LH levels and LH/FSH ratio in 30th minutes in girls with precocious puberty were significantly higher compared to other two groups (p<0.006, p=0.029, and p<0.001 respectively).

Bone age/chronological age ratio, endometrium thickness, and ovarian volumes in girls precocious puberty group were significantly higher compared to premature telarche and control groups (p<0.05). Nocturnal kisspeptin, leptin, prolactin, GABA and glutamate levels had no statistically significant difference among three groups (p>0.05).

First sleep interval (Stage N1) in polysomnography were shorter in girls with premature telarche than groups (p=0.031).

Conclusions: Interval of transition to sleep in girls with premature telarche are shortened. Sleep pattern of girls with precocious puberty is similar to non-pubertal girls. No change was found serum levels of hormones and neurotransmitters related with pubertal activation during deep sleep in girls with precocious puberty.Bone age, endometrium thickness, ovarian sizes, and LH/FSH ratio at 30th minute can be used for differential diagnosis of premature telarche and precocious puberty.
P2-d2-769 Puberty and Neuroendocrinology 2

Diet regulating factors and its relation to anthropometric parameters and metabolic bio-makers in female central precocious puberty

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Background: Factors affecting precocious puberty include genetic traits, nutrition (body fat) and exposure to endocrine disrupting chemicals. Especially, there is strong evidence that the increasing rates of obesity in children over the same time period are major factor.

Objective and hypotheses: The purpose of this study was to assess the relationships between diet regulating factors, somatic features, and metabolic bio-makers in female central precocious puberty.

Methods: We surveyed 38 female patients whose diagnosed precocious puberty (17 overweight/obese group, 21 normal weight group), and 14 age and sex matched healthy control group. We estimated anthropometric parameters, diet regulating factors (serum neuropeptide Y, NPY, leptin, and amylin) and metabolic bio-makers (serum glucose, insulin, total cholesterol, LDL, HDL and TG) in both group.

Results: Body weight, height, BMI, waist circumference, hip circumference, serum glucose, insulin, total cholesterol, LDL, HDL, and TG were significantly higher in overweight/obese group compared with healthy control group.

Conclusions: Precocious puberty was associated with diet regulating factors, and metabolic bio-makers. This result suggests that precocious puberty may associate with the risk of developing of metabolic syndrome.

P2-d2-771 Puberty and Neuroendocrinology 2

Optic glioma and precocious puberty in a girl with neurofibromatosis type 1 carrying mutation R681X

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Background: Optic glioma has been described in children with NF type 1 and is associated with different mutations causing putative truncated NF1 protein. Precocious puberty has been described in patients with NF type 1 due to optic glioma.

Objective: To describe a girl with neurofibromatosis type 1 with precocious puberty due to optic glioma, and a rare NF1 gene mutation.

Methods: A girl at the age 3 years was diagnosed with precocious puberty. Diagnosis of NF1 was established through a clinical check up, and molecular analysis through sequencing of NF1 gene. Precocious puberty was diagnosed by LHRH test. Bone age was assessed and MRI of the hypothalamic and pituitary region was performed.

Results: LHRH test showed high LH peak value of 12.6U/L. Bone age showed acceleration 1.3 SD. MRI confirmed optic glioma within the chiasm of the optic nerve. Molecular analysis by sequencing the NF1 gene confirmed de novo R681X mutation in the exon 13 of the NF1 gene. Therapy with depot triptorelin caused decrease of the telarche. No deterioration of the vision was revealed during the follow up of 3 years.

Discussion: Large number of early-onset cutaneous neurofibromas has been associated with large NF1 gene deletions. Mutation R681X has not been so far reported in NF1 associated with optic glioma. It causes C>T transition at nucleotide 2041 with frame shift reading thereafter and changed protein. No close correlation genotype/phenotype has been shown for the NF type 1. However, the girl with R681X had very extensive cutaneous pigmations, large chiasmal optic glioma endangering vision, and precocious puberty. In conclusion patients with NF1 and precocious puberty should be carefully monitored for optic gliomas and followed up by imaging techniques. Further exploration of genotype/phenotype correlation in patients with NF1 and optic gliomas is warranted.

P2-d2-772 Puberty and Neuroendocrinology 2

Penis length measurement in prepubertal children

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Background: Clinical penis length measurement which is a simple method gives a suggestion about sexual development.

Objective and hypotheses: The aim of this study is to evaluate abnormal penis length in children by establishing the reference values in Turkish population for investigating possible underlying diseases and to compare the mean penis length and other parameters with alternates from different ethnic populations and geography.

Methods: This study was multicentric and included 1420 children. Prematurity, obesity, chronic disease and hypospadias were exclusion criterias. Complete stretch penis length and midpenis circumference measurements were used for penis length and penis circumference evaluations, respectively. All measurements were done twice by only one investigator and mean values were recorded. In this cross sectional study, the relation of penis length and circumference with age, height, weight and height of age patient was investigated by Pearson correlation test. Single sample t test was used in order to compare the similarity of our study findings with the previous ones for penis length measurements. While composing reference percentage curves, LMS method with Penalized probability was used.

Results: Finally, normal values for penis length and circumference, percentile curves were established and these findings were compared with the results of previous studies. Significant differences were found between penis length of Turkish children and recently used reference values for evaluating penis length. Similar penis length values were detected in similar ethnic populations and children living in similar geography.

Conclusions: With this study novel reference values for penis length in prepubertal children were presented to the literature.

P2-d2-772 Sex Differentiation 1

Clinical, molecular and functional characteristics of a novel mutation in the CYP17A1 gene in patients with combined 17alpha-hydroxylase/17,20-lyase deficiency

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Background: Combined 17alpha-hydroxylase/17,20-lyase deficiency is a rare autosomal recessive form of congenital adrenal hyperplasia presenting with hypertension and sexual infantilism. This disorder is caused by defects in P450c17, encoded by the CYP17A1 gene.

Objective and hypotheses: The goal of this study is to describe the clinical and endocrinological features of two patients with 17alpha-hydroxylase/17,20-lyase deficiency, and to identify and characterize the functional activity of the CYP17A mutations.

Methods: Two female patients were evaluated for primary amenorrhea and hypertension at age 15 and 19 years, respectively. In both patients, serum gonadotropin, ACTH, progesterone, and 11-deoxycorticosterone levels were elevated. However, testosterone, dihydrotestosterone, and DHEA-S levels were low. The coding regions of the CYP17A gene were amplified by PCR and directly sequenced. Mutant cDNA was constructed by site-directed mutagenesis. Wild-type and mutant CYP17A1 cDNA was inserted into expression vector, pcDNA3.1-V5/His-P450c17, and transiently expressed in COS-7 cells. The 17alpha-hydroxylase and 17,20-lyase activities were assayed by examining the conversions of progesterone to 17-OHP and 17-hydroxyprogrenolone to DHEA using RIA.

Results: In Subject 1, sequencing of the CYP17A1 identified a compound heterozygosity consisting of p.H373L and p.W406L. Subject 2 was found to be homozygous for p.H373L mutation. To assess the functional consequences
of the novel mutation, p.W406L, COS-7 cells were transfected with the expression vector pCDNA3.1-V5/His-P450c17 containing either wild-type or mutant CYP17A1 cDNA. The p.W406L mutant protein expressed in COS-7 cells showed a complete loss of 17alpha-hydroxylase as well as 17,20-lyase activities compared to wild-type protein.

Conclusions: The novel P450c17 mutation p.W406L abolished both enzyme activities. The complete loss of both 17alpha-hydroxylase and 17,20-lyase activities in p.W406L indicates that this locus is essential for enzyme activity.

P2-d2-774 Sex Differentiation 1

Functional analysis of a hematopoietic-prostaglandin-D2-synthase mutation: evidence of its implication in cryptorchidism

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Background: Among other activities, the enzymes lipocalin-type prostaglandin D2 synthase (L-PGDS) and hematopoietic prostaglandin D2 synthase (H-PGDS) are involved in testis determination during fetal life through prostaglandin D2 pathway activation. Knock-out of L-PGDS in male mice induces delayed testicular organization and unilateral or bilateral testis migration defect. In a previous ESPE meeting, we reported the first H-PGDS mutation (p.[Ile91Val; Met128Thr; Val187Ile]) in a child with bilateral cryptorchidism.

Objective and hypotheses: The aim of this work was to confirm the involvement of H-PGDS mutations in cryptorchidism in this patient.

Methods: We performed in vitro (specific and glutathione-S-transferase [GST] activity tests) and in cellulo (prostaglandin D2 production test) experiments using the three variants identified on the same patient allele to demonstrate evidence of a functional defect.

Results: In vitro tests showed a 60% decrease in specific enzyme activity and a 45% decrease in GST activity. In Sertoli cell line, we tested the residual production of PGD2 using wild type and mutant transfection alone or in combination. We observed a 50% decrease in PGD2 production with the mutant plasmid but no evidence of a dominant-negative effect.

Conclusions: All three experiments demonstrate the high functional impact of these mutations on H-PGDS enzyme activity and confirm the involvement of H-PGDS mutant in abnormal testis migration in humans as well as in mice.

P2-d2-775 Sex Differentiation 1

Overexpression of 5α-reductase type 2 in genital skin contributes to higher degree of external genitalia virilization in CAH females

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Background: Classical form of 21-hydroxylase deficiency (CAH) is an autosomal recessive disorder characterized by ACTH-dependent hyperandrogenism resulting in prenatal external genitalia virilization in females. Despite the good genotype-phenotype correlation, the degree of external genitalia virilization (Prader) presents significant variability among females carrying similar CYP21A2 genotypes. It is thought that interindividual difference in the peripheral androgen action is the main determinant for this variability. However, this fact has not been demonstrated so far.

Objective: To evaluate if different AR, SRD5A1, SRD5A2, AKR1C3 gene expressions in genital skin influence the degree of external genitalia virilization in CAH females carrying similar CYP21A2 genotypes.

Patients and method: 12 CAH females, six with Prader 3 and six with Prader 4 external genitalia. CYP21A2 genotypes were classified in group A (Speiser et al, 1992). Genital skin samples were collected during genitoplasty, and RNA was extracted by Trizol method. AR, SRD5A1, SRD5A2 and AKR1C3 mRNA expressions were determined by real-time quantitative PCR (Taqman system). A pool of genital skin from healthy male child was used as reference sample. Relative quantification was determined by the 2-ΔΔCt method. A twofold change in mRNA levels was considered significant.

Results: Overexpression of SRD5A2 mRNA was observed in 4/6 patients with Prader 4 (5.5, 16.2, 6.1, 21.2 fold). Two out of 6 patients with Prader 3
had mild SRD5A2 overexpression (2.0, 2.9 fold). There was a significant difference of SRD5A2 mRNA expression between Prader 3 and Prader 4 groups (P=0.037). AR, SRD5A1 and AKR1C3 expressions were similar between Prader 3 and Prader 4 groups; but one out of two patients with Prader 4 with normal SRD5A2 mRNA expression had AKR1C3 mRNA overexpression.

**Conclusion:** Interindividual differences in the expression of sex steroid enzymes in genital skin could account for the severities of external genitalia virilization in classical form of CAH females with similar CYP21A2 genotypes. FAPESP#08/57616-5, 55546-0.

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**P2-d2-776 Sex Differentiation 1**

**Persistent Müllerian duct syndrome - a case series**

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**Background:** Persistent Müllerian Duct syndrome (PMDS) is characterised by the presence of Müllerian structures in 46 XY males, either secondary to Anti-Müllerian Hormone (AMH) deficiency or defects in the AMH receptor. AMH induces Müllerian duct regression at 7 weeks gestation, enabling the testes to move transabdominally to the deep inguinal rings and into the scrotum. The presentation in PMDS is with unilateral or bilateral undescended testes (UDT) and there is risk of development of adenosarcoma in the Müllerian remnant.

**Objective:** We aim to highlight the importance of considering PMDS in boys with UDT.

**Methods:** Retrospective case-note reviews of patients with PMDS were identified from paediatric urology and endocrinology databases.

**Results:** 6 patients were identified with PMDS, presenting between 2001 to 2011, aged 1 week to 9 years. 5 boys presented with bilateral UDT (all XY karyotype) and 1 with unilateral UDT (mosaic 46 XY/46 XY interstitial deletion). PMDS was diagnosed at laparoscopy to locate the testes prior to orchiopexy. 2 boys originally had open orchiopexies for bilateral UDT through bilateral groin incisions, but the testes ‘vanished’ and Müllerian remnants were subsequently diagnosed at laparoscopy. 3 boys had hysterectomy of the Müllerian remnants. 4 of the boys with bilateral (UDT) are from consanguineous families; 2 are siblings with confirmed AMH deficiency.

**Conclusions:** PMDS is an important differential diagnosis in males with bilateral UDT and should be considered in boys with ‘vanishing testes’. The Müllerian remnants were not observed originally in 2 cases as open orchiopexies were performed through bilateral incisions; hence midline structures were not seen. The Müllerian remnants are generally left in situ when orchidopexy is performed, however reports of adenosarcoma in the Müllerian remnants are now emerging in the literature. Practice at our institution is now to undertake laparoscopy in all cases of bilateral UDT and hysterectomy where possible.

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**P2-d2-777 Sex Differentiation 1**

**Phenotypic spectrum in mixed gonadal dysgenesis and the influence on sex of rearing**

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**Background:** Mixed gonadal dysgenesis (MGD) with mosaicism of 45 XO and 46 XY cell lines presents with a heterogeneous phenotypic spectrum as a consequence of the variable tissue proportion of the 2 cell lines.

**Objective:** To review 15 patients with MGD seen at our paediatric department over the past 20 years for their presentation, sex of rearing and use of growth hormone.

**Methods:** Retrospective review of case records.

**Results:** 15 patients with MGD were reviewed. The patients presented with 2 main phenotypes:

1. Ambiguous genitalia: 7 patients presented at birth with ambiguous genitalia, of whom 3 were reared as females and 3 were reared as males. The factors influencing the sex of rearing include: Prader grading of the external genitals, parental concern regarding potential for Y imprinting, and parental preference for a boy as the chosen sex of rearing in Asians, especially if short stature is a likely issue.

2. Short stature and delayed puberty: The remaining 8 patients were diagnosed with MGD after work-up for short stature and delayed puberty. Interestingly, 4 patients were completely female at presentation, and 1 patient was completely male, presumably as a result of the high percentage of 46 XY cell line. Two other patients were initially thought to have Noonan syndrome with associated cardiac lesions, but on screening, were found to have MGD.

One patient developed a gonadal malignancy at 15 years of age. Five patients were treated with Growth Hormone. The mean height velocity 1 year pre-treatment was 7.1 cm/year, as compared to the pre-treatment mean height velocity of 4.2 cm/year.

**Conclusions:** Apart from short stature and variable genital appearance that can occur in MGD, we highlight the considerations that impact the decision for sex of rearing in MGD and the importance of screening the chromosomal karyotype in Noonan syndrome in males. The significance of diagnosing MGD lies in removal of the dysgenetic gonads which are at risk of malignancy, and in the potential for improving the final height with GH treatment.

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**P2-d2-778 Sex Differentiation 1**

**Try235Phe homozygous mutation of the steroid 5α-reductase type 2 (SRD5A2) gene in a Turkish patient**

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**Background:** Steroid 5α-reductase type 2 isoform (SRD5A2) deficiency is a male-limited autosomal recessive disorder that results in decreased conversion of testosterone (T) to dihydrotestosterone (DHT) with various degree of incomplete virilization in affected 46,XY infants.

**Objective and hypotheses:** We report Try235Phe homozygous mutation of the SRD5A2 gene in a Turkish patient who initially assigned as a girl because of the predominantly female appearance of the external genitalia at birth.

**Methods:** After ambiguous genitalia had been observed by the pediatrician, the patient was admitted to the pediatric endocrine department for evaluation of disorders of sex development at six days of age. The infant presented extremely hypoplastic penis (stretched length 1.5 cm) with a single phallic urethral opening and palpable right testis in the labio-scrotum. Pelvic ultrasonography showed no evidence of any müllerian structures. Genitography revealed a urogenital sinus without vaginal pouch. The karyotype was 46,XY. A serum T/DHT ratio (28.1) under hCG stimulation provided evidence for the diagnosis SRD5A2 deficiency.

**Results:** SRD5A2 gene analysis revealed Try235Phe homozygous mutation in exon 5. This previously known mutation has been first reported in Turkish patients. To date, more than 50 SRD5A2 gene mutations have been identified. There is no clear genotype-phenotype relationship and moreover, the same mutation can result in considerable heterogeneity in the clinical manifestations. Of six documented cases with Try235Phe homozygous mutation of the SRD5A2 gene, three patients had predominantly female external genitalia whereas the other three had predominantly male phenotype.

**Conclusions:** This can be explained that some factors related to androgen receptor signal transduction, fetal effects of testosterone or steroid 5α-reductase type 1 isoform or exposure to environmental chemicals may affect clinical expression of the disorder.
P2-d2-779 Sex Differentiation 1
46, XY partial gonadal dysgenesis: clinical, biological, histological features of 29 patients with a long term follow up for half of them
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Background: 46, XY gonadal dysgenesis (GD) is a disorder of sexual development (DS) that leads to a defect in foetus's masculinization but its mechanisms are still unknown in most cases.

Objective: To describe patients with partial 46, XY GD (circumstances of diagnosis, anatomy of external/ internal genitals, biology, histology), their management (sex of rearing, attitude toward gonads, genitoplasty) and their long term follow-up including puberty.

Design and patients: 29 patients born between 1966 - 2006 were included in this retrospective, single-centre, clinical study. Inclusion criteria were external DS, 46, XY karyotype without mosaicism, diagnostic criteria for GD (persistent Müllerian structures, gonadal histology and/or low serum testosterone or anti-mullerian hormone (AMH) level).

Results: In 24 patients diagnostic was suspected at birth and later in 5 cases. External and internal genitals varied from very masculinized to very feminized with only a clinical enlargement. 14 patients had an uterus. AMH, LH, FSH, testosterone blood levels might be normal, especially in the first years of life, but AMH was the parameter the more often disturbed. Testosterone response after hCG stimulation varied widely (35% of response < 1 ng/ml vs normal > 3 ng/ml in 39%). 11 patients were raised as males and 18 as females. Genitoplastical procedures was higher for males than for females (2,8 per patient vs 2,2). 23 gonadal tissues were analysed: gonads were dysgenetic testes with peripheral tubules like embryonic cords and a thin albугinea, but few had only a reduced tubule density. 3 patients presented gonadoblastoma (before 7 years).

Conclusion: Phenotype of partial 46, XY GD is variable, as the gonadal histology. Then diagnosis can be difficult when biochemistry is normal with no histological analysis (patients raised as males), confirmed in those cases by long term evolution of altered testicular function.

P2-d2-781 Sex Differentiation 1
A new inactivating mutation of the LH receptor gene causes in a 46,XY girl a disorder of sex development and in her 46,XX sister amenorrhea
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Background: Leydig cell hypoplasia (LCH) is a rare autosomal recessive condition that interferes with normal development of male external genitalia in 46,XY individuals. In 46,XX women primary and secondary sexual characteristics are developed normally but suffering from amenorrhea and infertility.

Objective and hypotheses: Here we report a family with two affected sisters suspected to have an inactivating mutation in the LH receptor gene. A 14 year old girl was referred with lack of the progression in breast development and amenorrhea. The parents are first degree cousins. Breast development was Tanner stage I and pubic hair development Tanner stage III. She had female external genitalia with mild posterior labial fusion. Hormonal evaluation revealed FSH 2.62mIU/mL, LH 10.94 mIU/mL, E2 <20ng/dl. Karyotype was 46, XY. She had a gonadectomy. The histopathological examination of the gonads showed absence of Leydig cells. There weren’t any Müllerian derivatives. Her 21 year-old sister was also evaluated at the age of 15 years for amenorrhea. Her secondary sexual characteristics were well developed. Pelvic ultrasonography showed an uterus with atrophic endometrium. The ovaries were enlarged in size (right ovary 12.9 cm3, left 7.5 cm3) with multicystic appearance. Dominant follicle was not observed. In hormonal evaluation, serum LH level was 30.9 mIU/mL, FSH 7.68 mIU/mL, E2 35.44 pg/ml, testosterone 36.8ng/dl. An analysis of the LHR was initiated in both sisters.

Methods and results: Using PCR followed by sequencing the coding parts of all exons including the intron-exon boundaries resulted in the identification of a new homozygous mutation in exon 2, encoding a replacement of glycine to alanine(Gly71Ala, GGA>CGA).

Conclusions: This is a new missense mutation of the LHR, which is located in the extracellular ligand-binding domain in exon 2, probably interfering with binding of LH to the LH receptor. In vitro experiments with the mutant receptor will follow to get more insights into the binding capacity and activity of this receptor.
P2-d-782 Sex Differentiation 1

Hormonal and genetic work-up is useful in 46,XY neonates with milder forms of undervirilisation

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Background: Recently, mutations in specific genes (AR, SF1) or chromosomal rearrangements have been reported in 46,XY neonates with milder forms of undervirilisation. This raises the question who should be tested, and which protocol (patient-friendly, cost-effective) should be used.

Aims: To examine the efficacy of our in-house hormonal and genetic diagnostic protocol and to define which patients should be submitted to it.

Methods: A retrospective analysis of our Disorders of Sex Development (DSD) database for the period 2007–2011 identified twenty 46,XY neonates with abnormal External Masculinisation Score (EMS) (range 2-9, normal 12). Our diagnostic set includes a single hormonal bilan (Testosterone, DHT, Δ4-androstenedione, LH, FSH, AMH, Inhibin B) during mini-puberty, and a genetic screening by high-resolution array CGH (Agilent, resolution 150 kb), and sequencing of SF1 and AR genes.

Results: 3/20 patients had additional dysmorphic features, 6/20 were born SGA. Hormonal profiles suggested gonadal dysgenesis in 2 (10%) and 17β-HSD deficiency in 1 patient (EMS 3/12), gene sequencing is ongoing. In 2 boys (EMS 9/12 and 3/12) with normal hormonal profiles and normal adrenal function, hitherto unreported SF1 mutations (c.630_637del; c.1109G>A) were detected. 7 patients harboured chromosomal rearrangements, a causal relationship (DMRT deletion) with the DSD was suspected in only one (EMS 3/12) with associated dysmorphic features.

Conclusions: Our in-house diagnostic set is practical and minimally invasive during mini-puberty and allows detecting a cause for the DSD in 20% of all cases; namely in 20% with EMS 7-9, and in 20% with EMS>7. SF1 sequencing is useful, even in the presence of milder undervirilisation and a normal hormonal profile. Array CGH is informative mainly in the presence of dysmorphic features. As in other series, no abnormalities were detected in SGA-associated undervirilisation and mutations in the AR are infrequent.

P2-d-783 Sex Differentiation 1

A new SF1 mutation in two siblings with 46,XY disorder of sexual differentiation (DSD) and normal adrenal function

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Background: The steroidogenic factor 1 (SF1) encoded by NR5A1 gene is a nuclear receptor that regulates the transcription of many genes involved in steroidogenesis, gonadal determination, sexual differentiation and reproduction. The first human mutation was identified in a patient with adrenal failure and 46,XY sex reversal; recently several heterozygous SF1 mutations have been reported in patients with isolated 46,XY DSD. We describe a new SF1 mutation in two siblings of non consanguineous parents.

Clinical cases: The proband (patient 1) was referred to our clinic at birth for ambiguous genitalia. He had a 16-month-old brother (patient 2) who has been diagnosed with hypospadias without further investigation. Both patients had penoscrotal hypospadias with microphallus and hypoplastic scrotum with decreased smegma. Patient 1 had undescended testes. In both siblings, the karyotype was 46 XY and the pelvic ultrasonography didn’t notice Mullerian ducts. The testes were in inguinal position in patient 1 and in scrotal position in patient 2. The genitography revealed the presence of Mullerian structures in both patients. The endocrine evaluation showed normal adrenal function and low basal testosterone levels with an impaired response to human chorionic gonadotrophin (patient 1: 1.14 to 4.7 nmol/l, patient 2: 0.13 to 5.4 nmol/l).

The AMH levels were normal (311 pmol/l) in patient 1 but low in patient 2 (129 pmol/l). The FSH levels were slightly elevated in patient 1 (29 mIU/ml). The androgen sensitivity test resulted in only minimal changes in the penile length in both siblings (patient 1: 15 to 25 mm, patient 2: 18 to 28 mm). Mutation analysis of SF1 gene revealed a heterozygous mutation (c.370 del C) resulting in a damaged protein probably responsible of the ambiguous genitalia in our patients. Both siblings were assigned males and have to undergo a surgical treatment.

Conclusion: This report suggests that it should be useful to systematically investigate for SF1 mutations in all patients presenting with 46,XY dysgenesis.

P2-d-784 Sex Differentiation 1

Ovotesticular disorder of sexual development and a rare 46,XX/47,XXY karyotype

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Background: Ovotesticular disorder of sexual development (DSD) is characterized by the presence of both ovarian and testicular tissues in the same individual. Diagnosis can only be established by histologic examination of the gonads. The most common karyotype is 46 XX. To our knowledge there are only two cases of ovotesticular DSD with Klinefelter syndrome’s mosaic karyotype reported in literature. Here we report a boy with 46,XX/47,XXY karyotype diagnosed as ovotesticular DSD by gonadal biopsy.

Methods/patients: A 5-months-old boy presented with hypospadias, unilateral cryptorchidism and microepispadias. Pelvic ultrasound revealed left inguinal hernia and the left testis could not be visualised. Pelvic MRI marked a suspicious gonad tissue solid structure in the right scrotum and a suspicious gonad cystic structure in the left inguinal canal. He underwent a diagnostic laparoscopy. Cytogenetic analysis of peripheral blood revealed 46,XX/47,XXY karyotype. Histopathologic examination of left side gonad showed ovarian tissue containing primordial follicles with ipsilateral undifferentiated tuba uterina. The right side gonad showed immature testis tissue. Both of the two gonads materials’ cytogenetic analysis revealed 45,X;46,XX/47,XXY mosaicism.

Results: He underwent left gonadectomy, hypospadias repair and was raised as a male.

Conclusions: Gender assignment is a controversial issue in the following up period of ovotesticular DSD. In case of raising as a male, hypospadias repair, orchidopexy and removal of Mullerian remnants will be required. Despite the rare occurrence of malignancy, scrotally sited testicular tissue must be monitored for tumour development.

P2-d-785 Sex Differentiation 1

17 A hydroxylase deficiency; an interesting case of primary amenorrhoea with hypertension

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Background: Seventeen α hydroxylase deficiency (17OHD) is a rare form of congenital adrenal hyperplasia resulting from mutation in CYP17 gene. Patients present with hypertension and hypokalemia with undervirilized state in males and delayed puberty in females. We report 1 such female case.

Objective and hypotheses: To raise awareness of this rare condition, when patient presents with clinical scenario of hypokalemia, hypertension and hypergonadism.

Methods: A 14 year girl presented with acute onset quadriaparesis & hypertension. Parental consanguinity, primary amenorrhoea and absent breast development were added informations. On examination BP was 150/100 mm Hg with significant asymmetry or postural variation with palpable pulses in all extremities. Her height was 157 cm and weight was 45 kg with no stigma of Turner’s syndrome. There was generalized skin fold and knuckle pigmentation without mucosal pigmentation. Sexual Maturity rating was B1 PH1. Axillary hairs were absent. Muscle power was grade 3 with normal deep tendon reflexes and intact sensory, bladder & bowel functions.

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Results: Investigations revealed hypokalemia (1.9 meq/L), low 24hr urine potassium (7 meq/day) with metabolic alkalosis (pH 7.6, HCO3-30 mmol/L, PaCO2 40 mm Hg). Other positive investigations were low serum cortisol (1.5 mcg/dl), high ACTH (513ng/ml) and high FSH (45ml/L) Karyotype was 46XX and serum progesterone was 8.5 ng/ml (normal <1.5 ng/ml). Hypertension associated with hypokalemia & metabolic alkalosis, low cortisol, high ACTH & hypergonadotropic hypogonadism (high FSH) pointed to the possibility of 17OHD 46XX karyotype & high progesterone confirmed this (Figure 1). She was prescribed oral prednisolone, ethinyl estradiol. Hypokalemia and hypertension were normalized with glucocorticoid treatment.

Conclusions: 17 OHD should be considered when 46 XY sex reversal or 46 XX pubertal failure occurs in association with hypokalemic hypertension, so that appropriate therapy can be implemented. Lack of early treatment leads to uncontrolled arterial hypertension and its sequelae.

P2-d1-787 Thyroid 1

Serum concentrations of triiodothyronine and natural IgM antibodies against angiogenin in pediatric osteosarcoma patients as markers for monitoring activity of antiangiogenic therapy for the treatment of osteosarcoma

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Background: Development of new antiangiogenic treatments has increased the need for biomarkers that predict outcome and those that direct which treatment options are most likely to be effective for particular patients.

Objective: To study T3 and ANG—IgM expressions in the sera of pediatric OS patients for monitoring efficacy antiangiogenic therapy for the OS treatment.

Methods: The study included 50 pediatric OS patients received resection at the Department of Bone Tumours. All patients received, on average, antiangiogenic therapy for the treatment of OS during one year. Blood samples were taken from them 6 times: before therapy, at every 3 weeks during therapy, at the end of therapy. Biomarkers ELISA assay for measurement ANG—IgM levels in the human sera were developed in NIR. T3 concentrations were measured using a commercial Immunoassay kit R&D Systems.

Results: T3 concentration in the sera of healthy children ranging between 3.2 and 5.2 pmol/mL. Patients with T3 ranging from 5.8 to 7.4 pmol/mL were shown the generalisation malignant process during next 1-3 months; patients with T3 ranging from 4.0 to 5.2 pmol/mL were shown the remission during 6-24 months. After antiangiogenic therapy, all children achieved a response with serum ANG—IgM levels significantly lower than in untreated patients, but still higher than in healthy controls. Higher ANG—IgM levels were significantly associated with poor treatment response (r=0.75; P<0.001).

Conclusions: Serum ANG—IgM levels decreased after successful treatment of OS and increased in some cases of recurring OS, indicating that the measurement of ANG—IgM may be clinically useful in monitoring the antiangiogenic treatment efficacy of OS. Expression of T3 correlated with clinical features in children. ANG—IgM are very attractive candidates for use as markers of response to antiangiogenic therapy in pediatric OS patients. Combinations of T3/ANG—IgM may be administered together.

P2-d1-788 Thyroid 1

Initial Carbimazole dose for the treatment of childhood Graves’ disease

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Background: Carbimazole (CMZ) is often the first-line treatment for Graves’ Disease (GD). There is evidence that children who become euthyroid by 3 months have higher remission rates without radiodine or surgery, but what
P2-d1-789 Thyroid 1
Dysmetabolic phenotype in healthy pregnant women with lower free thyroxin
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Background: A lower free T4 (fT4), within the euthyroid range, has been shown in adults to associate with a poorer metabolic phenotype. Thyroid physiology changes significantly during gestation and affects the maternal and fetal well-being.

Objective: To test the hypothesis that a lower serum fT4 is in healthy euthyroid pregnant women related to a dysmetabolic phenotype.

Population and methods: We examined associations of thyroid function tests [TSH and free T4 (fT4)] and the fT4-to-T3 ratio (as a proxy of deiodinase activity) with a metabolic profile [post load glucose, HbA1c, insulin resistance (HOMA-IR), high-molecular-weight (HMW)-adiponectin and serum lipids], in 381 healthy pregnant women. Blood tests were performed in women between 24 and 28 gestation weeks. Placentas and newborns were weighed at delivery.

Results: All women were euthyroid and none received thyroid hormone replacement. While TSH was unrelated to metabolic parameters, decreasing fT4 and increasing fT3-to-T4 ratio were associated with higher BMI, post load glucose, HbA1c, fasting insulin, HOMA-IR, triglycerides and placental weight, and with lower HMW-adiponectin (all p<0.05 to p<0.0001). In multiple regression analyses, fT4 was independently associated with HbA1c (β=−0.192, p=0.003) and HMW-adiponectin (β=0.245, p=0.0001), while the fT3-to-T4 ratio was independently associated with BMI (β=0.367, p<0.0001), HOMA-IR (β=0.238, p=0.004) and HMW-adiponectin (β=−0.262, p=0.002).

Conclusions: Our data suggest that in children with Graves’ Disease, the initial CMZ dose should be based on age at diagnosis. This is consistent with our study. Non-compliance should be considered if the expected efficacy was not achieved. Higher doses to treat children who need beta-blockers for symptomatic control may result in a hypothyroid state within 3 months. For symptomatic control may result in a hypothyroid state within 3 months.
Cu levels are borderline low, findings of Cu deficiency should be cautiously followed.

Conclusions: The alteration in the serum thyroid hormone profile during VPA therapy may result from the reduction in serum Cu levels. It may be useful to determine serum thyroid hormone concentrations routinely in children with epilepsy receiving VPA, and if VPA therapy begins in patients whose serum Cu levels are borderline low, findings of Cu deficiency should be cautiously followed.

Background: Congenital hypothyroidism (CH) is the most frequent congenital endocrine disorder and most often due to thyroid dysgenesis. Although several candidate genes such as NKX2.1, PAX8 and TSHR have been identified, the molecular pathogenesis of thyroid dysgenesis still remains unknown in the majority of patients.

Objective and hypotheses: To further elucidate the molecular cause of thyroid dysgenesis, we aim to identify more genes expressed during thyroid development. Potential new candidate genes were selected based on two criteria: (I) involvement in the development of other endodermal derived organs such as liver and pancreas, (II) defects of the genes can cause malformations associated with CH, e.g. heart defects. Among others, the members of the cardiac group of GATA transcription factors (Gata4/5/6) meet both criteria.

Methods: We studied the expression of Gata4, Gata5 and Gata6 during thyroid organogenesis in NMRI wild type mice by in situ hybridisation (ISH).

Results: ISH on tissue sections of several embryonic stages (E9.5-E15.5) did not show an expression of any of these genes in the developing thyroid. Therefore, we can exclude a cell-autonomous function of Gata4/5/6 in thyroid development. Nevertheless, in stages E9.5-E11.5 Gata4, Gata5 and Gata6 are strongly expressed in immediate proximity to the thyroid anlage in the outflow tract of the heart (OFT).

Conclusions: It is known, that thyroid morphogenesis depends on the vicinity to the heart and co-developing major arteries, even though the molecular pathways mediating the co-development have not been described so far. Based on the expression pattern we have observed Gata4/5/6 may well be involved in the regulation of these pathways. Therefore, we postulate that Gata4/5/6 are good candidates that influence thyroid development in a non-cell-autonomous manner. Elucidation of the pathways regulated by Gata4/5/6 in the OFT is therefore likely to reveal promising new candidate genes for thyroid development and thus for understanding the pathogenesis of thyroid dysgenesis.

Background: Autoimmune thyroiditis (AIT) is the most common cause of goiter and acquired hypothyroidism in children and adolescents in iodine replete areas of the world. In patients with AIT, thyroid hormone status can be variable and may change over time.

Objective and hypotheses: We aimed to evaluate the clinical course of AIT, diagnosed in children and adolescents.

Methods: A total of 67 (59 females, 8 males) children and adolescents who were followed-up at least 12 months were included in this study. Patients were classified according to thyroid functions at diagnosis: euthyroid, subclinical hypothyroid, overt hypothyroid, and hyperthyroid. Serum free thyroxine, thyroid stimulating hormone (TSH), anti-thyroid peroxidase antibody and anti-thyroglobulin antibody were analyzed after a 6 weeks cessation of levothyroxine therapy.

Results: Mean age at diagnosis was 11.01±2.4 years (range 5.5-15.9), mean follow-up time was 33.6±14.3 months (range 12-61). At diagnosis 16 patients were euthyroid, 51 patients were subclinical hypothyroid and overt hypothyroid. After the cessation of treatment, 14 of 16 patients with euthyroidism had remained euthyroid while two patients had developed subclinical hypothyroidism. Of 30 patients with subclinical hypothyroidism, 16 remained subclinical hypothyroid, 4 have developed overt hypothyroidism and 10 recov-
erated a normal thyroid function. Twenty one patients were overt hypothyroid at the diagnosis and 10 of them remained overt hypothyroid, 8 showed an increase in TSH level consistent with subclinical hypothyroidism, 3 became euthyroid.

**Conclusions:** Thyroid hormone status may alter during the follow-up of AIT. Therefore, thyroid function tests should be repeated periodically to detect progression to hypothyroidism in initially euthyroid patients and also reversibility of hypothyroidism in order to achieve optimal therapy.

**P2-d1-794 Thyroid 1**

**Comparison of lymphocytes and thyrocyte interactions in Graves' disease and Hashimoto thyroiditis**

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**Background:** Graves' disease (GD) and Hashimoto thyroiditis (HT) are two common autoimmune thyroid diseases this pathogenesis is unsolved.

**Objective and hypotheses:** The aim of the studies was to compare the interaction of T and B cell subsets in the thyroid tissue in patients with GD and HT.

**Methods:** We have studied paraffin thyroid specimens obtained from 30 children with GD, 30 children with HT and 30 children without a thyroid disease. The mononuclear T-cells were detected by CD3+, CD4+, CD8+ antibodies, and the B-cells by CD79 alpha antibodies and the antigen presenting cells with CD1a+ antibodies (DakoCytomation Denmark) and counted. The specimens from each patients were routinely estimated and investigated under the electron microscope.

**Results:** In GD and in HT, we observed a statistically significant, higher number of antigen presenting cells, T and B cells in comparison to the control group. In GD, a statistically significant increase in the CD4+ cells, in comparison to HT, was found. In HT, CD8+ T cytotoxic-suppressor cells were predominant among T-cells.

The ultrastructural investigations showed diapedesis of T cells into thyroid follicles and formation of immunological synapses between thyrocytes and lymphocytes. In GD, the activity of B-cells producing antibodies involved in the processes of activation and proliferation of thyrocytes developed. In HT, a cytotoxic reaction against thyrocytes was induced.

**Conclusions:** 1. The autoimmune reaction in Graves disease consists in activation of T helper cells CD4+ and transformation of B cells to plasmocytes and production of thyroid antibodies which stimulate thyrocyds. 2. The autoimmune reaction in Hashimoto thyroiditis consists in activation of cytotoxic reactions between T-suppressor-cytotoxic cells CD8+ and thyrocytes.

**P2-d1-795 Thyroid 1**

**Hyperthyrotropinemia and metabolic syndrome in obese pediatric population**

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**Background:** Obesity may alter thyroid hormone levels by dysregulation of the endocrine crosstalk between the hypothalamic-pituitary axis and the adipose tissue (leptin). Several studies reported moderately elevated TSH in obese subjects.

**Objective and hypotheses:** To determine the prevalence of hyperthyrotropinemia in obese Spanish children. To investigate the correlation between TSH levels and components of metabolic syndrome (MS).

**Methods:** Prospective study of a cohort of 419 obese pediatric patients (BMI > 2SD, Hernández-2004). 51% male, 74% Caucasian, mean age 11.03±2.7 years. TSH was determined in all subjects (n=0.35-4.95) and when elevated, free thyroid hormones, antithyroid antibodies and thyroid ultrasounds were performed. Anthropometric, metabolic and hormonal features of metabolic syndrome were also ascertained. MS defined by Cook’s modified criteria. Statistical analysis performed with SPSS-program, parametric tests; data expressed in percentages, means and SD.

**Results:** Hyperthyrotropinemia was found in 31 patients (6%); 7 had positive antithyroid antibodies and were excluded for the analysis. The group with isolated hyperthyrotropinemia (24) invariable had normal fT4 and FT3 and normal thyroid ultrasounds.

**P2-d1-796 Thyroid 1**

**Thyroid hormone levels in severe bronchiolitis**

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**Background:** Previous studies in children with critical illness have showed alterations of thyroid hormones. In adults, thyroid hormones have been found to be an interesting parameter for evaluating disease severity and predict outcome. There are no previous reports about the thyroid hormone profile in infants with bronchiolitis.

**Objective and hypotheses:** Measure thyroid hormone levels in children with severe bronchiolitis who were admitted to the pediatric intensive care unit (PICU) in a tertiary hospital. Investigate the relationship of these hormones with the prognosis of the disease.

**Methods:** Observational study of children younger than 1 year old, admitted to the PICU because of severe bronchiolitis. Thyroid hormones (TSH, TT4, FT4, TT3 and FT3) were determined in the first 72 hours after admission. The main prognostic variables were the days of admission, and between group comparisons were made using the Mann-Whitney U test for continuous data. Spearman’s correlation coefficient (r) was used to evaluate the relationship between quantitative parameters.

In the subgroup of patients with isolated hyperthyrotropinemia, 8/24 were treated with levothyroxine, which did not leave to significant decreased in BMI over one year follow-up.

**Conclusions:** A moderate elevation of TSH is present in reduced proportion of obese children. No correlation was found between TSH and BMI. TSH index is statistically comparable between the two groups, suggesting pituitary compensatory mechanisms for TSH secretion and that children with elevated TSH may not need hormonal replacement.
Results: 41 children were initially included in the study; ten of them were excluded because of the presence of antithyroid antibodies or incomplete data. So 31 children (48% boys; 52% girls) aged between 10 days and 4.4 months (P90:1.3 months;QR2:6.7-1.8 months) were finally studied. Nine of them (29%; CI95%:16.4-46.6) meet the criteria for type 1 nonthyroidal illness syndrome (NTIS; low FT3 with normal TSH and T4); and 1 (3.2%; CI95%:0.5%-16.2%) for type 2 NTIS. FT3 values correlate inversely with days of admission in hospital (r=0.442; p=0.012) and in PICU (r=0.370; p=0.041). FT3 values were significantly lower in children who needed MV (3.1 +/- 0.8 vs 2.4 +/- 0.6 pg/ml; p=0.026).

Conclusions: 29% of infants younger than 1 year old with severe bronchiolitis have alterations in the thyroid hormone profile consistent with type 1 NTIS. We observed an inverse correlation between FT3 and days of admission in hospital and in PICU.

P2-d2.797 Thyroid 2

Thyroid peroxidase antibodies in euthyroid children - is long term follow up required?

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Background: The presence of thyroid peroxidase (TPO) antibodies in euthyroid children poses a potential risk for the development of autoimmune hypothyroidism. Little is known about the ontogeny of this process.

Objective: 1)To estimate the risk of developing hypothyroidism in euthyroid children with increased TPO antibodies. 2)To provide a guideline for follow up of these children.

Methods: This was a retrospective study. Children 0-16 years with increased TPO antibodies (1996-2005) were identified from the biochemistry database of a University Hospital. In those that were euthyroid on initial screen, follow up details and thyroid function tests (TFT) were obtained from case records.

Results: 208 children were identified with increased TPO antibodies, 164 had concurrent TFT results. 104 were excluded as they either had frank hypothyroidism, compensated hypothyroidism or thyrotoxicosis, leaving 60 euthyroid children (19 male, 41 female). 9/60 had no further follow up results. Within 2 years 2/51 (4%) had developed hypothyroidism requiring treatment. By 5 years a further 2 children had developed hypothyroidism (one had type 1 diabetes (T1DM) and the other Down syndrome). At 10 years another two children were being treated, one with T1DM and one with both T1DM and Down syndrome.

Conclusions: Risk of hypothyroidism in healthy euthyroid children with increased TPO antibodies is minimal after the first two years. Therefore a suggested policy of follow up with TFT at 3-6 months and then annually up to 2 years before discharging back to primary care would seem appropriate. Suggested policy of follow up with TFT at 3-6 months and then annually up to 2 years before discharging back to primary care would seem appropriate.

P2-d2.798 Thyroid 2

Use of triiodothyronine and natural IgM antibodies against angiogenin in pediatric osteosarcoma patients as markers for monitoring activity of antiangiogenic therapy for the treatment of osteosarcoma

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Development of new antiangiogenic treatments has increased the need for biomarkers that predict outcome and those that direct which treatment options are most likely to be effective for particular patients. The study included 50 pediatric OS patients received resection at the Department of Bone Tumors. All patients received, on average, antiangiogenic therapy for the treatment of OS during one year. Blood samples were taken from them 6 times: before therapy, at every 3 weeks during therapy, at the end of therapy. Biomarkers ELISA assay for measurement ANG—IgM levels in the human sera were developed in NIR. T3 concentrations were measured using a commercial Immunoassay kit R&D Systems. T3 concentration in the sera of healthy children ranging between 3.2 and 5.2 pmol/mL. Patients with T3 ranging from 5.8 to 7.4 pmol/mL were shown the generalisation malignant process during next 1-3 months; patients with T3 ranging from 4.0 to 5.2 pmol/mL were shown the remission during 6-24 months. After antiangiogenic therapy, all children achieved a response with serum ANG—IgM levels significantly lower than in untreated patients, but still higher than in healthy controls. Higher ANG—IgM levels were significantly associated with poor treatment response (r=0.75; P=0.001). Serum ANG—IgM levels decreased after successful treatment of OS and increased in some cases of recurring OS, indicating that the measurement of ANG—IgM may be clinically useful in monitoring the antiangiogenic treatment efficacy of OS. Expression of T3 correlated with clinical features in children. ANG—IgM are very attractive candidates for use as markers of response to antiangiogenic therapy in pediatric OS patients. Combinations of T3-ANG—IgM may be administered together. Association of laboratory investigations with clinical trials will be instrumental for the validation of biomarkers as ANG—IgM and T3 for improving the design, monitoring and evaluation of antiangiogenic treatments.

P2-d2.799 Thyroid 2

Challenges in managing paediatric endocrine disorders in a developing country

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Background: The population of children with endocrine disorders in Nigeria and other developing countries is increasing. This problem has been masked by the burden of infectious diseases and under nutrition in these regions. In most developing countries, children with endocrine diseases die undiagnosed and those who are diagnosed often do not receive adequate treatment, because of socioeconomic and cultural constraints.

Objective and hypotheses: To determine and highlight the challenges of managing paediatric endocrine disorders.

Methods: A three year review of medical admissions and follow-up of all endocrine cases seen between January 2008 and December 2010 in the Paediatric Endocrine unit UPTH, Nigeria. Data collected included bio data, contacts, anthropometry, symptoms, diagnoses, duration of disease before diagnoses, management modalities, follow up, and constraints in management. Data was analysed with SPSS 17.

Results: A total of 62 children were diagnosed with endocrine disorders. There were 30 females and 32 males. Age range was 1-184 months (Mean 66.91). Infants and adolescents accounted for 21 (33.9%) each. Thirty three (53.2%) children were from the middle and lower socioeconomic class. The commonest diagnosis were T1DM, 12 (19.4%), and hypocalcemia 13(21%). The duration of symptoms before diagnosis was 2 weeks to 7 years. Coun-
safety of all patients was done by the Endocrinologist, and only two had a professional psychological review. 41(66.1%) patients were lost to follow up. Financial constraints (63.4%), long distance to the hospital (24.4%), seeking alternative care (12.2%) were cited as reasons for default to follow up. 

Conclusions: Children with endocrine disorders are rarely fully evaluated and treated because of financial constraints and cultural beliefs. Education and health insurance must be strengthened to reverse this trend.

Socioeconomic class

<table>
<thead>
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<th>Difficulty in treating</th>
<th>No difficulty in treating</th>
<th>Total</th>
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<td>7(11.3%)</td>
</tr>
<tr>
<td>2</td>
<td>2(3.2%)</td>
<td>8(12.9%)</td>
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</tr>
<tr>
<td>3</td>
<td>1(1.6%)</td>
<td>8(12.9%)</td>
<td>13(21%)</td>
</tr>
<tr>
<td>4</td>
<td>2(3.2%)</td>
<td>6(9.7%)</td>
<td>2(3.2%)</td>
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<td>6(9.7%)</td>
<td>23(37.1%)</td>
<td>33(53.2%)</td>
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</table>

P2-d2-800 Thyroid 2

Treatment with methimazole in a 3-year-old male with thyroid hormone resistance

Sarah L. Tsai; Alexandra Ahmet

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Background: Thyroid hormone resistance (THR) syndromes are disorders in which there is decreased end-organ responsiveness to thyroid hormone. Patients typically present with elevated levels of thyroxine (T4) and triiodothyronine (T3) with a normal or increased serum thyroid stimulating hormone (TSH) concentration. This is the first reported case in which methimazole has been used to treat thyrotoxic symptoms in a patient with THR.

Case description: The patient is a male of Western European Caucasian ethnicity who was noted to have tachycardia at 6 months of age. He had persistently elevated free T4 (range 23.6-35 pmol/L, normal 8.7-16.0 pmol/L) and normal/mildly elevated TSH (range 3.98-5.97 mIU/L, normal 0.5-5.5 mIU/L) for the first 2 years of life. At 2 years of age, he was noted to have sinus tachycardia, a mildly enlarged thyroid, hyperactive behavior, and subtle developmental delay. The patient developed worsening hyperactivity, poor sleep, delayed developmental milestones, and had no weight gain over the subsequent 9 months. He was started on methimazole (0.3 mg/kg/day initially, then increased to 0.5 mg/kg/day due to lack of clinical response) at age 3 years to treat his symptoms. Since starting the medication, he has gained weight and his sleep patterns and behavior have markedly improved. Linear growth is appropriate for age. He remains mildly tachycardic and his thyroid has become more enlarged. The patient has a de novo mutation in the thyroid hormone receptor (TR) beta gene, which has been described in previous studies.

Conclusions: Methimazole has improved thyrotoxic symptoms in a 3 year old male with thyroid hormone resistance. The use of methimazole for this purpose has not been described previously.

P2-d2-802 Thyroid 2

Predictive factors of cognitive outcome in children with Congenital Hypothyroidism detected by neonatal screening

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Background: Children with Congenital Hypothyroidism (CH), if left untreated, are at risk for impaired cognitive development. The Portuguese CH Neonatal Screening Program began in 1981 and allows early detection and treatment. Nevertheless mild impairments in cognitive performances make neuropsychological follow-up mandatory.

Objective: To evaluate the role of the screening range of serum TSH, underlying etiology, age at onset of treatment, normalization time of free T4 and TSH and treatment compliance in the neuropsychological outcome of CH patients.

Population and methods: We studied 23 children detected by neonatal screening between 2002 and 2007 followed in our department. They were assessed with the Griffiths Mental Development Scale. Data were obtained from the medical records.

Results: The CH screening test was performed at a mean age of 5.3 days. Thyroid agenesis/hypoplasia accounted for 47.8% of cases, ectopia for 34.8% and dyshormonogenesis for 17.4%. Treatment was started at a mean age of 13.7 days. Normal levels of free T4 and TSH were achieved at a mean age of 30.6 and 87.4 days of life, respectively. The family of one patient had a poor compliance to treatment. Cognitive evaluation was performed between 25 and 59 months of age (mean 41.7±7). The mean General Quotient (GQ) was 97.6; 4 children (17.4%) rating below the normal range (GQ<88). The group with a normal GQ had a statistically significant correlation with a more rapidly normalization of serum free T4. Mean TSH at screening and time to it’s normalization were also lower in this group, although without statistical significance.

<table>
<thead>
<tr>
<th>General Quotient ≥ 88 (n=19)</th>
<th>General Quotient &lt; 88 (n=4)</th>
<th>Test</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
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<td>201.9</td>
<td>T-test (Significance level = 0.05)</td>
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<td>Mean age at first normal serum free T4 (days)</td>
<td>25.7</td>
<td>50.3</td>
<td>T-test (Significance level = 0.05)</td>
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<td>88.5</td>
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<td>Etiology</td>
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<tr>
<td>Mean age at onset of treatment (days)</td>
<td>14</td>
<td>11.75</td>
<td>Independent samples Mann-Whitney U Test (Significance level = 0.05)</td>
</tr>
</tbody>
</table>

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Horm Res 2011;76(suppl 2) 251
The most affected functions were Eye and Hand Coordination (43.5%) and Practical Reasoning (34.8%).

Conclusions: Correction of hypothyroxinemia at an earlier age, as described in literature, correlated with a better cognitive outcome. Although 82.6% of these children have a normal GQ, a significant percentage show some signs of minimal brain damage, being fine motor coordination the most affected area.

P2-d2-803 Thyroid 2
Effects of childhood cancer treatment on thyroid gland
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Background: Thyroid dysfunction is a well recognised complication of radiotherapy.

Objective and hypotheses: We aimed to investigate the late side effects of childhood cancer treatment on thyroid gland and functions.

Methods: The study included 120 pediatric cancer patients who were followed in Gazi University Hospital. Thyroid function tests, urine iodine levels and thyroid ultrasound imagings were evaluated. Regarding applied treatment methods, either chemotherapy + radiotherapy (n=68) or chemotherapy (n=52), the patients were divided into two groups. Chi-square test, ANOVA, Kruskal Wallis and Cox regression analysis were used as statistical methods.

Results: The patients in the chemotherapy + radiotherapy group developed hypothyroidism (n=31), heterogeneity in thyroid parenchyma (n=26) nodule in thyroid gland (n=25), increase in thyroid autoantibody level (n=20) and secondary thyroid cancer (n=3). Mean time interval that hypothyroidism was detected after the completion of chemotherapy + radiotherapy treatment was 5.34 ± 3.74 years. This interval for nodule development and secondary thyroid malignancy were 8.74 ± 4.68 and 12.06 ± 2.61 years respectively. In chemotherapy group, patients developed increase in thyroid autoantibody level (n=16), heterogeneity in thyroid parenchyma (n=14), thymeregaly (n=3) and nodule (n=2). Comparison of two groups showed that the incidences of nodule and hypothyroidism development were significantly higher in chemotherapy + radiotherapy group. It was suggested that chemotherapy might have an effect on development of parenchymal heterogeneity and thyroid nodule in both groups. Evaluation of risk factors leading to thyroid function disorder revealed that besides radiotherapy, alkylating agents and antimitabolites also increased the risk of thyroid disorder development.

Conclusions: The incidence of hypothyroidism, and nodule development increased in patients who received radiotherapy. Increased heterogeneity and increment in thyroid autoantibody level in chemotherapy group drew attention.

P2-d2-804 Thyroid 2
Effects of long-term idiopathic subclinical hypothyroidism on lipid profile and endothelial function
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1University Federico II, Department of Pediatrics, Naples, Italy; 2University Federico II, Department of Clinical Medicine and Cardiovascular Sciences, Naples, Italy

Background: Subclinical hypothyroidism (SH) is a biochemical condition characterized by increased serum levels of TSH with normal values of FT4. In SH children treatment is controversial for TSH values between 4.5 and 10 mIU/L. In adults SH has been associated with abnormalities in lipid profile and increased risk of atherosclerosis, while data in untreated SH children are scanty.

Objective and hypotheses: The aim of this cross-sectional controlled study was to evaluate in children the effects of long term untreated SH on lipid profile and endothelial function.

Methods: At study entry 20 children with long-term (3.5±0.5 years) SH, aged 9.7±0.6 years, underwent height, weight and BMI measurements and lipid profile evaluation. BMI was expressed as standard deviation score (SDS). Flow-mediated dilatation (FMD), an early marker of atherosclerotic event, was assessed by brachial Doppler ultrasound. Twenty age and sex matched children were used as controls.

Results: In SH children and in controls BMI (0.2±0.2 vs -0.3±0.3 SDS) total cholesterol (TC) (149.6±7.4 vs 141.8±7.5 mg/dl), LDL-cholesterol (LDL-C) (85.2±5.2 vs 81.6±4.7 mg/dl), triglycerides (TG) (72.0±8.3 vs 66.0±5.1 mg/dl) and atherogenic index (3.1±0.2 vs 2.8±0.1) were similar. HDL-cholesterol (HDL-C) was lower in SH children compared with controls (50.3±3.2 vs 68.0±7.8 mg/dl, p<0.05). No significant differences in mean FMD values (12.3±1.2% vs 12.9±1.1%) were observed between the two groups.

Conclusions: Long-term duration of untreated SH in children is not associated with significant abnormalities of lipid profile and endothelial function. However, the mild decrease in HDL-C might represent a first change in lipid profile. Therefore studies on a larger number of patients are needed to further clarify if SH in childhood is associated with subclinical abnormalities that may require levothyroxine treatment.

P2-d2-805 Thyroid 2
Which TSH response level to TRH test should be accepted for thyroid hormone replacement in Hashimoto’s thyroiditis?
Enver Simsek1; Yildiz Dallar2; Beray Selver3; Semra Celinkaya4; Cigdem Binay1; Kenan Kocabay2
1Eskisehir Osmangazi University School of Medicine, Paediatric Endocrinology, Eskisehir, Turkey; 2Dr.Sami Ulus Children Training and Research Hospital, Paediatrics, Ankara, Turkey; 3Dr.Sami Ulus Children Training and Research Hospital, Paediatric Endocrinology, Ankara, Turkey; 4Eskisehir Osmangazi University School of Medicine, Paediatrics, Eskisehir, Turkey; 5Duzce University School of Medicine, Paediatrics, Duzce, Turkey

Background: Hashimoto’s thyroiditis (HT) is the most common acquired thyroid disease in adolescents. The clinical presentations are different according to the thyroid hormone levels at the diagnosis. There was no consensus on the beginning of thyroid hormone replacement in the cases of Hashimoto’s thyroiditis.

Objective: To compare TSH response level to TRH test in different thyroid diseases and normal subjects. The second purpose of this study was to investigate the cut-off point of TSH level for thyroid hormone replacement treatment.

Population and method: This study includes 194 TRH test in different thyroid diseases and normal subjects. Between the age of 6.2 years old and 17.7 years old (details of the cases were given in Table-1). A bolus dose of Thyrotropin-releasing hormone (5 microgram/kg, maximum 200 microgram) was given and blood samples were taken at 0, 20, 40 and 60 min for measurement of TSH level.

Results: All TSH levels of different groups were statistically different (p<0.001). There was also statistical important difference between control subjects and Hashimoto’s thyroiditis with euthyroidism (p<0.001). The mean stimulated TSH levels in the group of Hashimoto’s thyroiditis with compensatory hypothyroidism showed pituitary thyrotrrop cell hyperplasia.

<table>
<thead>
<tr>
<th>Time</th>
<th>Groups</th>
<th>Number</th>
<th>Mean TSH levels (mIU/L)</th>
<th>Standard Deviation</th>
<th>95% CI Lower Bound</th>
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A female baby, born after an uneventful induced twin pregnancy, had a massive parotidal infantile hemangioma. Massive infantile hemangiomas (IH) and consumptive hypothyroidism, associated with large IH, depends on the effectiveness of treatment aiming at reducing the IH. Propranolol successfully decreased the significant size of the parotidal IH and should currently be suggested as an effective first-line therapeutic approach in treating massive IH.

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Conclusion: This study showed that the old test, TRH stimulation test, preserves its value in thyroid disease. To the best of our knowledge, there is no study in literature for the timing of thyroid hormone replacement in Hashimoto’s disease. Thyroid hormone replacement in Hashimoto’s thyroiditis has been commenced usually in compensated hypothyroidism or evident hypothyroidism. This study showed that, there was severe thyrotroph hyperplasia in patient with subclinical hypothyroidism in Hashimoto’s thyroiditis. We suggested that thyroid hormone replacement should be commenced earlier than compensated hypothyroidism in Hashimoto’s thyroiditis.

P2-d2-808 Thyroid 2

Difficult treatment of consumptive hypothyroidism in a child with a massive parotidal infantile hemangioma

Maria Cristina Vignone1; Francesca Cortinovis1; Marianna Di Frenna1; Arianna Passoni1; Sarah Rabbiosi1; Lorenzo Andrea Bassi1; Luca Persani2; Giuseppe Chiumello2; Carlo Gelmetti2; Giovanna Weber1

Vita-Salute San Raffaele University, Pediatrics, Milan, Italy; 2IRCCS Maggiore Policlinico, Anaesthesia, Intensive Care Unit and Dermatologic Sciences, Milan, Italy

Background: Massive infantile hemangiomas (IH) and consumptive hypothyroidism are rare conditions. This type of hypothyroidism is characterized by refractoriness to high doses of L-Thyroxine (L-T4).

Objective and hypotheses: In this case report we tried to clarify the mechanisms involved in the etiopathogenesis of hypothyroidism associated to IH and to evaluate the most appropriate therapeutic approach to obtain the regression of the IH.

Methods: A female baby, born after an uneventful induced twin pregnancy, presented a vascular lesion, which was diagnosed as IH of the left parotid gland, with extension to thyroid gland. The child was identified by the neonatal screening for CH and successively serum thyroid tests (TSH 174µU/mL, fT4 25.6pmol/L) and thyroid ultrasonography confirmed CH due to severe thyroid hypoplasia. Consequently L-T4 replacement therapy was initiated at a dose of 13 mcg/kg/day at 7 days of life.

Results: The IH increased in volume over time and the child presented severe hypothyroidism refractory to high doses of L-T4 therapy. The concentration of fT3 was elevated, so an excessive conversion of thyroid hormones by high D3 in the tumor was thought to be the underlying cause. Hormonal thyroid parameters improved concomitantly with involution of the IH, temporarily after corticosteroid treatment and then completely after introduction of propranolol (2mg/kg/day).

Conclusions: Normalization of thyroid function in children affected by consumptive hypothyroidism, associated with large IH, depends on the effectiveness of treatment aiming at reducing the IH. Propranolol successfully decreased the significant size of the parotidal IH and should currently be suggested as an effective first-line therapeutic approach in treating massive IH.

P2-d3-808 Thyroid 3

Congenital hypothyroidism screening program in Turkey: cut-off level for TSH and evaluation of the factors affecting the time of treatment initiation

Gül Yeşiltepe Mutlu1; Elif Ozsu2; Nilufer Çizmecioglu2; Sukru Hatun2

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Aim: We aimed to evaluate national CH screening program in terms of TSH cut-off level, frequency of cases which required treatment and the stages before treatment.

Methods: All babies (n: 25188) who were born in 2009 were evaluated. 107 babies required investigation with venous thyroid function tests because of having TSH levels in first heel blood samples >50 mIU/L or a level >15 mIU/L. In the second heel blood samples. Only 89 of these 107 patients could be contacted. Their previous laboratory data including heel samples and venous thyroid function tests (TSH, free T4 or total T4 levels) and current venous thyroid function tests, were analyzed.

Results: Heel blood samples (n: 49755) were taken from 25188 babies born in our region. TSH levels of 3355 babies in first sampling were greater than the cut-off level 15 mIU/L (recall rate was 13.3%). Venous sampling was required for 107 babies and 39 of them needed to be treated (treatment rate was 1/645). 11 of the babies who were treated were diagnosed with thyroid dysgenesis. The mean age for starting the treatment was 38.5±57.8 days. 60.3% of the babies whose heel samplings were suggestive of CH had impact venous thyroid function tests, were analyzed.

Conclusion: Taking two samples for CH screening may increase the cost of the program. Recall rate is high but raising the cut off level for TSH may lead to miss out the diagnosis of thyroid dysgenesis.

P2-d3-808 Thyroid 3

Abstract withdrawn.
P2-d3-809 Thyroid 3

A case of primary hypothyroidism with stimulated pituitary adenoma associated with hyperprolactinaemia and irregular vaginal bleeding

Maia Rekviashvili1; Ekaterine Kvaratskeliia; David Metreveli1; Rolf Peter Willig1
1JSC “Vere XXI”, Department of Physical and Sexual Development of Children and Adolescents, Tbilisi, Georgia; 2LTD “Enmedic”, Clinic for Diabetes, Endocrinology and Nutrition, Tbilisi, Georgia; 3Endokrinologikum Hamburg, Pediatrics, Hamburg, Germany

Background: In severe hypothyroidism TRH raises causing high prolactin levels due to a proliferation of prolactin secreting cells. It resembles the development of an adenoma like new formation in pituitary gland.

Objective and hypotheses: We describe a patient with a prolactin secreting adenoma of the pituitary gland stimulated by hypothyroidism.

Methods: A case report.

Results: We report a 11.1 years old girl: the complaints were tiredness, a tendency to the face, vaginal bleeding and bed time. She was treated for hypothyroidism. After 1 month of treatment the prolactin level dropped from 102 ng/mL to 11.5 ng/mL.

Conclusions: This case shows that severe hypothyroidism can mimic an adenoma of the pituitary gland by hyperprolactinemia.

P2-d3-810 Thyroid 3

Association of HLA alleles with autoimmune thyroid disease in Korean children

Won Kyung Choi1; Moon Hee Lee1; Choi Yun Jung1; Park So Hyun1; Hahn Seung Hoon1; Jung Min Ho1; Choi Hee-Baeg2; Kim Tai-Gyu3; Suh Byung-Kyu1
1College of Medicine, The Catholic University of Korea, Department of Pediatrics, Seoul, Republic of Korea; 2College of Medicine, The Catholic University of Korea, Catholic Hematopoietic Stem Cell Bank, Seoul, Republic of Korea; 3College of Medicine, The Catholic University of Korea, Department of Microbiology, Catholic Hematopoietic Stem Cell Bank, Seoul, Republic of Korea

Background: Data regarding differences in the genetic background of Hashimoto thyroid disease (HT) and Graves disease (GD) in Korean children are lacking.

Objective and hypotheses: We aim to analyse the association of the class I and II alleles in Korean children. The frequencies of the HLA-A, -B, -C, -DRB1 genotypes and the allelic association with autoimmune thyroid disease (AITD) in Korean children.

Methods: Between March 2009 and February 2010, 159 normal healthy children attending Seoul St. Mary’s Hospital and Yeouido St. Mary’s Hospital were recruited. We analyzed the polymorphism of HLA-A, -B, -C, -DRB1 alleles by PCR-SSP, and compared with those of 159 normal healthy children attending Seoul St. Mary’s Hospital and Yeouido St. Mary’s Hospital.

Results: There were significant increases in the allele frequencies of HLA-A*02, -B*46, -Cw*01 and -DRB1*08 in HT and GD, and no significant differences in allele frequencies between HT and GD. The risk of AITD in the presence of both HLA-B*46 and -Cw*01 is higher than the presence of either alleles alone.

Conclusions: The susceptible and protectable alleles observed in HT are similar to those observed in GD. Coexistence of HLA-B*46 and -Cw*01 may be a genetic gene marker to Korean children with AITD.

P2-d3-811 Thyroid 3

Factors associated with thyroid function abnormalities in HIV-infected children

Kayode Adeniran1; Zeev Hochberg2; Austeen Omoigberale3
1Federal Medical Centre, Paediatric, Asaba, Nigeria; 2Meyer Children’s Hospital, Rambam Medical Centre, Paediatric Endocrinology, Haifa, Israel; 3University of Benin Teaching Hospital, Child Health, Benin, Nigeria

Background: It has been shown that specific patterns of abnormal thyroid function test findings are frequently identified among HIV-infected adult patients. Thyroid dysfunction may exist in HIV-infected children, most of the studies regarding thyroid dysfunction in HIV infected children have reported incidence or prevalence of this condition. Although factors implicated in the causation of thyroid abnormalities are fairly well studied in the adult populations. However, there is paucity of information in children.

Objectives: To study thyroid function of HIV-infected children and to ascertain factors that may affect their thyroid function.

Methodology: One hundred HIV-infected children were enrolled into the study. Information such as age, age at diagnosis, gender, height/length, weight (calculated BMI), presence of other disease (Tuberculosis and opportunistic infections), medications and findings on examination were documented. 5 milliliters of blood was collected from each of the enrolled using aseptic techniques. The blood obtain was placed in a plain test tube and serum was collected. The samples were stored at -8 degrees until they were Analyzed (free T3, free T4, TSH) by competitive enzyme immunosorbent assay (ELISA) method, from the same sample the CD4 count was done before it was frozen.

Results: The mean age of the patients and age at diagnosis was 6.47±3.47 and 3.86±3.36 respectively. The mean serum levels of free T3 and T4 was (6.05±1.51 and 3.97±1.84)pmol/L and TSH 5.04±3.37 µIU/ml. Mean CD4 count was 648.17±408.47cells/µL. The following factors were observed to affect the thyroid function of the patients in this study: Duration of the disease, immunologic status, severe or advanced disease stage and anti Tuberculosis drugs.

Conclusions: This study shows that children with HIV infection may have subclinical hypothyroidism. We advice close monitoring of the thyroid function in HIV/AIDS children with disease duration above 2 years, severe or advanced disease and those on anti TB drugs.

P2-d3-812 Thyroid 3

Identification of CYP21A2 mutations in Czech patients with 21 – hydroxylase deficiency – structural analysis of chimeric gene

Zuzana Hruša; Eva Stahlova Hrabínová; Lenka Fajkusová; Zuzana Vrzalova
Center of Molecular Biology and Gene Therapy, Dpt. of Internal Medicine - Hematooncology, University Hospital Brno and Faculty of Medicine, Brno, Czech Republic

Background: Congenital adrenal hyperplasia (CAH) comprises a group of autosomal recessive disorders caused by an enzymatic deficiency. Approximately 90% of all CAH cases is associated with mutations in the steroid 21-hydroxylase gene (CYP21A2). The CYP21A2 gene and its inactive pseudogene (CYP21A1P) are located within the HTA region on chromosome 6p21.3. Their intergenic recombinations are responsible for about 95% of mutations.

Objective and hypotheses: In 267 Czech probands with 21-hydroxylase deficiency were identified 30 different CYP21A2 mutant alleles (4 of them were not described so far). The most frequent mutation, a chimeric CYP21A1P/ CYP21A2 gene, was found in 33,7% of mutant alleles (a new type designated...
CH-7 was characterized). Small DNA rearrangements of the CYP21A2 gene were present in 59.2% of mutant alleles (3 novel point mutations were detected). Total deletions of CYP21A2 were detected in 4.9% and duplications of CYP21A2 associated with a mutation on both copies were detected in 4.4% of mutated alleles.

Methods: Mutations in CYP21A2 gene were determined using a long-range PCR, secondary PCR and restriction analysis, direct sequencing, and MLPA method.

Results: In the set of 90 patients, we identified four types of chimeric CYP21A1P/CYP21A2 genes. The most common type was the newly characterized CH-7 type (21.4% of mutant alleles). We performed a detailed sequence analysis of chimeric CYP21A1P/CYP21A2 genes to determine the breakpoints in CYP21A1P/CYP21A2 conversion areas. All chimeric genes have the CYP21A1P promoter and p.Pro303Leu mutation in exon 1 but differ in the presence of other mutations and polymorphisms.

Conclusions: Our genotyping approach allowed accurate identification of CYP21A2 gene mutations in 21-hydroxylase deficiency patients and their families and can be used for final confirmation of diagnosis and for the prenatal diagnostics.

P2-d3-813 Thyroid 3
Is there a true increase in the prevalence of congenital hypothyroidism? 30 years of nationwide screening
Joseph Sack
Ministry of Health, Community Genetics, Tel Aviv, Israel

Background: A steady increase of Congenital Hypothyroidism (CH) among newborns has recently been reported in the USA. In Israel, a nationwide screening exists since 1978 covering 99% of the general population. The primary marker has been TT4 with a secondary TSH (above 40 mIU/L).

Objective and hypotheses: To study the prevalence of CH in the Israeli newborn-born populations (Jews and Arabs) and to find whether there is an overall change in the prevalence with time.

Methods: For the years 1970-2008, data were collected from the Israeli Bureau of Statistics. The data was analyzed based on ethnicity (Jews and Arabs). In order to avoid the large number of false positive, CH was defined for this study as low TT4 and TSH above 80 mIU/L.

Results: Image

Conclusions: During the study period there was a twofold increase in the number of newborns screened. There is a yearly prevalence fluctuation but there was no increase in CH in the overall population and not in either the Arab or Jewish populations.

P2-d3-814 Thyroid 3
Thyroid carcinoma in 12 children-characteristics and management
Feride Tahmiscioglu Bucak1; Oya Ercan1; Bahar Ozcab1; Ozge Yural Topuz2; Levent Babasaka2; Olicay Elyavgyliu1
1Istanbul University Cerrahpasa Medical Faculty, Pediatric Endocrinology, Istanbul, Turkey; 2Istanbul University Cerrahpasa Medical Faculty, Nuclear Medicine Department, Istanbul, Turkey

Background/aim: Thyroid cancer is rare in the pediatric and adolescent population. Female sex is a risk factor. The majority are well-differentiated thyroid carcinoma. Pediatric differentiated thyroid carcinoma (DTC) often presents at a more advanced stage than the adult variant. The aim of this retrospective study is to report the characteristics and management of 12 children with thyroid carcinoma referred to our clinic after thyroidecomy.

Patient characteristics-management: Of the twelve patients with thyroid carcinoma, 9 were girls. Age at diagnosis ranged from 3 to 13 years (median 8.75). Four patients had undergone total thyroidecomy (TT), 4 TT + modified radical neck dissection (MRND), 2 TT+MRND+ thyrosectomy and 1 right hemihyphyotomy- isthmusectomy and 1 right hemihyphyotomy -lent subtotal lobectomy. Post-operative hypoparathyroidism was observed in 9 patients, two had temporary hypocalcemia. Histopathological diagnosis was papillary thyroid cancer (PTC) in 4, PTC follicular variant in 5 and minimal invasive follicular carcinoma in 2. One had medullary thyroid carcinoma due to MEN type 2A. Six patients had regional nodal metastases; none of them had distant metastases. Ten patients received radioiodine ablation therapy (RIAT) at doses ranging from 30-120 mCi for 1-6 times. The total follow up period was 71,9 (median) 4.45 years for 12 patients. A detectable TG level measured while TSH levels were elevated was considered to be associated with recurrent disease in patients who received RIAT. Patients were treated with both L-T3 and L-T4 under 14 years of age but with only L-T4 after 14 years of age for TSH supression.

Conclusions: Female predominance was observed in a dozen of paediatric thyroid cancer patients all with DTC. Half of the patients had regional metastases already at presentation. Permanent hypoparathyroidism was frequent after surgery. Postoperative management needs to be tailored individually.

P2-d3-815 Thyroid 3
Analysis of serum levels of nesfatin in children and adolescents with autoimmune thyroid diseases
Beata Sawicka1; Artur Bossowski1; Beata Zelazowska- Rutkowska1; Edyta Pietrewicz1; Beata Noszka1; Beata Sawicka1; Beata Zelazowska- Rutkowska1; Edyta Pietrewicz1; Beata Noszka1
1Medical University in Bialystok, Department Of Pediatrics, Endocrinology, Diabetology with Cardiology Division, Bialystok, Poland; 2Medical University in Bialystok, Department Of Pediatric Labolatory Diagnostics, Bialystok, Poland

Background: Thyroid disease is leading to a change of weight. It is emphasized that changes in hormones such as peptide levels are in close relationship with regulation of body mass. Nesfatin is a recently described anorexigenic peptide produced by the brain. Nesfatin also reduces body weight gain, suggesting a role as a new modulator of energy balance. Excess nesfatin in the brain leads to a loss of appetite, less frequent hunger, a sense of fullness, and a drop in body fat and weight. A lack of nesfatin in the brain leads to an increase of appetite, more frequent episodes of hunger, an increase of body fat and weight, and the inability to feel full.

Objective and hypotheses: The aim of the study was to evaluate nesfatin levels in young patients with untreated Graves’ disease, subclinical Hashimoto’s thyroiditis and in healthy children. The study group formed 78 patients of the Outpatient Endocrinology of the Department of Pediatrics, Endocrinology, Diabetology with Cardiology Division.

Methods: In all patients nesfatin level was analyzed by ELISA’s method.

Results: In group with hyperthyroidism in Graves’ disease we found lower levels of nesfatin in the brain leads to a loss of appetite, less frequent hunger, a sense of fullness, and a drop in body fat and weight. A lack of nesfatin in the brain leads to an increase of appetite, more frequent episodes of hunger, an increase of body fat and weight, and the inability to feel full.
levels of nesfatin compared to a control group (14.5±32.96ng/ml; NS). We did not observe relationship between nesfatin and thyroid hormones.

Conclusions: We suggested that disturbances in thyroid hormones in thyroid diseases have not an essential effect on changes of hormone controlled appetite-nesfatin. Secondly, nesfatin levels were lower in children with untreated autoimmune thyroid diseases, but mechanism is also unknown.

P2-d3-816 Thyroid 3
Neck mass in an adolescent boy
Vera Zitrovicovic1; Silvija Sajic1; Dragani Vukanic1; Vladislav Bojic1; Maja Jesic1; Marija Mandic1; Zeljko Smoljancic1; Sanja Trajkovic1
1University Children Hospital, Endocrinology, Belgrade, Serbia; 2University Children Hospital, Surgery, Belgrade, Serbia; 3University Children Hospital, Radiology, Belgrade, Serbia; 4University Children Hospital, Anesthesiology, Belgrade, Serbia

Background: Neck masses are not common in childhood. The differential diagnosis include congenital lesions and their complications, lymphadenopathy, vascular, inflammatory and malignant lesions.

Objective and hypotheses: The objective is to present a boy with neck and mediastinal mass.

Methods and results: A 14-year-old patient was referred because of asymptomatic goitre. An enlarging mass was noticed 9 months ago. On the examination a painless, non-tender, firm, mobile, nontender mass was palpable. Ultrasound revealed a normal thyroid gland, with an enlarged right lobe containing a hypo-hyperreflective mass (8x4x5 cm). The patient was started on levothyroxine and an imaging study was performed. Computed tomography scans of the neck and chest revealed a mass in the right lobe of the thyroid gland adjacent to the trachea and mediastinum. It was thought to be lymphoma, as the commonest mediastinal mass. After the intervention the left thyroid lobectomy was done because mass was in a close contact with it. Pathohistological finding was normal thyroid gland and solid papillary carcinoma in the extirpated tumor. The plan is to perform a total thyroidectomy with dissection of lymph glands and to give the radioiodine.

Conclusions: We report a patient who presented with a neck and mediastinal mass thought to be lymphoma, as the commonest mediastinal mass. After the preoperative investigation and scintigraphy we did not expect to find a thyroid tissue in a biopsy. Since the papillary carcinoma was the final diagnosis, total thyroidectomy might have been a preferable option to avoid unnecessary risks.

P2-d3-817 Thyroid 3
Graves’ disease 3 years after classical autoimmune hypothyroidism in a 16 year old girl
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Doncaster Royal Infirmary, Department of Paediatrics, Doncaster, United Kingdom

Background: Hypothyroidism following Graves’ hyperthyroidism both spontaneously or after anti-thyroid drug treatment is well known, and is believed to be due to destruction of the thyroid gland or the appearance of blocking thyroid-stimulating hormones (TSH) receptor antibodies. However, the development of hyperthyroidism following primary hypothyroidism is uncommon and the mechanism of this phenomenon is unknown.

Presentation: AC, 13 year old girl presented with goitre, a raised TSH (>150) and a FT4 of <5 with TPO Ab (thyroid peroxidase antibodies) of 818 and a diagnosis of autoimmune hypothyroidism was made. She was commenced on thyroxine following which her symptoms improved and bloods normalised. She presented 3 years later with weight loss, goitre, tremors and palpitations. On examination there was a palpable, symmetrical goitre that was noticed 8 months ago. The thyroid scan revealed a decreased uptake with a cold area that was consistent with a lymph node that was not present on the earlier scan. Biochemistry, bone marrow aspiration and tumor markers were normal. US detected were normal thyroid gland and solid papillary carcinoma in the extirpated thyroid gland if necessary. During the intervention the left thyroid lobectomy was done because mass was in a close contact with it. Pathohistological finding was normal thyroid gland and solid papillary carcinoma in the extirpated tumor. The plan is to perform a total thyroidectomy with dissection of lymph glands and to give the radioiodine.

Conclusions: In summary, our patient developed hyperthyroidism 3 years after classical autoimmune hypothyroidism. Though, a rarity in the paediatric setting, it is important to be aware that hyperthyroidism due to autoimmune disease may not be a permanent state and that hyperthyroidism can develop in some patients.

P2-d3-818 Thyroid 4
Von WillebrandFactor, soluble ICAM and VCAM, as indices of endothelial activation, in patients with congenital hypothyroidism
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1Isfahan Endocrine & Metabolism Research Center, Isfahan University of Medical Sciences, Pediatrics, Isfahan, Islamic Republic of Iran; 2Child Health Research Center, Isfahan University of Medical Sciences, Pediatrics, Isfahan, Islamic Republic of Iran; 3Isfahan Endocrine & Metabolism Research Center, Isfahan University of Medical Sciences, Internal Medicine, Isfahan, Islamic Republic of Iran; 4Applied Physiology Research Center, Isfahan University of Medical Sciences, Physiology, Isfahan, Islamic Republic of Iran

Background: The prevalence of congenital hypothyroidism (CH) in Isfahan is high and there is the possible involvement of endothelial dysfunction in the pathogenesis of CH.

Objective and hypotheses: Due to the lack of studies in this field, the aim of this study was to determine endothelial function among CH patients.

Methods: During this case control study, endothelial function in CH patients and those with normal screening results was evaluated during CH screening in Isfahan. Peripheral blood samples were obtained for Von-Willebrand factor (vWF), Intracellular and Vascular cell adhesion molecule (ICAM &VCAM) measurements. In CH patients these biomarkers measured before and 4 weeks after treatment.

Results: During this study 56 neonates were studied; 30 of them as neonates with normal screening results and 26 with diagnosed CH in two different groups according to their TSH levels. Mean of ICAM, VCAM was higher in CH patients than control group(P<0.05). Mean of ICAM, VCAM decreased significantly after treatment in CH patients (P<0.05). There isn’t significant relationship between TSH and ICAM, VCAM and vWF (P<0.05).

Conclusions: The findings of this study demonstrated the possible involvement of endothelial system in the pathogenesis of CH and its cardiovascular complication. Further studies with larger sample size and with the measurement of other endothelial function markers is needed.

P2-d3-819 Thyroid 4
Clinical characteristics and immunological profile of basic and costimulatory molecules on T cells in children with Hashimoto’s thyroiditis
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Background: The Hashimoto’s thyroiditis is a consequence of pathological immune responses for thyroid autoantigens. The most important loci associated with autoimmune thyroiditis are HLA and CTLA-4 gene. The aim of the study was to specify the immune profile of peripheral T cells in children with HT, and to correlate it with clinical characteristics.

Material: One hundred children were examined: 45 with autoimmune thyroiditis and 55 healthy age- matched controls.

Methods: The T cell phenotype was evaluated by the flow cytometer Beckman Coulter EPICS XL 4C. Analysis was performed with the use of the combination: CD4- FITC/ CD28 -PE/ CD152 -PE and CD8- FITC/ CD28 -PCS/
CD152 - PE. Surface and intracellular T cell phenotype was evaluated at the baseline and after activation. TSH value and thyroid autoantibodies were evaluated by MEIA. Statistical analysis was performed using T-test, Mann-Whitney U-test, and the Pearson correlation test.

Results: At the baseline and after PHA activation the number of T cells with surface expression of CD152 was lower than in healthy controls (p<0.05). This difference was stronger at the baseline mainly in CD4+CD152+ subset and after activation mainly in CD8+CD152+ subset. Intracellular expression of CD152 did not differ in patients and controls at the baseline and increased after activation. The number of CD28+ T cells did not differ significantly. Anti TPO and anti Tg antibodies were higher in children with lower number of T cells with surface expression of CD152. The primary hypothyroidism was confirmed in 5 children and did not correlate with T cell phenotypes.

Conclusions: Children with HT have different immunological T cells profile than healthy children, especially in CD4+CD152+ and CD8+CD152+ T cell subsets. The only correlation with clinical markers is the negative correlation between thyroid autoantibodies level and the number of T cells expressed CTLA-4.

P2-d3-820 Thyroid 4
Thyroid hemiagenesis in two boys born small for gestational age-just one a coincidence?  
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Background: Thyroid hemiagenesis is a very rare anatomical abnormality in which one lobe of the thyroid gland fails to develop. The prevalence of this anomaly in systematic ultrasound studies in unselected population is estimated to be 0.05%. Being born small for gestational age (SGA) is a result of intrauterine growth restriction during critical phases of fetal development. The incidence of SGA is estimated to be 5% of the general population. A suboptimal intrauterine environment may have a detrimental influence on thyroid development. The purpose of this report is to present two cases of SGA boys with incidentally discovered agenesis of the left thyroid lobe and isthmus.

Results: Patient 1: An 11-year-old SGA boy was admitted to the Endocrinology Department with a 4-year history of short stature. His birth weight was 1500 g (~4.3 SD). His height was 130 cm (~2.7 SD), thyroid gland was not palpable. The concentrations of: TSH 7.8 mU/l, N: 0.3-5.0, fT4 10.9 pmol/l, N: 8.5-24 and fT3 3.1 pmol/l, N: 2.2-5.3, thyroid antibodies negative. Ultrasound failed to demonstrate either the left lobe of the thyroid gland or isthmus. The volume of the right lobe was 3 ml and normal echogenicity. Results were confirmed by technetium 99 scan of the thyroid which showed no activity of the left lobe. Patient 2: An 8-year-old boy was referred for ultrasound examination of the neck because of the enlargement of cervical lymph nodes during the course of mononucleosis. His birth weight was 1446 g (~3.9 SD). At the time of presentation he was asymptomatic, his height was 144.7 cm (2.86 SD). Thyroid function: TSH 1.9 mU/l, fT4 15.2 pmol/l, fT3 4.47 pmol/l, thyroid antibodies negative. Ultrasound showed no thyroid tissue on the left side. The volume of the right lobe was 2.86 ml with normal echogenicity and vascularization on color Doppler examination, the isthmus was absent.

Conclusions: The occurrence of thyroid hemiagenesis in SGA children is higher than would be expected from chance alone. It raises a question if it is a coincidence or unique correlation.

P2-d3-821 Thyroid 4
Follicular adenoma in goitrous congenital hypothyroidism due to thyroid peroxidase gene mutation in a Chinese patient  
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Background: Thyroid dysormonogenesis accounts for 10 – 20% of all cases of congenital hypothyroidism (CHT). Majority of cases are due to thyroid peroxidase (TPO) gene mutation, and the commonest mutation detected among Chinese population is c.2268insT. Besides, TPO gene mutation had been reported to be associated with thyroid follicular adenoma and carcinoma. Objective and hypotheses: We report a case of thyroid dysormonogenesis with c.2268insT mutation in TPO gene who had multinodular goitre and subsequently developed thyroid follicular adenoma.

Case: A Chinese girl was detected to have congenital hypothyroidism by neonatal hypothyroid screening and received treatment since birth. At 3 years old, diagnosis of thyroid dysormonogenesis was made based on normal thyroid Technetium (99Tmc) scan but persistent dependency on thyroxine treatment. At 12 years old she developed multinodular goitre despite adequate thyroxine replacement with normal thyrotropin (TSH) and negative thyroid antibody screening. Genetic analysis found that she was homozygous for c.2268insT mutation in TPO gene. At the age of 20 years, suspicious features were detected on ultrasound surveillance of the thyroid with elevated thyroglobulin (hTg) level. Total thyroidectomy was performed after initial fine needle aspiration cytology (FNAC) reported as follicular neoplasm. The final tissue diagnosis was thyroid follicular adenoma. Her hTg level returned to normal after thyroidectomy and there was no change in thyroxine requirement.

Conclusions: Genetic diagnosis is important to identify susceptible patient with thyroid dysormonogenesis who may develop thyroid neoplasm. A careful surveillance for potential thyroid neoplasm in such patients with clinical, biochemical and imaging assessment is necessary. In a multiracial community, knowledge in common genetic mutation from different ethnic background further enhances the understanding and management of such cases.

P2-d3-822 Thyroid 4
Ectopic thymic tissue in the thyroid gland - ultrasound features  
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Background: Although very rare there is a possibility that during the embryogenesis a small part of the thymus may malmigrate during its descend and unfold as a part of the thyroid gland. Evenhough it does not pose any threat to a patient, it is usually mistaken for a malignant tumor and is a cause of surgical intervention. The purpose of this study is to present our experience and to create a list of characteristic features of the thymic tissue in the thyroid gland.

Methods: We present a group of 10 children (6 boys, 4 girls) all aged <12 y.o. All of them were clinically-wise and laboratory-wise free from any thyroid gland disorders. All findings were accidental and occurred during standard thyroid examinations. In each of them we found small (3-7mm) focal changes which we diagnosed as intrathyroidal thymic tissue. In 2 cases biopsy confirmed our diagnosis and in 1 case we had a post-surgery confirmation. Other children are being observed.

Results: We suggest that the features that allow to diagnose the thymic tissue in the thyroid gland are as follows: the location in lower part of the thyroid gland near the parathyroid glands; an irregular shape with less than 1 cm in diameter; reduction of echogenicity with hypecchogenic focuses; no central and low peripheral intraparenchymal blood flow; similarity to the structure of the nearby thymus.

Conclusions: When diagnosing small focal changes in thyroid in children ectopic thymus tissue should be considered a possibility.

P2-d3-823 Thyroid 4
Hearing disorders in children and adolescents with congenital hypothyroidism  
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Background: Congenital hypothyroidism (CH) is one of the most frequent pediatric endocrine conditions. Its prevalence in Russian population by 2010 was 1: 3270. The prenatal and postnatal thyroid hormones deficiency cause negative effect on inner ear development. Recent data shows high incidence of hearing disorders in these patients which may consequently have an effect on social adaptation.
Objective and hypotheses: This study’s objective was to assess auditory function in children and adolescents with CH.

Methods: Hearing examination was carried out by pure tone threshold audiometry (“Interacoustics Clinical Audiometer AC-40”). Fifty-two patients with CH were studied (10.9 ± 4.1 yrs). There were 19 boys (36.5%) and 33 girls (63.5%). All patients received adequate long-term levothyroxine treatment before the examination and were euthyroid at the time of auditory evaluation.

Results: Various impairments of auditory function were identified in 23 patients (42.2%). The majority of affected children (16 of 23 patients) had no complaints of hearing loss. 12 patients had conductive hearing loss, 4 patients had sensorineural hearing loss, and 1 child had high-frequency bilateral conductive hearing loss combined with low-frequency bilateral sensorineural hearing loss. Local increase of hearing threshold for 1-2 frequencies within human speech range through conductive and/or sensorineural pattern was found in 5 patients. Unilateral deafness with abnormality of outer, middle and inner ear development was present in 1 patient. 5 cases of conductive hearing loss were unilateral, 7 – bilateral. All cases of sensorineural hearing loss were bilateral.

Conclusions: High frequency of hearing disturbances in children with CH defines necessity of audiology examination in all children in spite of the absence of complaints.

P2-d3-824 Thyroid 4
A pitfall leading to misdiagnosis of thyroid nodule in an infant: intrathyroidal thymus
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Background: Ectopic intrathyroidal thymus is an embryologic anomaly and has been recently reported to cause invasive diagnostic procedures in children when mistakenly considered as a thyroid nodule. It was shown to regress with advancing age which is parallel to the normal thyimic involution. Thymus has a unique appearance on ultrasound.

Case: A 48 day-old male who was diagnosed with thyroid nodule at another institution was referred to our clinic for evaluation of cervical mass. Ultrasonography revealed an ectopic thymus in attachment with left thyroid lobe and extending into thyroid tissue causing a false appearance of thyroid nodule. A normal thymus was also visualized on its normal localization. Thyroid function tests were normal. No further investigation was needed. The patient has been followed up by clinical and ultrasonographic evaluation.

Conclusions: Reporting this case, we want to emphasize that intrathyroidal thymic inclusions should be considered in the differential diagnosis of the thyroid nodules in children.

P2-d3-825 Thyroid 4
Congenital hypothyroidism referred to a Pediatric Endocrinology Center before and after national thyroid screening in Turkey
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Background: In Turkey, neonatal thyroid screening used to be performed by certain university hospitals with incomplete coverage until 2007, when national neonatal thyroid screening operated by state take over covering all newborns in the country.

Objective: We analysed age of diagnosis and severity of hypothyroidism in 175 patients with congenital hypothyroidism diagnosed by neonatal screening before and after 2007 in our center.

Results: The patients were classified as overt hypothyroidism (highTSH and low freeT4), or compensated hypothyroidism (high TSH and normal freeT4). Compensated hypothyroidism constituted 31% of cases before 2007 and 49% after 2007 (p<0.05). Serum total T4 and free T4 levels were significantly lower in patients diagnosed before 2007 (p<0.05). Age of diagnosis and TSH levels tended to be higher in patients diagnosed before 2007. Ratio of thyroid dysgenesis patients among all congenital hypothyroidism patients detected before 2007 was 29/93 where as this ratio was 19/82 in patients diagnosed after 2007 (p<0.03).

Conclusion: National neonatal screening operated by state, facilitated diagnosis of milder cases with congenital hypothyroidism and slightly decreased time to establish diagnoses.

P2-d3-827 Thyroid 4
Hashimoto’s thyroiditis in children and adolescents: a retrospective study on clinical and laboratory properties of the disorder
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Background: Hashimoto’s thyroiditis (HT) is the most common disorder leading to goitre and acquired hypothyroidism in children and adolescents, who live in iodine replete areas. The aim of this study was to analyze data of the patients with HT followed in our department in the years between 2007 and 2011.

Patients and methods: Sixty six patients (49 girls, 17 boys, median age 11,08±2,6 (3-21) years) who presented with HT were evaluated for their pubertal stage, thyroid functions, antithyroid antibodies and thyroid ultrasonographies. High titers of antithyroid antibodies and heterogeneous appearance of thyroid paranchyma in the ultrasound were the criteria for the diagnosis of autoimmune thyroiditis.

Results: At admission 71 % (n=47) of the patients were pubertal. Thyroid functions were normal in 54.5 % (n=36) of the patients. Subclinical and overt hypothyroidism, subclinical and overt hyperthyroidism were diagnosed in 28.8% (n=19), 10.6% (n=7), 1.5% (n=1), and 4.5% (n =3) respectively. Forty...
five patients (68.2%) had high anti-TPO and anti-Tg levels, whereas only high anti-TPO and only high anti-Tg levels were found in 16 (24.2%) and 5 (7.6%) patients respectively. Serum anti-TPO levels were positively correlated with serum TSH levels (r=0.419, p=0.01). We determined false-positive nodules by ultrasonography in 7.6% (n=5) of the patients but none of them had fine needle aspiration and surgery. In the follow-up 3 patients who were euthyroid at diagnosis developed hypothyroidism.

**Conclusions:** Hashimoto’s thyroiditis is more frequent in females, and it’s incidence increases in puberty. Normal thyroid functions can deteriorate in the follow up. Positive correlation between serum TSH and anti-TPO levels suggests that anti-TPO levels correlate with thyroid damage; following anti-TPO levels can be valuable for the disease control.

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**P2-d2-828 Turner Syndrome 1**

**Turner syndrome and Madelung deformity: prevalence and estrogen effect**

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**Background:** Haploinsufficiency of SHOX gene is considered responsible of short stature and skeletal anomalies in Turner Syndrome (TS) and Leri-Weill Dyschondrosteosis. However, Madelung deformity (Md) is reported in only 7% of TS despite SHOX haploinsufficiency. A role of estrogen in the development of Md has been hypothesized.

**Objective and hypotheses:** Aim of this study was (1) to evaluate the prevalence of Md in TS patients and 2) to assess the relationship between estrogen exposure and Md.

**Methods:** We retrospectively analyzed the hand and wrist X-Rays performed for routine bone-age evaluations of our patients. To realize a quantitative assessment of Md on X-ray, we used 4 main measures: ulnar tilt (U.T.), lunate subsidence (L.S.), triangulation index (T.) and palmar carpal displacement. The measurements were made on radiographs of 17 patients with TS; in 11 of them we evaluated the X-Rays performed before and after the induction of puberty with estrogen therapy; in other 5 patients only during estrogen therapy and in 1 during spontaneous puberty.

**Results:** Of the 17 patients included in the study, to date only 2 had a Md clinically detectable in both wrists (12%). In the other 15 patients although there was no evidence of Md clinically evident on physical examination, at least one of the three measures made on X-ray was not normal, showing a wide spectrum of severity of Md. Comparing the scores obtained in the three measures before and after treatment emerges that the mean score for both U.T., L.S. and T. was not worsened after estrogen exposure, in fact the difference was not statistically significant (p >0.05).

**Conclusion:** Even if the literature indicates a potential effect of estrogen on worsening of bone dysplasia, our preliminary data do not confirm this hypothesis. In addition our data suggest that Md is more frequent than reported and should be searched with an appropriate radiological evaluation.

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**P2-d2-830 Turner Syndrome 1**

**Adult height of growth hormone treated girls with Turner syndrome: an update of the Belgian experience**

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**Background:** Today, in most countries Turner syndrome (TS) patients are treated with high dose growth hormone (GH) to improve adult height (AH). The AH outcome differs between countries, which might be, besides genetic background, partly explained by the inclusion of (industry sponsored) trials, but also by country specific policies on GH and estrogen (for pubertal induction) dosing and initiation.

**Objective and hypotheses:** To study the AH outcome in Belgian TS girls, who were not included in clinical trials and were started on 50 µg/kg./bodyweight GH after the age of 5 years and had puberty induction with low starting dose ethinylestradiol at variable age.

**Methods:** Final AH data of TS girls responding to these inclusion criteria were retrieved from the database of the BSGFE. Height data are expressed as SDS using national (NR) and Turner specific (TR) references. Corrected mid parental height (CMPH) and gain over projected height (GPH) and remaining height deficit (RHD) (CPMH-AH) were calculated.

**Results:** At start of GH therapy, median age of the 121 included TS girls was 10.5 years (5.9–19.1), mean (SD) SDS DS (TR) 0.42 (1.0) and projected AH 148.9 (5.9) cm. Median duration of GH therapy was 5.8 years (1.2–12.4). Me-

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dian age at estrogen initiation was 13.8 years (11-20.6). Mean AH was 152.6 (6.6) cm. Seventy one (58%) girls achieved a height > -2SD (NR). Mean GPH was 3.7 (5.0) cm and the RHD was 10.7 (6.3) cm. HSDS at the beginning of treatment was the variable most strongly related to AH and remaining height deficit.

Conclusions: The current combined GH and estrogen regimen resulted in a mean gain above projection of 3.7 (5.0) cm. The great inter-individual variability in growth response to GH permitted only half of the patients to obtain a FH within normal limits. GH and estrogen therapy needs optimization, especially in those TS girls with the shortest stature.

P2-d2-831 Turner Syndrome 1
Retrospective evaluation of pubertal development and linear growth of estrogen treated hypogonadal girls regularly followed up in our pediatric endocrinology department

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Objective and hypotheses: The objective of the study was to evaluate pubertal development and linear growth of hypogonadal girls regularly followed up in our pediatric endocrinology department.

Methods: The data of the patients with hypogonadism or disorders of sexual development were evaluated retrospectively. Left hand radiograms were evaluated by three different pediatric endocrinologist to determine bone age by Greulich Pyle method.

Results: Data of twenty four girls were studied. Thirteen of the girls (53%) had Turner Syndrome (TS). Six (46.2%) of the TS girls were treated with oral estrogen, seven (53.8%) of the TS girls were treated with transdermal estrogen patches. Five (45%) of the patients with hypogonadism without TS were treated with oral estrogens, six (55%) of the patients were treated with transdermal estrogen patches. Five (83%) patients in oral estrogen treated TS group, progressed to thelarche stage three at the end of one year. Only five of the patients in transdermal patch treated TS group completed first year of treatment and four (%80) of them progressed to thelarche stage three. Five (100%) of the oral estrogen treated and five (83%) of the transdermal estrogen patch treated girls with hypogonadism without TS completed first year of treatment and three (60%) of the oral estrogen treated and all of the transdermal estrogen patch treated patients progressed to thelarche stage three.

In two groups of estrogen formulation treated TS patients; the ratio between treatment and three (60%) of the oral estrogen treated and all of the transdermal patch treated girls with hypogonadism without TS completed first year of treatment and four (%80) of them progressed to thelarche stage three. Five (45%) of the patients with hypogonadism without TS had Turner Syndrome (TS). Six (46.2%) of the TS girls were treated with oral estrogens, seven (53.8%) of the TS girls were treated with transdermal estrogen patches. Five (45%) of the patients with hypogonadism without TS were treated with oral estrogens, six (55%) of the patients were treated with transdermal estrogen patches. Five (83%) patients in oral estrogen treated TS group, progressed to thelarche stage three at the end of one year. Only five of the patients in transdermal patch treated TS group completed first year of treatment and four (%80) of them progressed to thelarche stage three. Five (100%) of the oral estrogen treated and five (83%) of the transdermal estrogen patch treated girls with hypogonadism without TS completed first year of treatment and three (60%) of the oral estrogen treated and all of the transdermal estrogen patch treated patients progressed to thelarche stage three.

Conclusions: While providing adequate breast development, bone age advancement is less significant with transdermal estrogen patches. These findings suggest a better height prognosis in patients treated by transdermal route.

Nevertheless, auxological screening of Turner syndrome in the general population has been studied relatively little.

Objective and hypotheses: To provide sensitive evidence-based growth screening cut-offs for height standard deviation score (HSDS) and target height (TH) SDS with reasonable levels of specificity for the early detection of TS.

Methods: Longitudinal height data of 124 TS girls and their 2,020 measurements were compared to population-based reference data of 30,428 healthy girls with 112,266 measurements. Analyses were performed by using Receiver Operating Characteristic curves.

Results: Sensitivity of the growth screening was 95% with the specificity of 95% for all TS girls when growth screening was performed against HSDS or TH SDS, and 98% with the specificity of 97% for the 45,X0 TS girls, respectively. All the 45,X0 TS girls were detected by the age of 4 and 8 years with the corresponding specificities of 95 and 97%, respectively.

Conclusions: Systematic growth screening in population level is useful for TS. Adding screening against TH SDS instead of HSDS alone improves accuracy.
Aims: to identify the main cause of growth failure in Turner Syndrome (TS) treated with GH. SHOX haploinsufficiency appears to be the main cause of TS associated with genetic abnormalities in TS patients. The presence of hypertension independent of adiposity in patients with TS.

Results: The 24-hour mean systolic or diastolic hypertension was found in 21.6% (8.1%, systolic; 19.4%, diastolic) of TS population. 66.7% of the patients had less than 10% fall in the night-time BP (non-dipping). High BP was not associated with smoking history, the presence of cardiac or renal anomaly, family history of cardiovascular disease. TS patients with DM were more likely to have hypertension than those without (P < 0.013). The HOMA-IR positively correlated with systolic BP (P < 0.005, 24-hour mean, daytime and night time) and diastolic BP (P < 0.01, 24-hour mean and daytime), independently with body fat. The 24-hour/daytime/nighttime systolic and diastolic BP were not correlated with CAVI and PWV. No significant difference in CAVI and PWV was found between dippers and non-dippers. The HOMA-IR positively correlated with CAVI, which was dependent on body fat.

Conclusions: Over 66.7% of TS patients have an abnormal BP circadian rhythm. This study suggests that IR and hyperglycaemia are associated with the presence of hypertension independent of adiposity in patients with TS.

P2-d2-834 Turner Syndrome 1

Karyotype analysis in girls with coarctation of the aorta: how many girls with Turner’s syndrome are we missing?

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Background: Cardiac abnormalities are seen in approximately 50% of girls with Turner syndrome (TS), most commonly bicuspid aortic valve, in 13-34%. Aortic coarctation with TS has prevalence around 4%, usually presenting in early infancy.

Aim: To audit frequency of karyotype analysis in girls with coarctation of the aorta, in one tertiary paediatric centre and frequency of TS in those who had karyotype analysed.

Methods: Using a combination of two electronic databases, reporting, archiving and recording cardiology and cardiac, we identified girls with a diagnosis of coarctation of the aorta. Karyotype analysis was identified by a combination of hospital electronic investigation reporting databases, together with genetic department records.

Results: We identified 138 girls with coarctation: coarctation in combination with no other cardiac abnormalities, 50.0% (69/138); coarctation in combination with other cardiac abnormalities 50.0% (69/138). Factors leading clinicians to investigate girls presenting with coarctation of the aorta. True prevalence of Turner syndrome is considered to be around 1 in 5000 live births. A 25% discordance may be taken into account. Multicenter studies are needed on a greater number of diploid subjects.

P2-d2-835 Turner Syndrome 1

SHOX dosage and final height (FH) in Turner syndrome (TS) treated with GH-therapy

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Results: 131 pts with FH (GH-dose 45-55 µg/kg/day) were studied for SHOX. SHOX dose was determined on karyotype as total allelic contribution (1 or 2 ratio or mosaic karyotype) and by MLPA analysis when the percentage of mosaic metabolism was not available or an alteration in Xp22/Yp11 region was present. Height(H) (cm, SDS) pre-therapy and at FH, TH, H gain SDS vs baseline were evaluated. Karyotype: 45.X0 (40.5%); X-XA (36.6%); X-mosaicism (13.7%) and Y- material (9.2%). 4 Groups were obtained on GH-therapy duration: Group A-33 pts (<4 yrs), Group B-19 pts (>4 and <6 yrs), Group C-34 pts (<6 and <8yrs) and Group D-45 pts (>8 yrs). Spontaneous menarche occurred in 18 pts (18.4%).

Results: FH was significantly different between the GH-Groups: 148.7±5.7 cm in Group A, 151.2±6.9 cm in Group B, 153.3±5.4 cm in Group C and 154.3±5.5 cm in Group D (P=0.9, p=0.0002). FH correlated significantly with SHOX dose (p=0.02). The effect of SHOX was observed only in pts treated for at least six yrs: SHOX-dose>1 subjects (13 pts) showed a significantly higher FH, close to their TH, than haplinsufficient pts (63 pts)(157.6±4.0 cm vs 153.2±4.8; p=0.03). At multiple regression analysis, FH appeared to be influenced by GH-duration, TH, SHOX dosage(p=0.04) and negatively by menarche.

Conclusions: SHOX is a gene that acts in a dose-dependent way. A SHOX-dose greater than 1 is supposed to contribute independently to the FH, in proportion to the dosage. TS pts with X or Y-mosaicism and Xp22 or Yp11 alterations may show partial or complete SHOX diplody: this seems to determine a better height gain after long term GH-therapy. In TS patients the SHOX-dose may be a further and disjointed element in response to therapy that should be taken into account. Multicenter studies are needed on a greater number of diploid subjects.

P2-d2-836 Turner Syndrome 1

Evaluation of the ovarian follicle stock in girls with Turner syndrome (TS) after prenatal diagnosis

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Objective and hypotheses: The purpose of this study is to evaluate the ovarian follicle stock in the case of low % of X monosomy mosaicism.

Methods: 14 girls TS with a prenatal diagnosis underwent a neonatal evaluation: karyotype confirmation was done on jugular mucosa smear (JK), hormone assays (FSH, AMH) and pelvic ultrasound (presence of follicles).

Results: All neonates were born at term (39.3 ± 1.3 weeks), the average birth weight and height were respectively 3.0 ± 0.5 kg, 47.3 ± 2.5 cm. Six girls were born small for gestational age (TN 44.9 ± 1.6 cm with a mean of 38.7 ± 1.6 wk). The jugal karyotype is consistent with the amniotic fluid karyotype (p = 0.001).

In 5 cases there was a high level of X monosomy with > 50% 45X (Gp1). In 9 cases it was a mosaic 45X/46XX with low level of X monosomy <50% (Gp2). The level of X monosomy is correlated with FSH (p = 0.002) and inversely with the rate of AMH (p = 0.02).

These 2 markers are necessary tools for assessing ovarian function. Ultrason of the ovaries is difficult at this age, follicles were visualized in only 6 cases of gpl2.

Conclusions: Early hormonal screening of FSH and AMH may assess follicular activity of the ovary. These early data does not predict the future normally puberty of these girls.
Familial Turner syndrome. Study of a Tunisian family

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Background: Turner syndrome (TS) is one of the most common chromosomal abnormalities affecting 1 in 2500 live births. Short stature and gonadal dysgenesis are known as the hallmarks of this syndrome. The vast majority of cases occur sporadically and familial forms have received little attention.

Objective and hypotheses: To describe clinical, hormonal and genetics features of familial TS.

Methods: A Tunisian family of four sisters exhibiting TS is described. Age at presentation ranged from 13 to 42 years. Clinical suspicion of TS was made on the basis of dysmorphic features and short stature in all cases. In addition, delayed puberty and primary amenorrhoea were noted in 3 sisters. Biochemical tests confirmed primary ovarian failure in all sisters. Chromosomal analysis confirmed TS in all cases and revealed 45X0 karyotype in two sisters, mosaic 45X0/46XX/47XXX form in one case and 45X0/46XX/46X, r(X) karyotype in the remaining sister. No clinical signs or chromosomal abnormalities could be detected in the mother. During follow-up, central hypothyroidism was confirmed in 2 sisters. Hormonal investigations showed also gonadotropin deficiency in these two patients and growth hormone deficiency in one of them. Pituitary imaging revealed pituitary hypoplasia in one sister and was normal in the remaining sister.

Conclusions: It seems that TS is more than an occurrence event, and familial forms raise new problems concerning etiopathogeny of this syndrome. To confirm this hypothesis more chromosome analysis are necessary. Fluorescence in situ hybridization (FISH) analysis is a sensitive and cost-effective adjunct to karyotype analysis to identify sex chromosome mosaicism in TS.