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). Thirty-five age-matched prepubertal children were studied as controls(CT).
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 (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 lower in GC and PC than in CT (246ng/ml, 891ng/ml and 4.9mg/l, respectively; P<0.0001). Regarding IGFBP-1, no difference was found between GC, PC and CT (86ng/ml).
Conclusions: IGF system is not restored to its physiological state in HIV children with GC. Difference in serum levels of IGF-I, IGF-II, IGFBP-3 and IGFBP-1 seems not to explain the difference in HV in GC and PC that seems to be determined mainly by paracrine/autocrine regulation at growth plate. The normal IGFBP-1 levels can further decrease IGF bioactivity on metabolism and contribute to the increased insulin resistance observed in these patients.

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) characterises individuals with a birth length/birth weight two standard deviations below the mean of a reference population. Several hetero-/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 leukaemia 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-d1-620 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 most be investigated for association with a number of disorders mainly on impaired growth, its impact on the metabolic of 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/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 obeisty children, d3/d3 and d3/fl polymorphism might play protective effect on metabolic syndrome development sensitivity.

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÷9.2 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 arginine (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 (GH-AUC), BMI-

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SDS, height-SDS and IGF-1 SDS were calculated.
Results: Results are shown in the table (mean±SEM).

	First test	Retesting	p value
Age (years)	4.9±1.3	11.9±0.9	
Height-SDS	-1.52±0.24	-0.78±0.45	0.051
BMI-SDS	1.40±0.35	1.64±0.32	0.09
GH peak (ng/ml)	36.6±8.8	20.2±4.8	<0.05
GH AUC	2474.7±551.5	1295.4±336.0	<0.03
IGF-I SDS	-0.15±0.41	-1.38±0.51	<0.02

GH peak, GH AUC and IGF1-SDS at retesting were significantly lower than at first test. Height-SDS tended to improve. First test was normal in 8/10 patients, while retesting was normal only in 4/10. Both tests were low in 2 patients and normal in 4. In other 4 patients first test was normal and retesting was low.
Conclusions: GH responsiveness to combined test is normal in the majority of PWS children during infancy, but decreases significantly after a follow-up of 7 years, independently from the BMI, meaning that PWS children have a normal GH pituitary reserve that gradually declines with age. This secretory pattern is also confirmed by decreasing IGF-1 levels with age.

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 I 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-I 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 heterozygous nonsense mutation resulting in an early truncated protein and probably a haploinsufficiency 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 heterozygous 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-I serum levels. The phenotype severity, the existence of a mental retardation and the GH response to treatment were variable.

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)

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Background: Adult height (Ht) 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 1st-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 1st-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, Ht SDS, Ht SDS–target Ht SDS and BMI SDS (table); 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, Ht 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 Ht 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]).

Parameter	CAH (N=17[a])	GHD (N=8161[a])	TS (N=1209[a])
Baseline age (yr)	9.9 ± 2.2 [8.7, 11.0]	9.5 ± 4.1 [9.4, 9.6]	8.9 ± 3.7 [8.7, 9.1]
Baseline bone age SDS (Greulich-Pyle)	2.4 ± 2.0 [1.1, 3.7]*	-2.2 ± 1.6 [-2.2, -2.1]	-1.4 ± 1.4 [-1.5, -1.3]
Baseline height SDS	-0.9 ± 1.4 [-1.6, -0.1]*	-2.5 ± 1.1 [-2.5, -2.4]	-2.6 ± 0.9 [-2.7, -2.6]
Baseline height SDS - target height SDS	-0.2 ± 1.6 [-1.3, 0.8]*	-2.0 ± 1.2 [-2.1, -2.0]	-2.6 ± 1.1 [-2.7, -2.6]
Baseline BMI SDS	1.1 ± 1.1 [0.6, 1.7]*	-0.3 ± 1.6 [-0.3, -0.3]	0.3 ± 1.4 [0.2, 0.4]
Pre-treatment height velocity (cm/year)	5.2 ± 2.0 [3.8, 6.5]	4.7 ± 2.4 [4.6, 4.8]	4.9 ± 2.3 [4.7, 5.1]
Baseline max GH peak µL/mL	14.1 ± 8.4 [6.3, 21.9]	7.5 ± 7.7 [7.3, 7.7]	13.5 ± 10.8 [12.2, 14.8]
Initial GH dose (mg/kg/wk)	0.34 ± 0.13 [0.27, 0.41]	0.25 ± 0.10 [0.24, 0.25]	0.32 ± 0.08 [0.32, 0.33]
First year height velocity (cm/yr)	6.2 ± 2.3 [5.0, 7.3]*	9.0 ± 2.6 [8.9, 9.1]	7.9 ± 1.9 [7.7, 8.0]
Δ height SDS after 1 yr of GH	0.1 ± 0.3 [0.0, 0.3]*	0.6 ± 0.5 [0.6, 0.6]	0.5 ± 0.4 [0.5, 0.5]
Final height SDS[b]	-0.9 ± 1.0 [-1.7, -0.2]	-0.9 ± 1.1 [-1.0, -0.9]	-1.7 ± 0.9 [-1.8, -1.6]
Final height SDS gain[b]	-0.1 ± 0.7 [-0.5, 0.4]*	1.4 ± 1.1 [1.3, 1.4]	1.1 ± 0.9 [1.0, 1.1]
GH treatment duration (yr)[b]	3.5 ± 2.5 [1.6, 5.5]	5.0 ± 3.2 [4.8, 5.1]	5.3 ± 2.7 [5.0, 5.7]

[a]Maximum N, lower for certain parameters; [b]N=10 (CAH), 2054 (GHD), 362 (TS); *Significantly different from GHD and TS ($p<0.05$).
Conclusions: GH treatment, started at close to 10 yrs of age, had no beneficial effect on 1st-yr GH treatment HV or FH in this small group of pts with CAH.

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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 GH (n=39), 0.067 mg/kg/day GH (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 (n=10) or 0.067 mg/kg/day (n=10) GH 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 after 260 weeks being 5.79 (1.05) years and 7.15 (1.05) 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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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 hypoglycemic episodes 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 homozygous 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-necrotic 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 effect 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 biochemical 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 contribute of calibrators used in GH assay in leading to different GH results and the impact on the formulation of GHD 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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provocation testing, were enrolled.
Results: GH levels after two pharmacological stimuli were obtained by Immulite assay using the newly adopted 98/574 recombinant human GH as calibrator material and enabled us to formulate a diagnosis of GHD in 20 out of 23 subjects. Thereafter, we repeated GH measurement in the same samples by Immulite using IS 80/505 pituitary derived GH as calibrator. In four out of 20 children, in whom we had formulated the diagnosis of GHD, peak GH levels resulted above 10 ng/ml. Therefore, the diagnosis of GHD was confirmed only in 16 out of 20 children. Furthermore, the total cost for GH therapy of patients diagnosed with 98/574 as calibrator was 165,468 euro, while the total cost for GH therapy of patients that would have been diagnosed with IS 80/505 as calibrator was 130,068 euro.
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.
Objective 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 (Increlex). 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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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.

	Baseline	Gain during 1st yr treatment	Gain during 2nd yr treatment	Total gain during 2 yrs treatment
Height velocity (cm)		8.1±1.9	6.2±1.7	14.3±3.1
Height (SDS)/ Sempe1	-2.80±0.83	0.42±0.33*	0.15±0.51	0.57±0.70**
BMI (SDS)/Sempe1	1.50±1.22	-0.12±0.94	0.21±0.72	0.09±1.08
Height/HCP (SDS)2	-0.53±1.09	0.75±0.55*	0.68±0.88*	1.43±0.96**
BMI/HCP (SDS)2	-0.38±1.45	0.01±0.82	0.34±1.12	0.35±1.26
Upper segment1 (SDS)	-0.90±1.14	-0.42±0.5	0.61±1.05	1.03±0.96**
% Fat body mass	1.13±0.81	-0.66±0.69*	0.07±0.52	-0.59±0.73**
BMD (Zscore)3	-1.90±1.21	0.034±0.6	0.29±0.65	0.32±0.72
IGF-I (Zscore)4	-1.07±0.89	1.39±.57	1.48±1.60	

*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.

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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 GHD 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 short stature and a characteristic dysostosis of the wrist (Madelung deformity). It was shown that the effect of growth hormone on final height of LWS patients is comparable to that of patients with Turner syndrome.
Objective and hypotheses: We present a family with SHOX deficiency due to a X/Y translocation and contiguous gene syndrome with lack of the SHOX, ARSE, MRX1 and STS genes. The male index patient presented 10.5 years with a height of 122.9 cm (- 3.3 SDS), facial dysmorphism, mental retardation and ichthyosis. Chromosomal analysis revealed a deletion of Xp including the PAR with translocation of the duplicated Yq to the X chromosome. After growth hormone (GH) treatment for 3.2 years the patient reached a final height of 145.9 (-3.8 SDS). Two adult sisters of the patient had the same chromosomal aberration and presenting with short stature (-2.6 and -2.0 SDS), but lacking ichthyosis 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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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 detected.
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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Background: EU IGFD follows postmarketing safety and efficacy of Increlex® (mecasermin[rDNA origin] injection) treatment (Tx).
Objective: Report baseline characteristics and safety data for children with IGF-I Tx and 1st-year height velocity (HV) in naïve 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).

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

† >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 a serious AE (SAE) related to Tx in 3 pats (4.3%). Other Tx SAEs: adenoidal hypertrophy (2 pats), tonsillar hypertrophy, loss of consciousness (that could be 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 reported hypoglycaemia was not higher than expected given pats phenotype and IGF-1 dose. First yr HV in this small group is encouraging but mean dose at one year remains suboptimal.

P2-d3-634 GH and IGF Treatment 2

Low incidence of persistent growth hormone deficiency (GHD) in the patients with isolated, non-acquired childhood-onset GHD, reevaluated after completion of growth promoting therapy

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Background: In growth hormone (GH) deficient patients, GH therapy should be continued after the attainment of final height (FH) up to the achievement of peak bone mass. However, not all the patients with childhood-onset GH deficiency (GHD) have still decreased GH secretion at FH, especially in case of isolated GHD.
Objective and hypotheses: The aim of the study was to assess the incidence of persistent GHD in the patients with isolated, non-acquired childhood-onset GHD, reevaluated after completion of growth promoting therapy.
Methods: Analysis comprised 100 patients (74 boys, age 17.9±0.9 years and 26 girls, age 15.7±0.9 years) with isolated, non-acquired childhood-onset GHD, who attained near-FH (height velocity <2 cm/year, bone age ≥16 years in boys and ≥14 years in girls) and completed GH therapy. In all the patients GH secretion in insulin tolerance test (ITT) with the cut-off level of 6 ng/ml and insulin-like growth factor-I (IGF-I) concentration was assessed. In case of discordant results of these diagnostic procedures, the stimulating test with clonidine was additionally performed.
Results: Decreased GH secretion in ITT (<6 ng/ml) was observed in 27 patients, however in 19 of them, both IGF-I level and GH secretion after clonidine presented normal. In 62 cases, GH secretion in stimulating tests was ≥10 ng/ml. Anterior pitutary hypoplasia was found in all the patients (n=6) with GH peak <3 ng/ml.
Conclusions: The low incidence of persistent GHD in the patients with childhood-onset, isolated, non-acquired GHD speaks for the necessity of reevaluation of such patients at FH. It seems useful to perform 2nd stimulating test in case of discordant results of ITT and IGF-I assessment.

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

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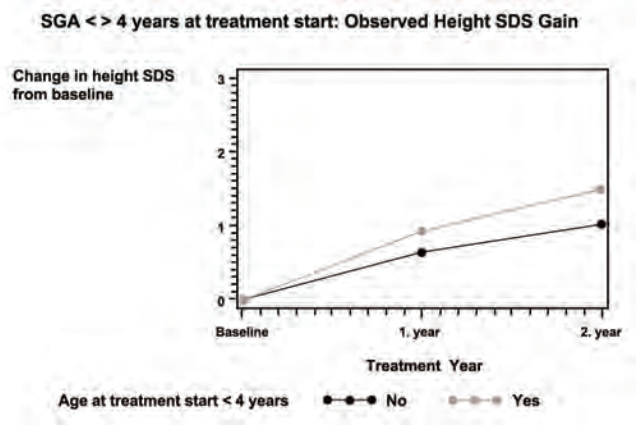
Background: Clinical studies have demonstrated a better 2-year growth response in children born small for gestational age (SGA) started on growth hormone (GH) therapy before 4 years of age. However, no such data have been documented in an observational cohort of short GH-treated SGA-children.
Objective and hypotheses: 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. All patients were treated with Norditropin® and included in the NordiNet® International Outcome Study (IOS).
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±4.1wks, respectively), birth weight (2011.9±689.0g and 2077.0±734.4g) and birth length (42.7±4.5cm and

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43.6±4.8cm). At baseline, mean age in group A was 3.3±0.6 yrs vs. 8.2±3.0 yrs in group B. At treatment start, patients in group A were shorter than in group B (HtSDS -3.7±1.2 vs. -3.2±0.8 SDS; p<0.001). The HtSDS change from baseline to one year and two years after GH treatment start (figure) was significantly greater in group A than in group B; 0.93±0.51 vs. 0.64±0.46 (p<0.001) and 1.49±0.57 vs. 1.03±0.56, respectively(p<0.001). When restricting analysis to include only prepubertal children (n=645) growth outcomes were still significantly better in group A.

Conclusions: A significantly better initial growth response was observed in those short SGA children started on GH therapy at a very young age (<4 years) compared with those started at a later time-point. Our data retrieved in a cohort of patients seen in clinical practice confirms those previously reported in clinical SGA studies. Benefit and safety of such an early treatment start have to be further evaluated in long term follow up observations.

P2-d3-636 GH and IGF Treatment 2

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

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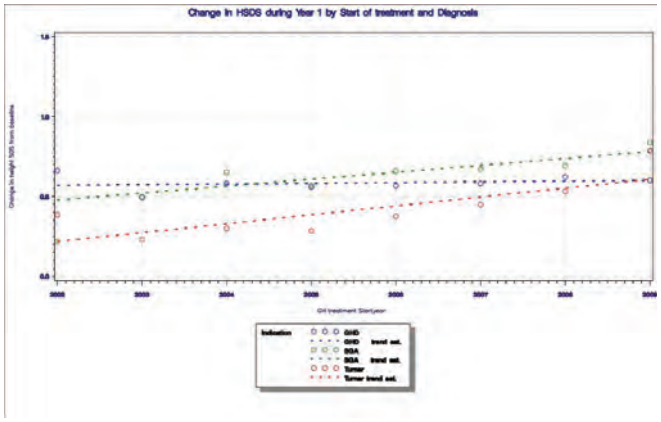
Background: Previous investigations from the German cohort of NordiNet® International Outcome Study (IOS), revealed a tendency towards a younger age at treatment start with growth hormone (GH) over the time period 2002-2009 in short children born small for gestational age (SGA) and patients with Turner 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 Norditropin® and enrolled in the NordiNet® IOS. Data were collected per year from 2002 through 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 2.82±1.01, 3.38±0.73 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.

P2-d3-637 GH and IGF Treatment 2

The insulin like growth factor axis and cytokine interactions in children with inflammatory bowel disease treated with recombinant human growth hormone

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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 controls(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(6.1,15.0)(p=0.003).

	rhGH T0	rhGH T6	P value	Ctrl T0	Ctril T6	P value
Total IGF1 (mcg/L)	119 (41,340)	295 (106,558)	0.03	77 (49,218)	135 (36,183)	0.14
Free IGF1 (ng/ml)	1.33 (0.34,3.42)	1.98 (0.1,4.63)	0.16	0.42 (0.15,3.28)	0.91 (0.1,1.82)	0.53
IGFBP2 (ng/ml)	636 (252.1628)	766 (214,1206)	0.67	550 (222,962)	568 (394,778)	0.99
IGFBP3 (ng/ml)	5675 (4140,7590)	7150 (1790,8490)	0.21	4210 (3240,7084)	4750 (1040,6890)	0.77
ALS (mU/ml)	1267 (731,1442)	1332 (342,1718)	0.29	1053 (736,1432)	1045 (518,1530)	0.66

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 IGFBP3 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, IGFBP2, IGFBP3, ALS with that of IL12, MIP1α and RANTES.

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

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P2-d3-638 GH and IGF Treatment 2

Growth responses to three different dosing regimens of growth hormone: two-year data from the North European Small for Gestational Age Study (NESGAS)

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Background: The optimal growth hormone (GH) dosing and duration of treatment in children born small for gestational age (SGA) without catch-up growth are matters of debate.
Objectives: The North European Small for Gestational Age Study (NESGAS) is a multicenter study involving the UK, Ireland, Sweden and Denmark. 110 short SGA children (69 males) were treated with high-dose GH (Norditropin; 67µg/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) 67µg/kg/day (N=37), one group was reduced to a lower dose (LD) 35 µg/kg/day (N=36) and in one group the dose was titrated according to serum IGF-I levels (IGF-I titr) (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 high-dose GH had a marginally, but statistically significantly larger change in height SDS, weight SDS, IGF-I SDS and IGFBP-3 SDS during the second year of treatment compared to the two other groups (table 1). No serious adverse events were seen.
In conclusion, treatment with high-dose GH during the second year of treatment resulted in the best growth response, whereas the 2nd-year growth response in children treated with standard dose and IGF-I titrated dose was similar.

	High-dose (N=31)	Low-dose (N=33)	IGF-I titrated dose (N=31)	ANOVA
Age (yr) at baseline	6.35 (1.85)	6.5 (1.71)	5.84 (1.47)	P=0.28
Height (SDS) at baseline	-3.29 (0.59)	-3.46 (0.82)	-3.53 (0.89)	P=0.43
ΔHeight (SDS) 0-1 yr	1.01 (0.36)	1.04 (0.41)	1.05 (0.40)	P=0.90
ΔHeight (SDS) 1-2 yr	1.23 (0.50)	0.94 (0.40)	0.90 (0.39)	P=0.007
IGF-I (SDS) at 1 yr	2.82 (1.37)	2.70 (1.33)	2.98 (1.77)	P=0.62
IGF-I (SDS) at 2 yr	2.89 (1.69)	1.67 (1.53)	1.84 (1.10)	P=0.002
ΔIGF-I (SDS) 0-1 yr	3.74 (1.80)	3.89 (1.28)	4.31 (1.96)	P=0.39
ΔIGF-I (SDS) 1-2 yr	0.08 (1.04)	-1.07 (1.22)	-0.96 (1.86)	P=0.006

P2-d3-639 GH and IGF Treatment 2

Near adult height in children born prematurely with different GH status and size at birth treated with growth hormone — data from KIGS

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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: idiopathic 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 puberty 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=-0.59, 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 observed in the AGA children. Prematurity did not interfere with the growth response during GH treatment.

	Preterm AGA (n=246, 141 boys)			Preterm SGA (n=39, 22 boys)		
	At GH start	At puberty start	Near adult height	At GH start	At puberty start	Near adult height
Age (yrs)	8.6±3.1	13.3±2.0	17.8±1.6	7.8±3.0	13.5±1.9	17.7±1.6
Height SDS	-3.55±1.36	-1.32±1.03	-1.51±1.31	-4.01±1.7	-1.68±0.72	-2.08±0.86
Weight SDS	-2.7±1.63	-1.36±1.35	-0.86±1.43	-3.69±2.09	-1.62±1.08	-1.45±1.38
Ht-MPH SDS	-2.41±1.68	-0.30±1.20	-0.35±1.30	-3.05±2.08	-0.78±1.18	-1.14±1.11
ΔHSDS	-	2.07±1.24	2.04±1.36	-	2.43±1.65	1.94±1.41
Max GH peak (µg/L)	7.07±6.45	-	-	10.38±10.68	-	-
GH dose (mg/kg/w)	0.22±0.08	0.22±0.07	0.22±0.08*	0.25±0.11	0.24±0.09	0.24±0.07*

Ht-MPHt SDS:= Parental Adjusted Height; HSDS= change in height SDS from GH start to this age, * mean pubertal dose.

P2-d3-640 GH and IGF Treatment 2

The patient with Kearns-Sayre syndrome treated with recombinant growth hormone

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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

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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-1 levels during rGH administration were within normal range. In the age of 15 years complete atrioventicular 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 exceptional 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 MNiSzW (2P05A07030).

	Age [years]	Height [SDS]	Height velocity [cm/year]	Predicted adult height [cm]
the beginning of rGH therapy	12	-3.5	8.5	161.9
after 12 months of rGH therapy	13	-2.6	7.5	161.7
after 2 years of rGH therapy	14 3/12	-2.2	10	168.5
after 3 years of rGH therapy	15 2/12	-2.3	4.5	168.5
after 4 years of rGH therapy	16	-2.3	2.5	
after 5 years of rGH therapy	17	-2.6	1.3	

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

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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-1/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.

	Pre-Treatment	Year 1	Year 2	Year 3
Height SDS ±SD	-3.1±0.7	-2.5±0.8	-1.9±0.9	-1.7±0.9

Abnormal glucose tolerance was observed on GH treatment in 2 patients with consequent GH dose adjustment; impaired glucose tolerance was observed in 1 patient pre-GH and resolved by 1 year on GH. No other relevant adverse events were noted.
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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Background: Moyamoya is a rare cerebrovascular disease that leads to a progressing occlusion of the basal intracranial vessels. A cloud of collateral vessels is developed for compensatory perfusion, not sufficient to prevent transient ischemic attacks, infarction or epilepsy. Children usually present with these signs before the age of six years. Hypothalamo-pituitary dysfunction has been reported as a consequence of brain hypoperfusion in a few children. Surgical intervention by encephaloduromyosynangiosis normalizes brain perfusion in most cases.
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 theapy 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 hypothalamo-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

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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, INT2) (n=30; n=32) or instruction (n=26; n=32) groups and performed a usability test (needle attachment, dose setting and injection into an Eppendorf 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: FP: 70%; GP: 30%; EP: 0%, INT2: FP: 78%; OP: 16%; NP: 6%). FP was rated significantly easier to learn to use 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 ($p<0.01$ for both) in INT2.
Conclusions: At least 70% of uninstructed 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 hGH 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: Three disease entitities were studied: a) 21 children (11M, 10F) with congenital IGHD; b) 20 prepubertal children (13M, 7F) with cMPHD 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 MPHD 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 linked to insulin alone as IGF-I suppresses insulin secretion.

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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Background: It has been proposed that appearance satisfaction and chronic illnesses influence emotional and behavioral development in children. Sandberg and Colsman 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 was meassured using the 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

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Background: Noonan syndrome (NS) is characterized by facial dysmorphisms, congenital heart defects, post-natal short stature, short and webbed neck, and chest deformities. Recombinant human growth hormone (rhGH) 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 rhGH therapy and to evaluate the influence of genotype on response to rhGH therapy in children with NS.
Methods: The study was designed as a single-armed prospective study. Eleven male and three female patients (range, 4.3-13.3 yr of age at onset of rhGH therapy) with NS with short stature whose height was less than 3 percentile 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.

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P2-d3-647 GH and IGF Treatment 3

Effect of 3 years of growth hormone (GH) therapy in children with Noonan syndrome

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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 (ΔHSDS) 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 continued increase in 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 ΔHSDS at Y1 (correlation coefficient R = -0.3102; p=0.0238) and Y2 (R= -0.4551; p=0.0068).
Conclusions: GH naïve subjects with NS from the ANSWER Program® showed continued increase in HSDS after 3-year treatment with GH with no significant differences between genders. Baseline age was negatively correlated with ΔHSDS at Y1 and Y2. Whether longer-term therapy will increase adult height in NS remains to be investigated with longer GHT duration and a larger patient population.
Table. Mean (SD) HSDS and ΔHSDS over Time

	All	All	All	Male	Male	Female	Female
	n	HSDS	ΔHSDS	n	ΔHSDS	n	ΔHSDS
Baseline	99	-2.7 (0.72)	---	75	---	24	---
Y1	53	-2.3 (0.75)	0.36 (0.40)	39	0.38 (0.40)	14	0.32 (0.42)
Y2	34	-2.1 (0.95)	0.66 (0.67)	27	0.69 (0.70)	7	0.54 (0.59)
Y3	15	-1.7 (1.36)	0.94 (0.74)	14	0.94 (0.77)	1	0.89 (-)

P2-d3-648 GH and IGF Treatment 3

Adult height of children receiving growth hormone therapy with Norditropin®

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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 HSDS> -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 (ΔHSDS) and the ΔHSDS 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 ΔHSDS was positively correlated with the ΔHSDS at final visit, consistent with early treatment response as a potential predictor of longer term growth.

P2-d3-649 GH and IGF Treatment 3

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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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 4-12y participated in the study. 32 and 5patients 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:

	1 year	2nd year	3rd year	3rd year	5th year
Average patients´ height increase (cm)	9.4	17.4	24.2	31.1	39.2
Mean differences in HV compared to the start of treatment (cm/year)	5.5	4.1	3.1	2.4	3.5
Mean differences in HVSDS compared to the start of treatment	6.3	3.9	3.2	3.5	3.5

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.

P2-d3-650 GH and IGF Treatment 3

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. At the cessation of

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growth, IGFI—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 KIGS 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±0.61mg/day). The latest IGF—I levels 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.

	Before Final Height	During Transition	P value
n=	20	24	
Gender (Females/Males)	8/12	10/14	
Age (years)	16.4 (1.5)	18.6 (1.3)	<0.001
Idiopathic GHD/Organic Pituitary disease	10/10	12/12	
Height (cm)	161 (9.3)	163.8 (9.7)	0.33
Weight (kg)	59.1 (18.5)	68.4 (20.9)	0.13
BMI	22.9 (4.9)	25.2 (5.9)	0.11
GH dose (mg)	1.7 (0.66)	0.9 (0.61)	<0.001
IGF—I (nmol/L)	43.2 (28.4)	20.9 (12.1)	<0.001
IGF—I SDS	-0.84 (2.25)	-2.63 (1.93)	<0.001

Means (SD)

P2-d3-651 GH and IGF Treatment 3

Successful treatment of psuedotumor cerebri complicating GH therapy

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Background: Pseudotumor Cerebri is a rare complication of GH therapy.
Case: A 13 year-old female with short stature (height: 127.5 cm -4.5 SD below the mean). She has no puberty signs. Her brother has panhypopituitarism. Growth evaluation showed IGF-1: 4 ng/ml (76-494), GH (baseline & clonidine-stimulated): 0.39 & 0.32 mIU/L, bone age: 10 years, TSH: 1.7, mU/ml (0.7-6.4), FT4: 0.69 mcg/dL (0.8-1.8), Estradiol <5 Pg/ml. Growth hormone was started at 0.04 mg/kg/day, and levothyroxine was started at 50 mcg/d for central hypothyroidism; in addition to calcium and vitamin D. After 3 months, she developed nausea, vomiting, headache and generalized edema, then she had strabismus. Head CT was normal. A clinical diagnosis of Pseudotumor Cerebri was made. GH was held, and she was started on Acetazolamide 250 mg three times/day and furosemide 20 mg/d. In few days, she showed a significant improvement with resolution of her symptoms completely in 2 weeks. GH therapy was re-started at a lower dose with no recurrence of this complication.
Conclusions: Pseudotumor Cerebri should be suspected in any patient receiving GH therapy presenting with Headache, vomiting, papilledema, vision loss or 6th nerve palsy. It should be differentiated from a CNS mass lesion, hydrocephalus and sinus thrombosis. Treatment should be initiated promptly with Acetazolamide and loop diuretics.

P2-d3-652 GH and IGF Treatment 3

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

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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 3480g, length 59 cm, Apgar 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 4.36 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 was 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 3400g. Height before treatment 109.5 cm (–3,0 SDS), bone age delay 30 months, puberty 1st stage. Stimulated GH 23.9 ng/ml. IGF1 <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, Apgar 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 5.1cm/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 Gynaecology 1

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

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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 sulfate, 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

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compared to lean ones ($p<0.05$). Homocysteine levels didn't correlated with body mass index, but positively correlated with insulin resistance ($p<0.05$).
Conclusions: Elevated plasma homocysteine levels in polycystic ovary syndrome were 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 was 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 excluded, and urinanalysis was normal. The ultrasound pelvic investigation revealed no intraabdominal or pelvic abnormalities. She underwent a vaginoscopy with excision and biopsy of a vegetating bleeding mass localized in the posterior wall of vagina.
Cytologic findings: On histology the diagnosis of embryonal rhabdomyosarcoma was ruled out because immunohistochemistry for miogenin and Myo+D1 was negative, and the lesion was classified as fibroepithelial polip.
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, more common over a wide age range. Therefore an accurate diagnosis is necessary for appropriate treatment with local excision. The prognosis of these benign tumors is good (only a case of malignant transformation was reported), even with recurrences.

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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.
Objectives: To determine prevalence, phenotype and features associated with PCOS in obese or type 1 diabetes adolescents and to compare gynecological and androgenic profiles between them.
Methods: 82 girls aged 12 to 17 years, Tanner V (mean gynecological age 2.7 years [min 2 - max 5 yrs.]), 48 with common obesity (mean Z-score BMI 3.9+/-0.8) and 34 with type 1 diabetes. PCOS was defined according to Rotterdam criteria.
Results: High prevalence of PCOS was found in obese and type 1 diabetes adolescents (29% and 38.2% respectively). The prevalence of different phenotypes according to Rotterdam criteria in obese/diabetes girls were as follow: 71/69% had oligomenorrhea, 57/46% hyperandrogenism, 50/100% hyperandrogenemia, 71/54% polycystic ovary morphology. Obese with PCOS showed pubertal development, anthropometric and metabolic parameters not significantly different compared to those without PCOS. However, for the entire obese group, waist circumference was correlated with free androgen index (FAI) ($R2= 0.35$; $p <0.01$). Type 1 diabetes adolescents with PCOS had similar pubertal development, anthropometric parameters, HbA1c and daily insulin dose compared to those without PCOS. However, for the entire diabetic group, BMI and HbA1c were correlated with FAI ($R2= 0.34$; $p <0.01$, $R2= 0.44$; $p <0.001$). Obese and diabetes adolescents with PCOS had elevated and comparable FAI but different androgenic profile: the first had normal total testosterone and androstenedione, associated with low SHBG, but diabetes girls had elevated total testosterone and androstenedione, associated with normal SHBG.
Conclusions: This study has confirmed high prevalence but different phenotype and androgenic profile of PCOS in obese and type 1 diabetes adolescents. Hyperandrogenemia was the most frequent feature described in diabetes girls with PCOS. Waist circumference and BMI/HbA1c were correlated with FAI in obese and diabetes girls.

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Steroid receptor density in breast tissue from boys with pubertal gynecomastia

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Background: Gynecomastia in pubertal boys is a common phenomenon descibed up to 80 %. It is more pronounced in obese boys, but does not correlate with estrogen, progesterone or androgen blood levels.
Objective and hypotheses: To elucidate, why only some boys suffer from breast enlargement not reducing by itself, hardly treatable by drugs, but efficaciously tractable by mastectomy. It was hypothesized that breast tissue of severe gynecomastia contains more receptors for sex hormones compared with breast tissue of a control group.
Methods: Breast tissue was examined for receptors of estrogen (E), progesterone (P), and androgen (A) as well as for proliferation factor (PF). Tissue was obtained following mastectomy in 33 boys and young men (12-22 ys of age). A control group of normal breast tissue from 27 patients (2-40 ys of age) without gynecomastia was obtained from the department of forensic medicine. In all samples of breast tissue malignancy was ruled out by routine histology. Steroid receptores were visualized by immunhistology using specific monoclonic antibodies combined with peroxidase and flurochrome dye. Density of A, E and P receptors were calculated semiquantitative by microscopy.
Results: Boys with pubertal gynecomastia (n=33) showed significantly higher concentrations of all steroid receptors (A: 60 %, E: 45,5 %, P: 64,4 %) compared with the control (n=27) group (A: 19,5 %, E: 14 %, P: 28 %). Those boys with gynecomastia and additional obesity (n=4) had their receptor density level higher than the control group, but lower than the rest of pubertal boys with gynecomastia. There was no significant difference between the groups as far as PF is concerned.
Conclusions: High concentrations of steroid receptors in breast tissue of boys with gynecomastia during puberty seem to explain the pronounced tissue reaction to relative low estrogen levels in blood. Those boys without breast development (control group) during puberty (with comparable estrogen levels) exhibit low steroid receptor density allowing no significant breast enlargement.

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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±1.3 ys with PCOS diagnosed according to Rotterdam criteria and 17 healthy controls matched for chronological and gynecological age as well as for 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<0.001) 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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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 puberty may suggest early diagnosis of endometric pathology and a choice of optimal therapeutic method which will allow avoiding development of expressed anemia in girls.
Objective 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 dopplerography. 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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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 *NBN* 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), homozygous for c.657_661del5 mutation, followed between years 1993 and 2008, assessed for growth and sexual development. Concentrations of gonadotropins and testosterone were evaluated using IRMA and RIA assays respectively. Patients after chemotherapy were excluded.
Results: Puberty commenced 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/V).
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.

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P2-d2-660 Gonads and Gynaecology 1

Measurement of inhibin B (InhB) by a newly developed ELISA in the assessment of ovarian function from birth to adulthood

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Background: The stage of follicular development, the degree of granulosa cell differentiation and the concentration of local regulators determine the characteristics of serum InhB pattern in females form birth to adulthood. A third generation of immunoassay has been developed shortening the time of the whole procedure.

Objective: Our aim was to establish the normal range of inhB levels using a newly developed assay (Active® Inhibin B Gen II ELISA, Beckman Coulter, USA), in females from birth to puberty and in different stages of the reproductive life.

Methods: 97 normal girls, 43 fertile menstruating women and 8 cycling perimenopausal women were included. Serum levels of gonadotrophins, estradiol and inhB were determined.

Results: During the first month of life, very low or undetectable inhB levels were present: 9.1±6.3 pg/mL (mean ±SD). A transient increase was observed around day 30 of life; however, these values did not reach the pubertal range ($p<0.01$). During infancy and before the onset of puberty, although inh B levels remained low (14.9±10.6), only in 3/21 samples inhB fell below the detection limit of the assay. During puberty, inhB levels increased significantly but they did not reach the mid follicular phase values determined in normal ovulating 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 ELISA and the previously used OBI method was found: $r=0.71$, $p<0.001$.

Conclusions: 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.

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Heterozygosity of CYP21A2 mutations does not contribute to the pathogenesis of PCOS

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Background: The question of the contribution of CYP21A2 heterozygosity to the development of Polycystic Ovary Syndrome (PCOS) has repeatedly been raised in the literature. The available data, however, do not offer a satisfactory answer. The discrepancy must be attributed, primarily, to the small number of studied subjects, the selected phenotype and the number of searched mutations.

Objective and hypotheses: To define the contribution of CYP21A2 heterozygosity in the pathogenesis of PCOS, by searching for 14 molecular defects of the gene in a large number of PCOS women and controls.

Methods: DNA analysis was carried out, by employing Allele-specific PCR and direct sequencing, in 197 women with PCOS, classified into two groups. Group 1 (n: 103); women with chronic anovulation, biochemical signs of hyperandrogenism and PCO on sonography and Group 2 (n: 94); women with the same phenotype but without PCO sonographic findings. Basal androgen levels were also determined by appropriate methodology in the follicular phase. The molecular data were compared to those obtained from 497 subjects from the general Hellenic population and those of androgens to 68 women without PCOS characteristics, matched for age. PCOS women with 17- hydroxyprogesterone (17OHP) basal values >2ng/ml and post ACTH >10ng/ml were excluded.

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% ($p=0.352$)]. The basal values of androgens (Testosterone, Δ4-androstenedione, DHEAS and 170HP) 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.

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Early-onset primary hypogonadism revealed by serum anti-Müllerian hormone (AMH) determination during infancy and childhood in trisomy 21

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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 hypogonadism is established earlier and affects other testicular cell populations.

Methods: We assessed the pituitary-testicular axis functional status, especially Sertoli cell function. To compare 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 increase in testis volume and serum testosterone. Serum AMH was above assay sensitivity at all ages (Table). In trisomy 21, AMH was lower than normal, indicating Sertoli cell dysfunction, from early infancy (Table).

		Serum AMH (pmol/liter) Control		Serum AMH (pmol/liter) Trisomy 21	P
Age group	n	Median (3rd-97th percentiles)	n	Median (3rd-97th percentiles)	
15 d - 2.9 yr	70	921 (436-2423)	22	379 (68-906)	<0.001
3 - 8.9 yr	76	597 (235-1489)	47	470 (163-897)	<0.001
9 - 18 yr G1	34	713 (257-1371)	9	389 (228-932)	<0.05
G2	34	295 (69-1017	7	163 (31-464)	NS
G3	42	71 (30-423)	6	60 (29-100)	<0.01
G4	41	65 (33-164)	17	26 (9-103)	<0.001
G5	60	82 (38-195)	9	57 (6-64)	<0.001

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FSH was elevated in 100% of patients <0.5 yr, 41% aged 0.5-2.9 yr, 18% aged 3-8.9 yr, 13% >9 yr G1, 50% G2, 50% G3, 88% G4 and 100% G5. Testosterone was within the normal range, but LH was elevated in 75% of patients <0.5 yr, 6% 0.5-2.9 yr, 13% 3-8.9 yr, 0% >9 yr G1, 17% G2, 50% G3, 71% G4 and 50% G5, indicating a mild Leydig cell dysfunction.
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.

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The antagonistic effects of traditional Chinese medicine on estrogen-like activity of environmental endocrine disrupptors

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Objective: The children with precocious puberty, who have exposed to higher pollution of EEDs, are treated with traditional Chinese Medicine (TCM). It is varified that the entagonistic 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 overy, 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 before and after therapy. The data were analysed by SPSS 11.5.
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 decended 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 um to 17.45 +/- 4.30um ($p<0.05$), thickness of the myometrium decreased from 82.29 +/- 13.92um to 55.20 +/- 10.20um ($p<0.05$), positive cell area of PCNA descended from 5490.25 +/- 678.58um2 to 4301.59 +/- 464.02um2($p<0.05$).
Conclusion: The present therapeutic regime of TCM could effectively against the estrogen-like activity of EEDs.

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Novel FOXL2 double heterozygous variants in an adolescent girl with premature ovarian failure

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Background: 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.
Objective: To find the etiology of POF in an adolescent.
Methods: A 16 years old female was investigated for primary amenorrhea. Thelarche 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 mIU/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 penetrance observed in inherited conditions such as POF.

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Analysis of the effects of metabolic syndrome and insulin resistance in juvenile polycystic ovary disease

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Background: The polycystic ovary syndrome affects approximately 10% of women of childbearing age, 70% of which is insulin resistance, which would be the basis for future metabolic syndrome.
Objectives: 1) Determine the presence of insulin resistance. 2) Assess risk factors for metabolic syndrome.
Method: Descriptive, cross sectional study, targeting women between 13 and 21 years, who were assisted in the Instituto de Maternidad, Tucumán, Argentina. The analysis was performed using descriptive statistics, the association of variables with SPSS V75.
Results: N: 293. PCOS was diagnosed in 12% of patients, 65% were obese, 19% had normal weight and remaining underweight. 72% recorded blood glucose greater than 100 mg / dl and the remaining 28% between 90 - 100 mg / dl. 81% scored higher value insulin with HOMA index higher than 2.9 in all cases. 69% had androgen values significantly higher than the maximum. 77% received high readings of cholesterol, LDL cholesterol and triglycerides and low HDL cholesterol, whereas in the remaining 23%, borderline values.
Conclusions: The insulin resistance in young patients with PCOS is still above average and the risk factors for metabolic syndrome are common, which is highly disturbing. We propose measures to increase the amount of information on the underlying disease to prevent its development and thus reduce the incidence of metabolic syndrome.

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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: TIII: 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.

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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 idio-pathic hypogonadotropic hypogonadism (IHH).
Methods: Serum AMH, gonadotropin and sex steroid levels were measured in 14 peripubertal boys with idiopathic short stature (ISS) who had been followed-up for 3 years, and in 20 patients with IHH.
Results: In healthy boys with ISS, serum AMH levels decreased before a significant increase in testis volume had oc-curred, 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 IHH displayed AMH levels that were lower than those observed in prepubertal boys.
Conclusions: In boys, the pubertal decline in AMH starts before the clinical onset of puberty. The data on patients with IHH suggests impaired development of the Sertoli cell population.

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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 vas deferens and abnormal morphology of the spermatozoids.
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 biological evaluation of growth and puberty by evaluating testosterone, anti-mullerian 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 +/- 1.07, 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 Inhibin B 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 (r^2=0.318, p=0.0004). FEV1 didn't influence neither INHB SDS (r^2= 0.001, p=0.83) nor AMH SDS (r^2= 0.006, p=0.61). BMI didn't influence neither INHB SDS (r^2= 0,031, p=0.234) nor AMH SDS (r^2= 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.

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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 micropolykystic 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 lenght 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 didelphys uterus with the absence of corporeal isthmic portion, 2 micropolycystic kydney and pancreatic hypoplasia. The laparoscopy confirmed the presence of 2 uterine horns, more voluminous at left and the cervical agenesis. Given this association, the molecular biology HNF1β gene (hepatocyte nuclear factor1β) 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, uterus duplex, 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. Reconstructive 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.

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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(13,8±1,2years) 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 metrorrhagic 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<3years.
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.

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

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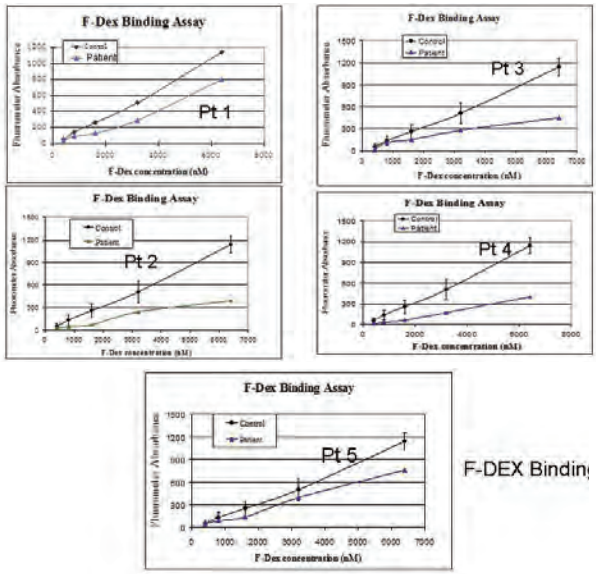
Background: PCOS is a heterogeneous group of diseases presenting with ovarian and/or adrenal hyperandrogenism. Although insulin resistance at the level of the ovaries seems to be the main cause of PCOS, other causes have been attributed to the cause of PCOS. There have only been a few reports of glucocorticoid 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.



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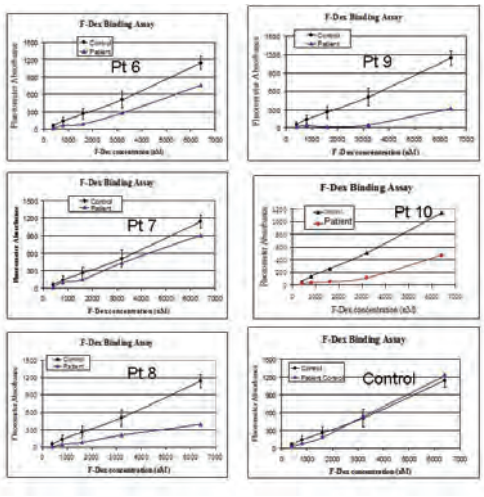

F-DEX Binding Studies

Patient	Age at Presentation	ACTH	Cortisol	NR3C1	FKBP4	FKBP5
1	17y	59	29.2	Pending	Pending	Pending
2	16y	18	25.2	Pending	Pending	Pending
3	14y	39	22.2	Pending	Pending	Pending
4	15y	168	16.9	E22E/R23K	Negative	Pending
5	14y	13	89.9	Negative	C6130G	Pending
6	15y	11	16.3	Pending	Pending	Pending
7	16y	60	30.5	Negative	C6130G	Pending
8	16y	39	11.5	N766N	Negative	Pending
9	16y	13	12.4	Pending	Pending	Pending
10	17y	20	9.3	Pending	Pending	Pending

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Galactorrhea due to contact dermatitis of breast

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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 moderate increase of serum prolactin level. Therefore, we think that nipple stimuli such as sustained scratching due to contact dermatitis should have been taken into consideration in the patients with hyperprolactinemia before meticulous investigation of its etiology.

P2-d1-674 Growth 1

Comparison of two different treatment patterns for tall stature in boys

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Background: Height reduction by testosterone treatment is a well known though still controversial therapy in boys with tall stature. The recommended doses of testosterone differ widely from 250mg up to 1000mg/month.
Objective and hypotheses: We compared the effectiveness of two different treatment approaches (250mg versus 500mg testosterone esters very 2 weeks i.m.).
Methods: All boys with constitutional tall stature treated at two different treatment centers (center A: 114 patients, center B: 47 patients) were included in this retrospective chart review. In center A 500 mg and in center B 250 mg testosterone esters were injected every two weeks i.m.. Predicted height was calculated according to Bayley and Pinneau from bone age using the Greulich-Pyle hand standards.
Results: At onset of treatment, the patients of the two centers did not differ in respect of age, height, bone age or predicted height based on bone age. Mean treatment duration was significantly longer and cumulative dose of testosterone was significantly higher in center A compared to center B. At end of testosterone treatment the predicted height did not differ significantly at the two treatment centers. The treatment regimes did not differ in respect to adverse side effects (64% acne in both centers, no further adverse side effects). Table 1: baseline data of patients before initiating of testosterone treatment separated to treatment center (data as mean and standard deviation; p-value derived from t-test).

	Treatment center A	Treatment center B	p-value
Number	114	47	
Age at onset [years]	14.2 ± 1.3	13.5 ± 1.1	n.s.
Height at onset of treatment [cm]	187.8 ± 7.3	185.5 ± 5.5	n.s.
Bone age at onset of treatment [years]	13.8 ± 0.8	13.6 ± 0.7	n.s.
Predicted height at onset of treatment [cm]	205.2 ± 5.2	205.6 ± 3.8	n.s.
Testosterone dose	500 mg every 2 weeks i.m.	250 mg every 2 weeks i.m.	<0.001
Duration of treatment [months]	14.2 ± 4.0	11.3 ± 2.2	<0.001
Total dose of testosterone [mg]	14,246 ± 3,986	5,638 ± 1,101	<0.001
Height velocity during treatment [cm/year]	6.2 ± 3.1	7.3 ± 4.2	0.118
Height at end of treatment [cm]	195.1 ± 5.0	192.4 ± 4.4	0.002
Bone age at end of treatment [years]	16.9 ± 0.5	15.9 ± 0.7	<0.001
Predicted height at end of treatment [cm]	197.7 ± 5.3	196.2 ± 4.6	0.085
Delta bone age / delta chronological age	2.7 ± 0.8	2.5 ± 1.0	0.293
Reduction of height based on predicted height at end of treatment [cm]	7.6 ± 5.0	7.9 ± 4.8	0.306

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.

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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 haploinsufficiency have been reported in some individuals with idiopathic short stature (ISS) and in many patients with Leri-Weill-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 use 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 (PARI) 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 plane angle between the wrist distal ulna and radius (140.89±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.
Population and methods: 39 children with ISS and 53 normal height controls of similar age (4-16years) and sex distribution, all of them ethnic Greeks, were included in the study, following exclusion of identifiable causes of short stature. Peripheral blood was used for genotyping and biochemical analyses, following informed consent of the children's guardians. Genotyping of 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 (gen otypes,p=0.036;alleles,p=0.05) was observed with respect to the VDR FokI polymorphism, as a result of the complete absence of ff genotypes 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 FokI 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: Preterms 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: Auxological 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.

	BMI-SDS (0.5y)	BMI-SDS (1y)	BMI-SDS (2y)	BMI-SDS (4y)	BMI-SDS (5.7y)	BMI-SDS (9.5y)
triceps-skinfold-thickness-SDS	r=0.588 p=0.000	r=0.598 p=0.000	r=0.650 p=0.000	r=0.397 p=0.027	r=0.732 p=0.000	r=0.802 p=0.000
DXA-total fat mass	r=0.429 p=0.010	r=0.346 p=0.042	r=0.355 p=0.037	r=0.317 p=0.068	r=0.691 p=0.000	r=0.814 p=0.000
abdominal fat mass	r=0.437 p=0.009	r=0.328 p=0.054	r=0.298 p=0.082	r=0.261 p=0.036	r=0.651 p=0.000	r=0.771 p=0.000
hip fat mass	r=0.443 p=0.008	r=0.319 p=0.062	r=0.335 p=0.049	r=0.323 p=0.062	r=0.684 p=0.000	r=0.702 p=0.000
lean-body-mass	r=0.346 p=0.042	r=0.478 p=0.004	r=0.456 p=0.006	r=0.332 p=0.055	r=0.476 p=0.004	r=0.471 p=0.003

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 ascertained 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.

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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 individualized 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], weekly number of injections [6 or 7]); Model 2 added genetic markers (from a list of 4 identified by genetic screening analyses 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 R^2 and root-mean square error (√MSE) of the model. Selection of auxological parameters was fixed and from historical data (Ranke). Addition of biomarkers and/or genetic markers was controlled by minimizing model √MSE.
Results: In 34 girls with TS, auxological parameters alone explained 39% (=R^2) of response variability. The R^2 increased to 57% when adding a selection of genetic markers, to 62% when adding a selection of baseline biomarkers and to 76% when adding a combination of genetic markers and baseline biomarkers. Karyotype 45X estimate was significant in genetic and combined markers 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-d1-679 Growth 1

Severe growth failure in an infant with novel mutations in the ATP6V1B1 gene exhibiting incomplete distal renal tubular acidosis

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Background: Many patients with distal renal tubular acidosis (dRTA), a rare disorder, initially present with growth failure.
Objective: To describe the case of an 8-month-old girl with sensorineural deafness who was referred to our hospital for investigation.
Results: An 8-month-old girl was referred to our hospital to investigate the cause of her failure to thrive (body height, -4.66 SD; body weight, -3.66 SD). She was generally doing well except for muscle weakness and thin hair. The blood tests showed hypokalemia (K 2.5 mEq/L). A month later, she was brought to the emergency department because of unconsciousness after frequent vomiting. Except for hypokalemia (K 1.8 mEq/L) and leukocytosis, laboratory findings were within normal ranges. She was treated for hypokalemia with intravenous administration of potassium and spironolactone. Endocrinological tests revealed increased plasma renin activity and aldosterone levels; these findings suggested type 4 Bartter syndrome. However, at follow-up, her blood gas analysis showed slight acidemia (pH 7.325), which returned to within the normal range spontaneously. Her diagnosis was reconsidered, and a thorough examination including loading tests confirmed the diagnosis of dRTA. Treatment with bicarbonate and potassium is improving her growth. Genetic analysis revealed novel compound heterozygous mutations of the *ATP6V1B1* gene with an A326 insertion A in exon 10 and a maternally inherited nonsense mutation of Y417X in exon 13.
Conclusions: In this patient, novel mutations in the *ATP6V1B1* gene were detected. dRTA should be given consideration as a potential cause of failure to thrive or short stature which could be severe. As in this case, some dRTA patients present as "incomplete types" associated with an atypical clinical course or inconsistent findings. Appropriate assessment including blood gas analysis is recommended for patients with growth failure accompanied by an electrolyte disorder.

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 osmolarity.
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 to what has previously been reported. In these children the TBI was mild, frontoparietal-located and with subarachnoid haemorrhage in the CT.

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P2-d1-681 Growth 1

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 radiogram 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 auxological 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 haploinsufficency 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.

P2-d1-682 Growth 1

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.
Methods: 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: Causative 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 polypyrimidine 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 missense/nonsense GHR mutations ($p<0.05$) than in subjects with splice site GHR mutations including the pseudoexon defect.

Mutation	Number of individuals
GHR nonsense/missense	
S40L	7
V125A	2
R161C	1
G223G	2
L229P	1
R43X	7
C48X	2
Q65X	1
E180X	1
Q216X	1
GHR splice site	
IVS2 ds+1 G to A	2
IVS6 ds+1 G to A	1
Pseudoexon insertion	15
IVS7 as-6 T to A	1
IVS8 ds-1 G to C or R274T	3
IVS8 as-6 G to A	1
IVS9 ds+2 T to C (heterozygous)	2
GHR deletion	
c.1323_1344del22 (450X)	2
STAT5B	
c.1680delG	2
IGFALS	
P73L	1
L134Q/546-548delGGCinsAG	1
L134Q	2
c.1490insT	1
D440N	1
Unknown	10
Total	70

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.

P2-d1-683 Growth 1

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 tall stature is a sign that that child will end up on a lower 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.

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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 <- SDS 1) 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 $r^2 = 0.39$ range 0.35 to 0.45 for boys at age bins 8 to 14; mean $r^2 = 0.27$ 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 nomral-tall adults. This rule is only altered when bone age SDS deviates from height SDS (i.e. when BA deviates from "height-age").

P2-d2-684 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 also determined in all children at baseline. GH and IGF-I were measured by chemiluminescence assay.
Results: Mean BMI-SDS in the entire cohort was -0.86±0.92 (range -1.95-1.75). Three patients had a nocturnal PGH <10µg/L and 32 patients had a PGH >10µg/L. All patients had mean GH concentration (MGHC) >4µg/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 with baseline IGF-I in all patients and with BMI-SDS and IGF-I in prepubertal or pubertal children. Mean PGH and MGHC (21.15±11.31 and 4.8±1.6µg/L, respectively) were similar between subjects with BMI-SDS -2 to 0 (n=29) and those with BMI-SDS 0 to +2 (16.37±4.29 and 6.19±1.58µg/L, n=6).
Conclusions: In this cohort of short children with normal BMI-SDS, BMI has no significant impact on nocturnal spontaneous GH secretion. These findings suggests 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-d2-685 Growth 2

A novel mutation in a mother and a son with Aarskog-Scott syndrome

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Background: Aarskog-Scott syndrome which is also termed as faciogenital dysplasia, is a X-linked disorder consisted of short stature, craniofacial dysmorphism, shawl scrotum, cryptorchidism, interdigital webbing. Cardiac, central nerve system abnormalities and behavioral disorders can also be detected. The gene responsible for the syndrome is called FGD1 gene and is located at the Xp11.21.
Case presantation: Seven years old boy was admitted to our hospital with a complaints of short stature. He was born to nonconsanguineous parents after an uneventful term pregnancy. He was operated for bilateral cryptorchidism when he was two years old. He has a healthy sister. On physical examination, his height was 113.5 cm (-2,12 SD), and weight was 21 kg (-1,1 SD). He had a broad nasal bridge, hypertelorism, wide filtrum, brachydactily, interdigital webbing. His cranial MRI and echocardiography were normal. On his eye examination amblyopia and astigmatism were detected. His mother had also short stature and interdigital webbing.
Results: Mutational analysis were done from the mother and the son. Hemizygos IVS2 -2A>G mutaion at boy was detected. His mother was also heterozygos fort he same mutation. It was a novel mutation.
Conclusions: Aarskog-Scott syndrome should be kept in mind in children with interdigital webbing, short stature and faciogenital dysplasia.

P2-d2-686 Growth 2

Abstract withdrawn.

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 2-3% using water displacement by head immersion.
Results: Headless/standard weight ratio increased from 0.82 (age 2) to 0.91 (age 9) in girls and from 0.83 to 0.91 in boys. Height 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 BMI headless/standard ratio remained constant at 1.06-1.08 for boys and girls, reflecting the head's smaller specific gravity. In 3 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.

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P2-d2-688 Growth 2

Serum testosterone levels and growth velocity in healthy boys

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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^2=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/L. 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

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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-L05096.
Results: Twelve individuals carried a large deletion starting in PAR1 and extending to PAR8/9 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.

P2-d2-690 Growth 2

The effects of anti-TNF-α treatment with adalimumab on growth in children with Crohn's disease (CD)

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Introduction: Adalimumab is used to treat children with Crohn's disease (CD), but the effects of adalimumab on growth in CD have not yet been studied. Aim: To study growth, disease activity over the 6 months prior (T-6) to starting adalimumab at baseline (T0) and for the following 6 months (T+6) in children with CD.
Subjects and methods: The growth and treatment details of 36 children (M: 22) <18 years old who were started on adalimumab at a median (10th, 90th) age of 14.7years (11.3, 16.8) were reviewed retrospectively. Response and remission was assessed using the Paediatric Crohn's Disease Activity Index (PCDAI)/ Physicians Global Assessment (PGA). Results are expressed as median (10th, 90th).
Results: Growth details of a previously published cohort of 72 children were examined. Of these 36 could be used for further analysis; 34 out of 36 had previously received infliximab. Out of 36 cases, 28(77.7%) went into remission. In the whole group median change in height SDS (ΔHtSDS) increased from -0.2 (-0.7, 0.2) at T0 to 0.0 (-0.5, 0.8) at T+6, (p=0.005) at T+6. In children who achieved remission, median change in height SDS (ΔHtSDS) over the previous 6 months increased from -0.2 (-0.9, 1.0) at T0 to 0.2 (-0.6, 1.6) at T+6, (p=0.007) as compared to those not in remission where median change in height SDS (ΔHtSDS) decreased from -0.1 (-0.7, 0.1) at T0 to -0.3 (-0.8, 0.2) at T+6, (p=0.87). In the subgroup of 23 children who were on background immunosuppression therapy at adalimumab commencement, median change in height SDS (ΔHtSDS) increased from -0.2(-0.9,1.0) at T0 to 0.1 (-0.8,1.3) at T+6, (p=0.03). Median change in height SDS (ΔHtSDS) also increased from -0.4 (-0.8,0.7) at T0 to -0.0(-0.6,1.6) at T+6,(p=0.04) in a subgroup of 15 who were on prednisolone therapy at starting adalimumab.
Conclusion: Clinical response to adalimumab therapy is associated with an improvement in linear growth over the short term in children with CD and is more likely in patients taking immunosuppression and is not solely due to a steroid sparing effect.

P2-d2-691 Growth 2

The spectrum of growth failure in fetal alcohol spectrum disorder (FASD)

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Background: The exposure of a developing fetus to alcohol can cause physical anomalies and neurodevelopmental disorders described as fetal alcohol spectrum disorder (FASD) including fetal alcohol syndrome (FAS), partial FAS (pFAS), and alcohol-related neurodevelopmental disorder (ARND). The most severe form of FASD, FAS, has growth retardation as one of the diagnostic features. The spectrum of growth failure in FASD has not been previously described.
Objective and hypotheses: This study tested the hypothesis that growth fail-

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ure would be seen in all forms of FASD.
Methods: An IRB-approved, retrospective chart review of individuals seen in FASD Clinic at the University of Minnesota was performed. Height (Ht), weight (Wt), head circumference (OFC) and FASD diagnosis were obtained. Predicted means for each group using least squares means in SAS were compared by ANOVA with Bonferroni correction.
Results: Of 173 charts, 147 had growth data (n=82 male, ARND=50, FAS=13, pFAS=37, Non-FAS=47).
Mean Ht SDS (-0.78; 95% CI: -1.43 to -0.13) was significantly lower in FAS than CDC norms but not other groups. Mean Wt SDS (-1.03; 95% CI: -1.75 to -0.30) and mean OFC SDS (-1.50; 95% CI: -2.23 to -0.78) were significantly lower in FAS than CDC norms and all other groups. Wt SDS was higher than CDC norms in ARND, pFAS and Non-FAS.
When analyzed by gender, males with FAS (-1.17; 95% CI: -1.94 to -0.41) were found to have more severe linear growth failure than females (+0.10; 95% CI: -1.09 to + 1.29).

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.

P2-d2-692 Growth 2

Satisfaction and psychological well-being in estrogen-treated tall women

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Objective: Our aim was to study satisfaction, associated side effects and psychological well-being in adult tall women who were treated with high-dose estrogens 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 psychological well-being did not differ between the groups. Overall happiness at adult age was reported by 71.8 % and 73.3% in treated and untreated patients, respectively.
Conclusions: Most tall women treated with high-dose estrogen were satisfied being treated during adolescence. Their overall psychological well-being did not differ versus untreated tall women when evaluated at an adult age.

P2-d2-693 Growth 2

Dental and skeletal maturity in children with growth hormone deficiency

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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 periodontal 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 skeletal 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 ($p<0.05$).
Conclusions: When comparing the mean difference between dental maturity at baseline and one year later, in the children with growth hormone deficiency 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.

P2-d3-694 Growth 3

IGF-1 and IGFBP-3 levels and distribution of IGF -1 gene polymorphisms in idiopathic short stature

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Background: Idiopathic short stature (ISS) is a heterogeneous disorder. Defects in growth hormone (GH) – insulin like growth factor-1 (IGF-1) axis have been implicated in the pathogenesis.
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 (rs35767 and rs17032362) in ISS patients and compared them with controls.
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±3.1years) 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 diffirence 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 diffirences 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.

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P2-d3-695 Growth 3

Final heigth after treatment with growth hormone in three brothers and sister with Marshall syndrome

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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 COL 11A1 gene. Mean final heigth 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 were 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 heigth, and the growth data are presented to final heigth. Genetic data and preliminary growth data were earlier presented at ESPE in 2000 and 2004.
Method: They have all been treated with hGH dosages within normal or sligthly increased ranges to near final heigth.
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 acheived before puberty for pats. 2 & 3 after which they grew less well during puberty and lost relative heigth, opposite to pat. 1 who gained most in puberty.
Conclusions: Growth hormone therapy in MS is efficient in increasing final heigth, but most of the effect seem to be achieved before start of puberty.

P2-d3-696 Growth 3

A cross-sectional clinical assessment of growth and puberty in adolescents with Crohn disease

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Background: Growth impairment and delayed puberty are observed in Crohn disease (CD) due to under nutrition and chronic inflammation. Objectives. To assess growth and pubertal development in CD adolescents.
Methods: Inclusion criteria (IC) for endocrine evaluation were: established diagnostic of CD, chronological age (CA) between 11 to 15 years in girls and 12 to 16 years in boys. Height (H), target height (TH), body mass index (BMI), pubertal stage were recorded.
Results: Among the 244 CD patients evaluated from 2004 to 2010, 68 met the IC and 45 CD adolescents (mean CA: 14.1 ± 1.2 years, 25 boys) were prospectively evaluated from May to August 2010. Their CD treatment was either a monotherapy in 73% (TNF antibody, infliximab or adilimumab, 45%; other immunosuppressive drugs, 51%) a bi-therapy in 18% (steroids and/or immunosuppressive drug and/ or infliximab) or exclusive enteral nutrition (9%). 9% of patients were off treatment. Mean height SD and BMI SD were -0.3 ± 1.2 and -0.6 ± 1 respectively, 3.1 ± 1.7 years after diagnosis. Nine patients (20%) had a height SD or a delta (height-target height) SD below -2. Patients were pre pubertal (n=1) or at pubertal stage II (n= 10, 22%), III (n=6, 13%), IV (n=14, 31%) or V (n=14, 31%). Mean CA for boys at stage II was 14.2 ± 0.9 years (12.7-15.9 years). Mean CA for girls at stage III was 13.5 ± 1.3 years (12.2-15.1 years). Ten girls (50%) had not yet experienced menarche at a mean CA of 13.3 ± 1.2years (11.9-15 years).
Conclusion: CD had a negative impact on growth in about 20% of patients. Delayed onset or slow progression of puberty were observed in both sexes. Factors linked to CD that might influence the tempo of puberty of these patients are currently under study.

P2-d3-697 Growth 3

Growth in children with Crohn's disease receiving contemporary therapy in the United Kingdom

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Introduction: It is unclear whether recent advances in therapeutic regimens have had a beneficial impact on growth in children with Crohn's Disease (CD).
Aim: To study growth and its relationship to therapy at diagnosis (T0), after 1 year (T1), 2 years (T2), 3 years (T3) and at maximum follow-up (MF) in children with CD.
Subjects and methods: The anthropometric and treatment details of 116 children (68 M, 48 F) with onset of CD before the age of 17yr were reviewed. Median age at diagnosis was 11years (4.9, 15.5). Median age at MF was 16.1yr (9.4, 19.3).
Results: At diagnosis, HtSDS was -0.4(-2.0, 0.9) compared to midparental Ht SDS of 0.2(-1.2, 0.9) (p=0.003). Median Height Velocity (HV) SDS increased from -1.9(-7.4, 7.5) to -0.7(-7.5, 6.1) (p=0.005) between T1 and T2, and from -0.7(-7.5, 6.1) and -0.5 (-6.8, 7.7) (p=0.01) between T2 and T3 and from -0.5 (-6.8, 7.7) and 0.0(-4.9, 7.8) (p=0.03) between T3 and MF. HVSDS at T2 and T3 showed an association with the average ALP over the previous one year (r, 0.34, p=0.03) and (r, 0.36, p=0.02), respectively. Although HVSDS improved during follow up HtSDS did not change from T0 to MF. No single drug or marker of disease activity showed a significant association with growth parameters.
Conclusion: At maximum follow-up about two-thirds of children in a contemporary cohort of children with CD are shorter than average and about 40% of children have a HVSDS <1.Thus, short stature and slow growth continue to be encountered in children with CD despite improvement in clinical management of the disease.

	At diagnosis (n,116)	T1 (n,116)	T2 (n,98)	T3 (n,78)	MF (n,78)
HtSDS	-0.4 (-3.3,2.6)	-0.6 (-3.7,2.2)	-0.7 (-2.9,2.2)	-0.7 (-3.6,2.5)	-0.5 (-3.5,3.2)
%HtSDS<-2	10%	10%	12%	10%	8%
%HtSDS -2 to -1	23%	18%	24%	23%	27%
%HtSDS <-1 to 0	31%	36%	33%	38%	29%
HVSDS		-1.9 (-7.4, 7.5)	-0.7 (-7.5,6.1)	-0.5 (-6.8, 7.7)	0.0 (-4.9, 7.8)
%HVSDs<-2		48%	39%	24%	20%
%HVSDS -2 to -1		17%	9%	22%	20%
%HVSDS <-1 to 0		13.3%	7%	9.5%	8.5%
%BMISDS -2 to -1	25%	12.1%	23.5%	16.6%	11.5%
Pubertal status (I,II,III,IV,V)		(18,4,0)	(14,5,3)	(10,8,4)	(6,6,10)

P2-d3-698 Growth 3

"PATRO children" - first data from the patients treated with Omnitrope® study

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Background: The "PATRO children" study has been initiated to increase data on the safety and efficacy of Omnitrope treatment and is intended as a global patient outcome database.
Objective and hypotheses: "PATRO children" is a post-marketing surveillance study designed to monitor the long-term safety and efficacy of Omnitrope (recombinant human growth hormone [rhGH]) in infants, children and adolescents with particular reference to the risk of diabetes, malignancies and occurrence of anti-rhGH antibodies.

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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	Patients, n (%)
Male	438 (56.2%)
Chronological age / bone age (years)	8.97 (SD 3.60) / 7.48 (SD 3.70)
Height Standard Deviation Scores (accoring to Prader et al, 1989)	-2.33 (SD 1.15)
Diagnosis at presentation	
—Growth hormone deficiency	457 (59.9%)
—Small for gestational age	212 (27.8%)
—Turner Syndrome	36 (4.7%)
—Prader-Willi Syndrome	20 (2.6%)
—Chronic renal insufficiency	3 (0.4%)
— Other	35 (4.6%)
Country of origin	
—Germany	441 (56.0%)
—France	197 (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%) / 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 cases of new-onset diabetes or malignancies 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-d3-699 Growth 3

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 dysmorphologycal 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 LWD. 2) To determine who among the subjects of short stature should be tested for the gene SHOX.
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.

TAB. A	NON SHOX-D	SHOX-D	p
n. (%)	57 (82)	12 (18)	
M/F	26/31	6/6	-
Age	8.8 (± 2.9)	9.9 (± 3.6)	0.3
H SDS	-2.3 (± 0.9)	-2 (± 0.7)	0.3
VC SDS	-1.5 (± 1.7)	-1.2 (± 1.7)	0.6
BMI DS	-0.2 (± 1.2)	0.6 (± 1)	0.001
SH DS	-0.26 (± 1.09)	0.62 (± 0.5)	0.02
TH DS	-1.1 (± 0.8)	-1.1 (± 0.9)	0.82

TAB.B	n.	NON SHOX-D n. (%)	SHOX-D n. (%)
LWS (MD, mesomelia, dismorfic signs)	18	9 (50)	9 (50)
NO LWS (with dismorfic signs)	20	17 (85)	3 (15)
no dismorfic signs	31	31 (100)	0 (0)

TAB.C	NON SHOX-D	SHOX-D
High-arched palate n. (%)	7 (12.3)	5 (41.6)
Cubitus valgus n. (%)	12 (21)	9 (75)
Short forearm n. (%)	9 (15.8)	9 (75)
Madelung deformity n. (%)	9 (15.8)	9 (75)
Sitting height >50°pct. n. (%)	17 (29.8)	11 (9.3)
Bowing of tibia n. (%)	5 (8.7)	6 (50)
Genu valgum n. (%)	7 (12.3)	8 (66)

Conclusions: 1) the only significant parameter auxlogical found in patients with SHOX-D is a higher BMI.
2) Only 50% of LWS are detectable as SHOX-D.
3) SHOX-D was never detected in individuals with no anthropometric or defects dismorfic.
4) seat height / standing height ratio is the sign with the highest sensitivity.

P2-d3-700 Growth 3

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

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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(+) than in HP(-) group (1088.77 ±271.48 vs. 1535.70 ±838.54 pg/ml, $p<0.05$) while the leptin concentration did not differ significantly between both groups (3.94 ±4.79 vs 5.96 ±8.58 ng/ml, ns) In children with HP(+), there was no correlation between ghrelin levels and both patients age ($r=-0.37$, $p>0.05$) 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.

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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

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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, thigh 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.

Age (years)	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	28
P3	45,8	46,5	48,5	50,2	52,4	53,8	55,9	57,4	60,4	61,5	62,3	66	67,8	69,8	70,3	69,1	74,1
P10	46	47,2	49	51,5	53	54,8	56	58,5	61,6	62,5	65,3	68,2	69,7	73	73,6	73,6	79
P25	46,5	48,5	50,2	52	53,5	56	58	60	63,1	65,9	68	70	72,5	74,5	75,5	76,8	81,8
P50	47,8	49,5	51	53,6	56,5	59	62	65	66,5	70,1	72,7	74,5	76,2	77	79	80,5	90,3
P75	48,7	51	53,2	57	59,5	62,5	66	69	72,5	75,5	80	80	81	81,5	83,5	84	97,9
P90	51,7	52,1	54,7	58,3	62,7	66,6	71	74	79,6	83,1	81	84,5	87	86	88,7	89,7	102,3
P97	53,5	53,5	59,3	59,9	67,6	70,1	73,5	80	84,6	87,8	87,4	89,7	93	95,1	95,7	95,9	104,9

Waist circumference men (n=42)

Age (years)	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	28
P3	43,1	44,9	46,7	48,1	51	54,1	55,2	59,3	60,3	61,1	63,3	65,1	67	66,4	65,8	66,1	67,7
P10	44,6	46	48	50,1	52	54,5	56	59,5	61,8	62,5	66,3	66,4	68,9	68	67,5	68,6	69,4
P25	46,8	47,5	49,4	51,7	54	56	58	61	64	65,4	68,4	70	71,8	69	70,6	72	72,5
P50	48	49,5	50,5	54,5	56,5	60	61,5	66,1	67,3	69,6	72,4	74,3	75,7	75,2	75,5	75	75
P75	49,7	51	54	57	60	64,7	68	72	76,3	76,3	79,6	78,6	78,1	79,6	80,6	79,1	86
P90	51,5	53	57,4	63,7	64,3	68,4	70,9	80	81,2	84,6	88,1	84,7	80,6	83,6	87	87	95
P97	52,9	55,8	59,9	68,1	73	75	80,9	92,5	93,5	99,7	94,9	97	95,7	95,3	90	94,9	107,7

Waist circumference women (n=45)

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)

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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 (subxiphoid) 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=0.03) 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 defficiency (GHD)?

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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: Fourty 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 elemens. IGF-1 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.

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P2-d3-704 Growth 4

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

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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 clinidine 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 over night fast, after abase line blood sample (0min) clonidine tablet (0.15mg/m2) given by oral route and blood samples for GH measurement were drown 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 of (10ng/ml) occurred, in dependant of the fact that higher values is reached later.
Results:

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

Baseline characteristic of the patients.

	30 min	60 min	90 min	120 min
GHD	2	22	17	1
ISS	2	58	13	1

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

	< 90 min	>90 min
All subjects%	97.4	2.6
ISS%	98.6	1.4
GHD%	96	4

Percentage of GH peaking during clonidine in all subjects and in ISS and GH children before and after 9o min.

	30min	60 min	90 min	120 min
Frequency distribution	12	51	6	1
Percentage	16.1%	72.8	8.5%	1.4%

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

	<90min	>90min
Percentage	98.6	1.4

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.

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 NFI were café au lait macules (96.3%), 1st degree relative with NF1 (41.5%) and axillar or inguinal freckles (23.2%). At the di-

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agnosis, 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 SD) in 33.3% of the patients.
Conclusions: Elevated HCHR is an early and common feature for NF1 in children below 7 years and it is strongly suggestive for NF1 when the disease is suspected but yet not fulfilling the NIH criteria.

P2-d3-707 Growth 4

Factors affecting growth velocity during gonadotropin-releasing hormone agonist treatment in girls with idiopathic central precocious puberty

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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.

P2-d3-708 Growth 4

First year growth response to growth hormone therapy in patients with short stature associated with SHOX deficiency

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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 (Roelants 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 (-1.9±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 50 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.

P2-d3-709 Growth 4

Growth factors evaluation in Babinga Pygmy from childhood to adulthood

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Background: The Pygmy is a paradigmatic model for Idiopathic Short Stature to better understand the mechanisms regulating human growth.
Objective and hypotheses: In this study we investigated height and hormonal levels in 136 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 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 (Pygmy: -2.96±1.14 SDS, Bantu: -0.55±1.09 SDS; p<0.0001). Pygmy showed significantly decreased levels of IGF-I (Pygmy: -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: 26.33±6.72 µg/ml, Bantu: 33.50±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.

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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 6 years, 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 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-d3-712 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 year 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 hypoglycemia and L-dopamine tests. Children were classified as: severe GH deficient (SGHD) (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(Ht), 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 1st 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 dimorphism, short stature, congenital cardiopathy, chryptorchidism. Three sporadic families who had Noonan Syndrome suggestive features and were negative for mutations in previously identified disease genes showed an heterozygote mutation of CBL gene.
Case report: We report a case of 12 years old girl who had clinical features of Noonan syndrome: Height : 133cm (Short stature <P3), characteristic face : Ptosis, down-slanting palpebral fissures, low-set posteriorly rotated ears, clinodactily, pigmented naevi, cafe-au-lait spots, mental retardation, cardiac ultrasound showed a Mitral valve prolapse, caryotype was normal : 46XX. Mutations PTPN11, KRAS,RAF1,SHOC2,SOS1 has been researched but were negative. Heterozygote mutation of CBL gene (C.1100A >C (p.GLn367pro) was detected.
Conclusions: These findings document that mutations in CBL alter development and may cause a Noonan –like syndrome and predisposes to malignancies showed in this syndrome. Mutations were shown to affect CBL-mediated receptor ubiquitylation and dysregulate signal flow through RAS.

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 b-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-

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ments below average. Vineland questionnaires revealed that 9 children were rated by their parents lower on adaptive skills compared to the age-adjusted average of the general population.
Conclusions: Despite previous studies that showed a higher prevalence of neurodevelopmental difficulties and even severe mental retardation among children diagnosed with CHI, our study showed mostly normal cognitive achievements. The good neurodevelopmental outcome can be explained by the better management of the disease in the last decade.

P2-d3-715 Hypoglycaemia 1

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

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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 diagnostic fast was 26 days (range 7 to 70 days). The mean glucose concentration during the fast was 2.1mmol/L (SEM±0.13) and the mean insulin level was 12.4mU/L (±2.6). The mean serum GH concentration during the hypoglycaemia was 12micrg/L (±1.69).The data on serum IGF-1 was available in 8 babies and revealed a mean value of 36.5ng/ml (±4.8). The mean cortisol concentration was 215nmol/L (±39).
Conclusions: The serum GH counter regulatory hormonal responses to HH are markedly elevated whilst the serum cortisol counter regulatory hormonal responses are blunted. However despite the exaggerated serum GH response the serum IGF-1 levels are relatively low, demonstrating a degree of GH resistance. Further studies are required to understand the mechanism/s of the paradoxical serum GH and cortisol counter regulatory hormonal responses in neonates with HH.

P2-d3-716 Hypoglycaemia 1

GH deficiency presenting as hypothermia and hypoglycemia in a 4 year old

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Background: Hypoglycemia may occur in association with various hormone deficiencies. It is common among children with primary or secondary GH and cortisol deficiency, and has been reported in children with hypothyroidism. The pathogenesis of hypoglycemia in these disorders is incompletely understood. The management and prevention of hypoglycemic episodes in children who have associated hormone deficiencies center on diagnosis of the deficiency and appropriate hormone replacement therapy.
Objective: To present a case report of patient that presented with hypoglycemia and hypothermia secondary to GH deficiency.
Method: 4 year old male, presented to the ER with flu like symptoms and hypothermia (93° Farenheit). Physical examination only showed cervical and axillary lymph node enlargement. During the periods of hypothermia the patient presented with signs of adrenergic surges, which included diaphoresis, cold and clammy skin, shakes and tachycardia. Hypoglycemia was suspected and a glucometer showed 50 mg/dL. a 72 hour fasting protocol was started.
Results: The 72 hour fasting protocol (Table 1) was stopped during the 21st hour because of Whipple's triad and a central glucose of 52 mg/dL.
The insulin, glucagon, epinephrine and cortisol response were adequate for the hypoglycemia, but the peak GH response was 0.61 ng/mL. An IGF-1 and IGF-2 were performed with a result of 53.3 (normal ranges 49-283) and 468 (normal range 754-1216) respectively.
A Clonidine stimulated test was done (Table 2), with a peak GH of 5.43 ng/ml at 120 minutes. An MRI of the Sella Turcica was performed and showed a Rathke pouch remnant (Figure 1) that was compressing the pituitary gland. The rest of the Pituitary hormones were normal (LH: 0.2, FSH: 1.3, T4: 8.5 TSH: 2.0, ACTH 15, Prolactine 8.).

Day	Hour	Glucose (mg/dL)	Insulin (uUI/L)	Cortisol (mcg/dL)	Epinephrine (pgr/mL)	Glucagon	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	23:00	60	0.97	18	N/A	N/A	N/A
2	00:00	181	50	7	40	N/A	1.21
	06:00	66	0.6	21	35	82	3.3

Time (minutes)	HGH (ng/mL)
basal	0.38
30	5.07
60	3.40
90	4.15
120	5.43

Conclusions: We concluded that the patient suffered from hypothermia due to hypoglycemia due to GH deficiency due to a Rathke pouch remnant. GH replacement was started at a dose of 0.3 mg/Kg/Week divided in daily doses. No further hypoglycemia or hypothermia were reported.

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 $34^{4/7}$ 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^{1} 4^{5} 8^{10}, 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 mU/L) and high carbohydrate requirements to maintain normoglyceamia (> 15 mg/kg/min), while growth hormone (47.5 mcg/L) and cortisol (464 nmol/L) levels during hypoglycemia were adequately elevated confirmed the diagnosis of CH.
Treatment with Diazoxide (5 mg/kg/d) promptly resolved the hypoglycemias. Treatment could be discontinued at age 15 months. Growth and psychomotor

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development were normal. Oral glucose tolerance test in the mother revealed hyperinsulinism (185.5 mU/L at 30 min.) inducing a symptomatic hypoglycemia (3 mmol/L at 120 min.). We identified a novel heterozygous mutation in exon 12 of *ABCC8* (c.1780T>C) in our patient, his mother, and his maternal grandfather. This mutation is predicted to be pathogenic because the amino acids involved are evolutionary conserved.
Conclusions: We describe a novel maternally inherited heterozygous mutation in the *ABCC8* gene causing CH in the patient and symptomatic hyperinsulinism in his mother. The same mutation in *ABCC8* seems to lead to different phenotypes. Since the natural history of the disease is not well established a long-term follow-up is required.

P2-d3-718 Hypoglycaemia 1

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 laparoscopy. In three patients, heterozygous and paternally inherited mutations were found, suggesting focal disease. Altogether, 4 different ABCC8 mutations including two novel alterations (F686I, G1379S) and two reported mutations (F686S, IVS27-1G>A) were identified. The mutations IVS27-1G>A and F686S occurred in four and two families, respectively. The novel mutations F686I and G1379S occurred in two unrelated families. KCNJ11 mutations were not found in any patients.
Conclusion: Our results extend the knowledge of the molecular genetics behind CHI in Vietnam.

P2-d3-719 Hypoglycaemia 1

Genotype-phenotype associations in children with congenital hyperinsulinism

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Congenital hyperinsulinism (CHI) is a heterogeneous disease in terms of clinical presentation, genetics and histology. Mutations in eight genes are known to be a cause of CHI, of which *ABCC8*, *KCNJ11* and *GCK* are among the most common.
We investigated genotype-phenotype associations in a cohort of Russian patients with CHI by clinical characterization and bidirectional direct sequencing of the *ABCC8*, *KCNJ11* and *GCK* genes.
33 children were identified, of which 18 (54,5%) responded to the medical therapy (diazoxide and/or somatostatine) and 15 (45,5%) were resistant and underwent subtotal or partial pancreatectomy. Histological examination of the removed pancreatic tissue revealed 7 (47%) diffuse, 7(47%) focal, and 1 (6%) atypical form of CHI. Among medically responsive, 4 children (22%) spontaneously recovered during one year after the diagnosis. Mutations were found in 12 patients (36%); 4 (22%) of the medical responsive and 8 (53%) of the medical 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.

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

	ABCC8	KCNJ11	GCK
Number of patients	8	2	2
Mutations found in medically responsive cases	R74L hetz Q444H hetz	A96T homoz	V91L hetz, de novo
Mutations found in medically resistant cases of focal forms	Q444H hetz, paternal Q444H hetz Q444H hetz R841P hetz, paternal	R136AfsX5 hetz, de novo	-
Mutations found in medically resistant cases of diffuse forms	R998X hetz delF1387 hetz, de novo	-	Y241C hetz

Hetz – heterozygous; homoz – homozygous

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

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P2-d3-720 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-glycemic 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 assumed 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 his influence on hypoglycemia episodes. Our findings suggests that LGI diet could help to minimize MH in patients, contributing to better quality of life.

P2-d3-721 Hypoglycaemia 1

Molecular and clinical analysis of Italian patients with congenital hyperinsulinism of infancy

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Introduction: Congenital Hyperinsulinism of Infancy (CHI) (1:50,000 births, 1:2,500 births in some ethnic groups) is the most common cause of hypoglycaemia and may be associated with three histological forms: the diffuse form (Di-HI) that involves all pancreas, the focal adenomatous hyperplasia (Fo-HI) and the atypical form. The Di-HI form is most frequently of autosomal recessive inheritance. The Fo-HI is sporadic, due to the coexistence of a paternally inherited mutation in one of the genes encoding the subunits of the beta-cell ATP-sensitive potassium channel (ABCC8 and KCNJ11) and somatic loss of maternal 11p15 alleles within a limited region of the pancreas. Up to date 50% of genetic mutations causing CHI are found in ABCC8 and KCNJ11. Recessively inherited mutations are associated with severe forms of CHI which are not responsive to diazoxide, while compound heterozygous mutations show a milder form. Patients with dominant mutations seem to be responsive to medical treatment, may present a later onset and do not require pancreatectomy.
Material and methods: Thirthy-three children affected by CHI and their parents underwent direct sequencing of ABCC8 and KCNJ11.
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.

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, oculogyric crises and autonomic features. Prognosis is poor and available treatment options like dopamine agonists, vitamine B6, monoamine oxidase inhibitors and atropine agonists only have marginal therapeutic effect.
Objective and hypotheses: We describe a five year old boy with AADC-deficiency confrmed by mutation analysis. He showed a severe neurologic clinical picture and no improvement was found under several dopamine agonists, high dosis of vitamin B6 and an atropine agonist. Severe, unpredictable, episodes of hypglycaemia were documented when he was switched from bromocryptine to pramipexol, a more potent dopamine agonist, in order to try to improve his motoric disabilities. Episodes of hypoglycaemia are documented in other patients with this metabolic disease although they were mostly misdiagnosed as having epilepsy. The pathogenesis of hypoglycaemia in these patients is unknown. I hypothezise that the potent dopamine agonists in these patients can give rise to hypoblycaemia based on inhibition of growth hormone secretion through activation of dopanine 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 insuline 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 bromocryptine.
Conclusions: Dopamine agnonists can give rise to episodes of hypglycaemia 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 clitoromegaly 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 ges-

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tational ages 28 weeks or more were enrolled in the study. Clitoral or penile lengths and widths were taken less than 72 hours after birth in all of them.
Results: The mean penile length in the 264 Nigerian males studied was 3.4 + 0.49cm while the mean width was 1.2 + 0.17cm. Nigerian newborn had similar penile sizes as the Caucasians (3.4 + 0.3cm); larger than the Chinese (3.1 + 0.4cm) but significantly smaller than those of Indian (3.6 + 0.4cm), Turkish and Malaysian origin. The mean clitoral length in the 251 Nigerian females studied was 7.5 + 1.8mm while the mean clitoral width was 4.4 + 0.89mm. The clitoral sizes were significantly larger than those in the Caucasian (4 + 1.24mm), Korean and Japanese babies.
Conclusions: The overall figures in Nigerian newborns deferred from values obtained from other countries. There were significant variations in clitoral and penile sizes between different ethnic populations. The measurement of genital sizes should be part of routine newborn physical examination.

P2-d3-724 Perinatal and Neonatal Endocrinology 1

Neonatal diabetes: six Moroccan cases

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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 EIFK2A 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 emphasize 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.

P2-d3-725 Perinatal and Neonatal Endocrinology 1

Pseudohypoaldosteronism type 1 caused by a novel point mutation of mineralocorticoid receptor gene NR3C2

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Background: Autosomal dominant pseudohypoaldosteronism type 1 (PHA1) is caused by mutations of mineralocorticoid receptor gene NR3C2. More than 20 different mutations have been described; so far no clear genotype-phenotype correlation has been established.
Objective and hypotheses: An 11 weeks-old male was admitted to our hospital because of failure to thrive. Parents reported a tendency to vomit, but other clinical symptoms were absent. Laboratory examination showed metabolic acidosis, hyponatriemia of 125 mmol/l and hyperkalemia of 6.6 mmol/l. Infectious, renal or gastrointestinal causes could be excluded. ACTH, cortisol, DHEAS, progesterone, testosterone, androstenedione and 17-OH-progesterone were measured within the normal ranges. In further investigations, markedly elevated levels of aldosterone (5789 ng/l, normal <300) and renin (560 ng/l, normal <60) were discovered. After initiation of an oral replacement therapy with 2.0 – 2.5 mmol/kg sodium chloride, electrolytes and acid-base status normalized and the patient experienced a normal weight gain. We assumed that the symptoms were caused by a mutation in NR3C2 and tried to identify the putative mutation.
Methods: As clinical assessment was indicative for a defect of mineralocorticoid receptor gene, we performed sequencing of NR3C2.
Results: Analysis revealed a novel point mutation c.2297T>G in exon 5 leading to replacement of leucine by arginine in the final transcription product (p.L766R) which was present in the patient and his father but not in 100 control alleles. Having a highly variable penetrance, absence of symptoms in the father do not contradict the diagnosis of PHA1. It is also known that symptoms tend to ameliorate with age because of compensatory sodium absorption in the proximal tubulus of the kidneys.
Conclusions: A salt loss crisis in young infants can be due to pseudohypoaldosteronism in rare cases. We report a novel mutation of mineralocorticoid receptor gene NR3C2 which leads to autosomal dominant pseudohypoaldosteronism type 1.

P2-d3-726 Perinatal and Neonatal Endocrinology 1

Growth factors and metabolic markers in cord blood: relationship with birth weight and length

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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: One hundred fifty eight random subjects (77F, 81M) - who were born at two birth centres in Genoa, Italy - were analyzed. 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.
Results: 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 values 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.
Conclusions: Our data highlight the influence of IGF-II on fetal size, and suggest that gender differences should be taken into consideration when evaluating prenatal growth.

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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

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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 VLBWPT born SGA or AGA.
Methods: We recruited 87 VLBWPT,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 length and weight increment SDS/week were observed ($p<0.01$) independent of Birth W or L. After CA 0, both PT increase a mean of 0.1 SDS/month. No differences in nutrition (total calories and nutrients) were observed. A steady increase in tricipital skin fold of 0.25 mm/week is observed similarly in all subjects. A 28 % of SGA had length <-2SDS by 3 m CA vs. none of the AGA ($p<0.001$). Only in SGAs IGF-I decreases at 15d and recovers by 60d ($p<0.02$) Glycemias differ by age 15 d ($p<0.01$) and 28d ($p < 0.02$). Changes in Igf-II, leptin and glycemia were larger in AGA ($p<0.05$). Outpatient hormonal profiles also differed: Only in SGA IGF-I increases by 12m and IGF-II by 6,12 m. When hormonal values were adjusted by weight SDS: In all subjects IGF-I and insulin decreased and IGF-II, leptin and glycemia increased over first yr of life in parallel but always with higher levels in AGA subjects. A higher IGF-I and lower IGF-II were predictor of better length SDS by 12 m. The increase in length SDS is similar in all VLBWPT whereas weight SDS increase is lower in those born SGA.
Conclusions: Differences in patterns of growth and hormonal profile are present in SGA vs AGA VLBWPT during all first yr of life which may lead to later differences in metabolic risk

P2-d3-728 Perinatal and Neonatal Endocrinology 1

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

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Background: Ex-preterm infants are at risk of osteopathy of prematurity which may present as fractures.
Aims: To identify the prevalence and characteristics of rib fractures in ex-preterm infants.
Methods: All infants born at <37 weeks gestation at two regional neonatal units between 2000-2010 were identified and all reports of their chest radiographs performed up to the age of 1yr were examined. The case notes of children with a rib fracture were further studied.
Results: 1780 infants with a gestational age<37 weeks were identified and 7488 chest radiograph reports were reviewed. From these, 27 infants(16 male) were identified as having rib fractures. Their median(range) gestation at birth was 26wks(24,34). The median chronological age of these infants at the time of X-ray was 3months(2,7.5). The median corrected gestational age at the time of X-ray was 36wks(34wks,4months).The number of cases where the site of fracture was bilateral, only-left or only-right was 7(26%), 14(52%) and 14(22%), respectively. A total of 56 rib fractures were noted in these 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(15/56,27%). Out of 56, 24(43%) 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 hyperbilirubinaemia, 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 parathyroidectomy

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Background: Neonatal severe hyperparathyroidism (NSHPT) is a rare disease caused by homozygous inactivating mutations of Ca-SR gene. Total parathyroidectomy was curative in most published cases of NSHPT.
Case: A boy was born to consanguineous parents, gestation 42th weeks, birth weight 3950g , length 55 cm. He had delay and hypotonic muscles from the first month of life, but 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.

	Boy	Mother	Father
S-total calcium (mmol/l)	4.5	2.8	N/A
S-ionized calcium (mmol/l)	2.5	1.38	N/A
s-phosphorous (mmol/l)	1.03	0,86	N/A
u-calcium/creatinine	0.0023	0,209	N/A
s-PTH (9-74 pg/l)	199	45.9	N/A
CaSR gene analysis	R220W/R220W	R220W/wt	R220W/wt

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 homozygousity for p.Arg220Trp mutation. Ibondronate 1 mg i/v and Zolendronate 4mg i/v led to no, and, transient serum calcium decrease, respsectively. The patient underwent surgery: three parathyroid glands were removed and the fourth was 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 additional parathyroid glands.
Conclusions: Severe NSHPT lasting 5 yrs dramatically influenced mental and physical development but did not result in renal failure or bone fractures. Sestamibi Scan and surgery failed to reveal additional ectopic parathyroid tissue which suspectably keeps on overproducing PTH.

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P2-d3-729 II Perinatal and Neonatal Endocrinology 1

Circulating cytokines influence fetal growth in pregnant women with rheumatoid arthritis (RA)

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Background: High RA disease activity during pregnancy is associated with a lower birth weight standard deviation score (bwsds). Lower birth weight has been linked with cardiovascular disease and metabolic syndrome later in life. High levels of circulating cytokines are a hallmark of RA.
Objective: To assess the influence of cytokine levels on bwsds in offspring of women with 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 (0.92 (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.

P2-d1-730 Pituitary 1

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

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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 consanguineous pedigree with a novel and highly distinct phenotype comprising familial panhypopituitarism, including central DI, and a number of unusual features.
Methods: Here we will describe the phenotypic, 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 polyuria 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 urodynamic 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.

P2-d1-731 Pituitary 1

An atypical acute pituitary lesion

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Background: In child, pituitary lesions are usually tumors.
Patient report: A 13-year old girl, no past history, presented with meningitis. Cerebrospinal fluid analysis showed 908/mm3 white cells (70% lymphocytes) and a 0.83 g/l protein count. Bacterial culture and enterovirus PCR were negative. Two months later, headaches remained; polyuro-polydipsia occurred. She had nor clinical, neither biological infectious sign. Brain T1-wheighed MRI showed a pituitary iso-intense tumor, with peripheral enhancement and mild hypothalamic infiltration after Gadolinium, pressing on the optic chiasma. Posterior pituitary signal was missing. Optic tests were normal. Hormone tests showed diabetes insipidus, ACTH and TSH deficiency, requiring replacement therapy. GH deficiency was not replaced. FSH-LH axis was normal. Brain tomography did not show any sellar calcification. Medullar MRI was normal. Brain germinoma was suspected, but hCG and alpha fetoprotein levels were found to be normal in serum and cerebrospinal fluid. Tumor biopsy was decided to prove histology. Unexpectedly, biopsy caused pus leakage. Emptying was complete. Histology showed chronic inflammatory process within normal pituitary tissue, with no sign of malignancy. Diagnosis was pituitary abscess. Bacterial culture of pus remained sterile. There was no sign of tuberculosis, sarcoidosis, Langerhans cell histiocytosis. Anti nuclear antibodies were absent. She had no immune deficiency. Body scan and echocardiography were normal. Only dental examination and radiography showed infectious process on four teeth, requiring dental care. One month later, brain MRI showed partial regression of the pituitary abscess. Two months later, hormone tests showed ACTH recovery. Diabetes insipidus, GH and TSH deficiency remained unchanged. Follow-up is required.
Conclusion: We report a unique atypical pituitary apoplexy-like lesion in a child: a pituitary abscess likely due to dental infection. Meningitis followed by headaches and acute hypopituitarism with diabetes insipidus seem to be important for differential diagnosis.

P2-d1-732 Pituitary 1

Endocrine dysfunction after traumatic brain injury in children and adolescents (a single centre prospective study)

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Background: The neuroendocrine dysfunction after traumatic brain injury (TBI) is described in 23-60% of adults and 15-21% of children in retrospective studies.
Objective: To find out the prevalence of the endocrine dysfunction in children after a TBI and its dependence on the course of acute post-traumatic phase.
Methods: We evaluated somatic development in 58 patients (29 boys) after TBI. They underwent standard endocrine tests: TSH, fT4, IGF1, PRL, morning cortisol, FSH, LH, testosteron (in boys), estradiol (in girls) in early post-

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traumatic period (2-14 days, T0) and in 3, 6 a 12 months after the injury (T3, T6 a 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 inspidus (DI) was occured 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 occured 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-d1-733 Pituitary 1

Clinical and MRI imaging follow-up in a girl with POU1F-1 gene mutation

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Background: Mutations in different transcription factors genes involved in the development of the anterior pituitary may result in variable combined pituitary hormone deficiency and MRI imaging of the hypothalamic-pituitary region. Although pituitary hypoplasia is the most common finding, an early pituitary enlargement with later involution was reported in PROP1 mutation and normal or hypoplastic pituitary in patients with POU1F-1 mutation. We report an 18 years clinical and pituitary MRI imaging follow-up of a girl with POU1F-1 gene mutation.
Clinical report: TJ is the first and only daughter of non-consanguineous Italian healthy parents, with deficiency of TSH, PRL and GH, diagnosed at two months of age as a results of investigations for failure to thrive, hypotonia and anemia. She started replacement treatment with L-thyroxin at three months of age and with GH six months later.
Genomic analysis showed a R271W POU1F-1 mutation. MRI of hypothalamic-pituitary region, performed at the age of 2.5 months, 7 years and 16 years shows an anterior pituitary height of respectively 2, 2.6 and 5 mm (all within the normal reference values for age). The signal intensity of the anterior pituitary was normal, the pituitary stalk and the posterior pituitary hyperintensity were normally located.
The girl started a normal pubertal development at nine years of age and she had menarche two years later followed by normal menstrual cycles. When she was 15 years old she achieved her adult height (154 cm) corresponding to the lower limit of the genetic target height.
Conclusions: To our knowledge this is the case with earlier diagnosis and longer follow-up of a girl with POU1F-1 gene mutation suggesting that the genetic change does not cause progressive pituitary hypoplasia. This observation further supports the hypothesis that POU1F-1 mutation affects the activation of hormone expression, but not the pituitary cells growth.

P2-d1-734 Pituitary 1

Idiopathic Panypopituitarism (IP): associated radiological and perinatal factors

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Background: Panhypopituitarism is defined when more than two pituitary hormones are deficient. Although panhypopituitarism can be acquired, a proportion are idiopathic. Whilst genetic factors are implicated, perinatal factors which might be associated with idiopathic panhypopituitarism (IP) have been poorly explored.
Objective and hypotheses: To determine perinatal risk factors and radiological features associated with IP.
Methods: Systematic analysis of paediatric IP cases in the West Midlands from 1998-2009. Patients with additional defects eg. septo-optic dysplasia (SOD) were excluded.
Results: 56 patients were identified: 21 (37.5%) female. 32 (65%) were born by spontaneous vertex delivery. Only 1 was breech presentation and 3 instrumental deliveries. When compared to maternal age in the United Kingdom (mean 29.3 years) the median maternal age of IP patients was reduced at 26.0 years (95% CI 23.5-29) ($p=0.036$), as was median paternal age (28.5 cf. 32.4 years) (95% CI26-31) ($p= 0.006$). 57% were born to primigravida mothers. 43 patients had full pituitary imaging details.
Hypoplastic anterior pituitary was seen in 27/43 (62%), ectopic posterior pituitary in 28/43 (44%) patients, whilst 9 had normal MRI findings. Three patients with ectopic posterior pituitary had a normal anterior pituitary. Of only two patients with diabetes insipidus (DI) plus anterior pituitary hormone deficiencies only 1 had an absent posterior pituitary signal. A further 2 had an absent posterior pituitary signal but no DI.30% of mothers admitted to smoking, 16% to consuming alcohol and only one to taking cocaine during pregnancy. Mixed ethnicity (Caucasian/Afro-Caribean) was over-represented in patients with IP (16%) compared to the background regional population (1.4%).
Conclusions: As with septo-optic dysplasia IP is associated with reduced maternal and paternal age, and also increased mixed race ethnicity. Breech delivery and instrumental delivery taken together was seen less frequently in this cohort. Ectopic or absent posterior pituitary signal did not predict DI.

P2-d1-735 Pituitary 1

Central diabetes insipidus in infants

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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 hypernatraemia 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 intra-nasally (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 hypernatraemia. Presentation, clinical features, biochemistry and initial DDAVP doses are very variable.

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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

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Background: The diagnosis of septo-optic dysplasia (SOD) is assessed when two or more of this features are present: optic nerve hypoplasia (ONH), pituitary hormone abnormalities, midline brain defects-agenesis of septum pellucidum (SP) and/or corpus callosus (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 pitiuitary (EPP), anterior pituitary hypoplasia (APH) and pituitary stalk (PS). GroupA (n=9): 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; GroupB (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; GroupC (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

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Introduction: Craniopharyngioma are rare embryogenic malformationsof 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 craniopharyngoma and following a full safety of hypothalamic-pituitary function. A7.8-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), growth velocity in the last year was 6 cm/year. 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 DDAVP, taken only for a month. Visual acuity improved postoperatively. During 2 years' follow-up, hypothalamic-pituitary functions remained unchanged and annul 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-I 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 craniopharyngoma 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

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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 m-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 hypothyroidism. Following partial tumour resection, the patient developed discrete signs of Cushing 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-6-methylguanine-DNA-methyltransferase. Polychemotherapy with vincristine, cyclophosphamide, VP-16 and cisplatin was started. Genetic analyses in peripheral blood leukocytes detected a microduplication involving 1q21.3 of 516 kb containing at least 6 potential oncogenes as well as a novel germline DICER1 nonsense mutation (c.2379T>G; Y793X) which will presumably also be present in his second cousin. At 20 months the child remains well. The residual tumour is stable and signs of Cushing syndrome have receded.
Conclusion: This is the second reported case of pituitary blastoma in infancy; we suspect that other cases previously labelled as pituitary 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.

P2-d1-739 Pituitary 1

Severe viral illness mimicking transient hypopituitarism in a 1 year old boy

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Background: Transient hypopituitarism is rare with few cases reported in literature especially following a viral illness. In contrast, abnormalities in thyroid function test without preexisting pituitary or hypothalamic disease in non thyroidal illness or sick euthyroid syndrome is not uncommon.
Presentation: A 20 month old boy was admitted to hospital with unexplained high temperature followed by severe lethargy. Infection screen including blood urine and CSF cultures were negative. A full blood count showed lymphopenia and electrolytes showed hyponatremia with normal potassium. Baseline pituitary function tests were done by the acute on call team as his lethargy was disproportionate to his temperature and revealed central hypo-

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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 TFTs have been normal.
Discussion and conclusion: This young boy had a presumed viral illness causing profound lethargy resulting in a prologed 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-d1-740 Pituitary 1

Familial hypogonadotropic hypogonadism

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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 year 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. Hormonal 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.
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)

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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

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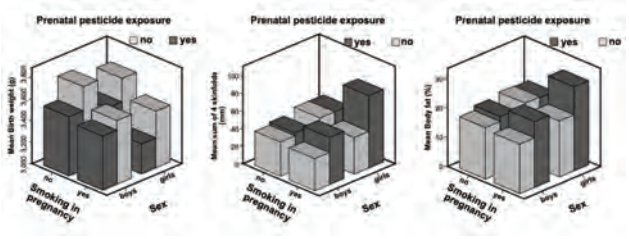
were tested by linear multiple regression analysis, adjusting for relevant confounders.
Results: Birth weight and weight for gestational age were 4.1% lower in the exposed children (p<0.02). Exposed children had significantly higher (0.55 SD) ΔBMI Z-score from birth to school age (p=0.018) and a non-significant 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% CI: 8.1; 99.5, p=0.015) and body fat percentage 29.1% higher (95% CI: 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 percentage than unexposed.
Conclusions: 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.



P2-d3-743 Programming/Epigenetics 1

Maternal cardiovascular risk factor profile determines that of the child – results from the Ulm Birth Cohort Study (UBCS)

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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, IL6, 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 look for intrafamilial associations (correlation and regression analysis).
Results: For FBG, insulin and HOMA-IR significant correlations were found between the offspring and the mother but not between the offspring and the father (r=0.21, p<0.05 vs. r=0.27, p<0.0001 vs. r=0.30, p<0.0001). ApoB levels of the mother and child showed the highest intrafamilial correlation (r=0.37, p<0.0001). 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 =0.31, p<0.0001). 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 apoB 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 endocrine and metabolic system by the mother is suspected.

P2-d3-744 Programming/Epigenetics 1

SGA (small for gestational age) children with no severe fetal growth restriction are not at increased metabolic risk at 2 years of age

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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 ± 1,1 vs. -0,09 ± 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±3.5 vs. 19.1±4 %: p=0.09 ; 2 years 18±4.6 vs. 20.3±4,2 %: p=0.009) . No significant 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 thinner than those of AGAs (paternal BMI 24,2 ± 2,8 vs. 26,1 ± 5, 1 kg/m2: p=0,03 ; maternal BMI 23 ± 4,6 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 early (0-4th month) and moderate catch-up growth. Assessing fetal growth restriction at birth with an accessible surrogate would be helpful to distinguish between innate "small size babies" and those who previously faced fetal growth restriction.

P2-d3-745 Programming/Epigenetics 1

Effect of small birth size on inflammatory markers associated with cardiovascular diseases in young adulthood

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Background: Small birth size for gestational age (SGA) has been associated with risk factors for cardiovascular diseases (CVD) in young adulthood. It is, however, not yet known whether SGA birth affects serum levels of inflammatory markers which are associated with CVD, such as monocyte chemotactic protein-1 (MCP-1), interleukin-8 (IL-8), and soluble vascular adhesion molecule 1 (sVCAM-1).
Objective and hypotheses: We aimed to study the effect of SGA birth and subsequent catch-up growth during childhood on serum inflammatory markers in young adulthood. We hypothesized that catch-up growth, rather than SGA birth, is associated with increased serum levels of inflammatory markers in young adulthood.
Methods: In 474 adults of the PROGRAM/PREMS study aged 18-24 yr, the influence of birth weight SDS, birth length SDS and adult height SDS, was studied on MCP-1, IL-8, and sVCAM-1, using multiple regression (MR) modeling. Models were stepwise adjusted for confounders such as gender, age, smoking, HDLc, and LDLc. Inflammatory markers were also analyzed in subgroups: young adults born small for gestational age (birth length <-2 SDS) with short stature (adult height <-2 SDS, SGA-S) or normal stature (adult

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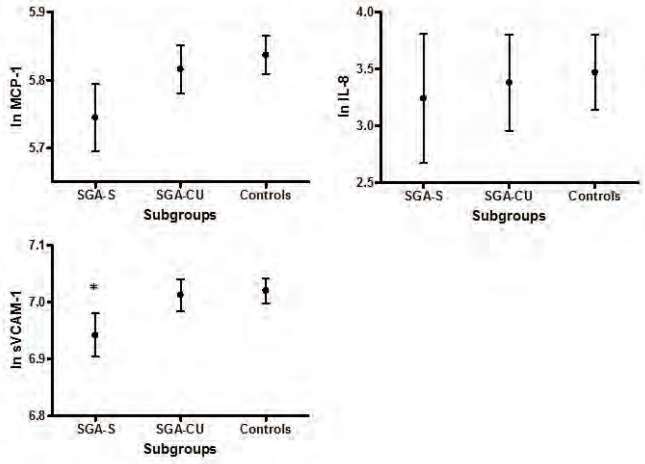
height >-1 SDS, SGA-CU), and young adults born appropriate for gestational age with normal stature (birth length and adult height >-1 SDS, controls). Subgroup analyses were adjusted for variables with a p-value <0.10 in the MR models.
Results: Birth length SDS and birth weight SDS did not significantly influence any of the inflammatory markers. After adjustment, adult height SDS was inversely associated with IL-8 levels (p=0.040, R^2=0.035), and positively associated with sVCAM-1 levels (p=0.005, R^2=0.363). There were no differences in MCP-1 and IL-8 between subgroups after adjustment for confounders, and a tendency to lower sVCAM-1 in SGA-S (Figure 1).
Conclusions: SGA birth, as well as subsequent catch-up growth during childhood, does not influence serum levels of inflammatory markers related to CVD in young adulthood.

Figure 1. Adjusted differences in MCP-1, IL-8 and sVCAM-1 between subgroups



Mean (SE) after adjustment for confounders
* p=0.081

P2-d3-746 Programming/Epigenetics 1

Does preterm birth affect vascular health status in young adulthood?

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Background: Both preterm birth and small birth size for gestational age (SGA) have been associated with an 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

	Preterm (n=163)	Term (n= 243)
Systolic blood pressure (mmHg)	112.3(8.0)*	110.0(9.0)
Diastolic blood pressure (mmHg)	63.3(5.3)#	66.1(5.9)
Pulse pressure (mmHg)	48.9(6.2)#	43.8(5.8)
Coefficient of Variation, Systolic blood pressure	5.17(1.8)*	4.77(2.7)
Coefficient of Variation, Diastolic blood pressure	9.77(3.2)#	7.98(3.7)
Heart rate (beats/minute)	70(9.1)#	65(9.0)
PWV (m/sec)	7.60(1.0)	7.59(0.9)
cIMT (mm)	0.52(0.1)	0.52(0.05)

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

P2-d3-747 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 relative macrocephaly, characteristic dysmorphic features and feeding difficulties. In young age, bone age (BA) is usually delayed. In over 50% cases, SRS is due to *IGF2/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 IGF2/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, it occurred after a rapid rise in BMI (BMI increase of + 1 to +7.9 SDS per year). In all cases, SDHEA and IGF-I levels were higher than the upper limit for age. Despite GH administration and treatments aiming to slow down BA maturation (Cyproterone Acetate and/or LHRH 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-I levels may play a role in the onset of adrenarche in these SRS patients.

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P2-d3-748 Programming/Epigenetics 1

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 height147cm, 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, trigyceride16.1mmol/L and gonadal impairment with LH 15.9 IU/L, FSH 27.2 IU/L. Case 2 had IUGR with full term birth weight1.4 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 13 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.

P2-d3-749 Programming/Epigenetics 1

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 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 17,7 ±1,8, BMI at 4 years was 16,4 ±1,8 kg/m2 and the sum of four skinfold thicknesses 30,1 ±12,4 mm. There are positive association among pre-pregnancy BMI and birth weight, BMI at 18 months, BMI and the sum of the four skinfold thicknesses at 4 years (Pearson correlation 0.150, 0.162, 0.286, 0.229; p<0.01). GWG was only associated with birth weight (0.143; p<0.001). BMI at 18 months was correlated with BMI (0.502; p<0.01) and the sum of the skinfold thicknesses at 4 years (0.430; p<0.01).
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.

P2-d1-750 Puberty and Neuroendocrinology 1

Modified Spectria Testosterone RIA detects same testosterone levels in prepubertal and pubertal children as liquid chromatography-tandem mass spectrometry

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Background: Direct Immunoassays for determination of serum testosterone has been questioned. However, there are direct RIAs that are sensitive, have low cross-reactivity and perform well in routine clinical practice.
Objective and hypotheses: Our modified testosterone RIA (Spectria testosterone; Orion Diagnostica, Espoo, Finland) perform well in routine clinical practice. The lower limit of detection is 0.03 nmol/L and lower limit of quantification is 0.1 nmol/L (Eur J Endo 151:747-757) and the method is an accredited assay by SWEDAC quality control agency in Sweden, SS-EN ISO 15189. In present study we compare our modified testosterone RIA and with results from two different liquid chromatography tandem mass spectrometry (LC-MS/MS) assays.
Methods: We attended an International External Quality Assessment program for laboratory medicine, with blinded samples. We compared our results with their reference method that is LC-MS/MS (Helsinki University Central hospital). We have also compared our earlier published data on morning testosterone levels in boys (Eur J Endo 151:747-757) and girls (JCEM 84:975-984) using the same pubertal classification for boys and girls as done in a study by Kulle et al (JCEM 95:2399-2409) using ultra-pressure LC-MS/MS.
Results: In the International External Quality Assessment program for laboratory medicine our modified testosterone RIA have participated 10 times and reports similar values (r=1.00, n=20, p<0.0001) on the test samples (range 0,85-24,4 nmol/L) as the reference method, LC-MS/MS. The pediatric reference intervals determined by ultra pressure LC-MS/MS and our modified testosterone RIA, were similar across the different pubertal stages.
Conclusions: Our modified testosterone Spectria RIA delivers clinical useful information. This is based on a direct comparison with LC-MS/MS as well as a comparison to pediatric reference intervals determined by ultra pressure LC-MS/MS.

P2-d1-751 Puberty and Neuroendocrinology 1

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 classical 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 laughers 40-50 times a day since 2 months of age. He had acne on the cheeks and forehead. Penile size was 7x1.8 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 32.9 and FSH:4.16). Abdominal and scrotal ultrasound examinations were

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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.

P2-d1-752 Puberty and Neuroendocrinology 1

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 gold standart test in the diagnosis of central precocious puberty (CPP) as well as in the assessment of pubertal supression 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 validitiy 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.
Patiens and methods: One hundred and fourty 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 GnRH tests. In 25 patients gonadotropin suppression was not found in the GnRHa test. However 16 of them were suppressed according to the iv GnRH 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.

P2-d1-753 Puberty and Neuroendocrinology 1

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 smell abnormalities wich suggests a more severe 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 micropenis, 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 nWH. Genetic results: In 47.8% of MH mutations were identified. There were 5 with monogenic disease (*FGFR1, KISS1R, KAL1*), and 6 with digenic mutations (*TAC3R, KAL1, PROK2, FGFR1, KISS1R*). There were 6/31 WH (19.4%) with mutations: one with digenic mutations (*GNRHR/PROKR2*), 4 were heterozygous 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, meanly in men.

P2-d1-754 Puberty and Neuroendocrinology 1

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 the12-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 meliorate 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 4l/d. The aquaretic effect of Tolvaptam 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 meliorated his clinical symptoms without the need of titrating the dose and without adverse events.

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P2-d1-755 Puberty and Neuroendocrinology 1

Urinary gonadotrophins: a useful non-invasive marker of activation of the hypothalamic-pituitary-gonadal (HPG) axis

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Background: There is no useful non-invasive screening investigation to assess activation and progression of the hypothalamic-pituitary-gonadal (HPG) axis.
Aims: To establish a normal range for urinary gonadotrophins in healthy children as they progress through puberty Patients: 100 healthy children (55 girls; 45 boys) aged 5.5-18 yrs were recruited from schools in different areas of Glasgow as part of a study examining bone health.
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 Jaffe assay with a limit of quantitation of 0.35mmol/L, was used to correct data.
Results:

	Age, years	Age, years	LH: Creatinine	LH: Creatinine	FSH: Creatinine	FSH: Creatinine	LH: FSH	LH: FSH
	Med	Range	Med	Range	Med	Range	Med	Range
Pre-pubertal								
Girls (n,14)	9.3	5.5-12.8	0.02	0.01-0.04	0.29	0.10-1.01	0.04	0.02-0.12
Boys (n,15)	7.8	6.1-13.3	0.01	0.01-0.19	0.17	0.01-1.00	0.10	0.01-0.45
Early-pubertal								
Girls (n,21)	12.3	10.0-15.1	0.06	0.01-0.98	0.49a	0.02-3.63	0.15	0.02-0.95
Boys (n,14)	12.4	10.0-16.9	0.10a	0.01-0.28	0.22c	0.11-0.68	0.33	0.02-1.43
Late-pubertal								
Girls (n,20)	15.6	13.5-17.2	0.12b	0.01-1.06	0.49b	0.16-2.56	0.26b	0.03-1.03
Boys (n,16)	16.2	13.0-18.0	0.12b	0.01-0.26	0.20c	0.03-0.46	0.47bc	0.04-1.77

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 girls and boys 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.

P2-d1-756 Puberty and Neuroendocrinology 1

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 16,38±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 4,66±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-d1-757 Puberty and Neuroendocrinology 1

Relation between Korean female adolescents' sexual and risk behaviors in accordance with their precocious puberty

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Objective and hypotheses: This study aims to examine relation between Korean female adolescents' sexual behaviors and risk behaviors in accordance with their precocious puberty.
Methods: The result of the 2007 Youth Health Behavior Online Survey conducted by the Korea Center for Disease Control and Prevention was used for this study. For analysis, the subjects were divided into two groups: a group with precocious puberty whose menarche started before the fourth year in elementary school and a group with normal puberty development whose menarche started from the fifth year in elementary school or later, or whose menarche did not start until the first year in high school. The relation between their sexual behaviors and risk behaviors in accordance with whether or not they had precocious puberty was analyzed using a logistic regression model.
Results: Among the 35,075 female adolescents included in this study, the number of those who belonged to the group with precocious puberty was 1,147(3.27%). Compared with the normal group, the group with precocious puberty had more tendency to be from a one-parent family.
In addition, their mothers' educational backgrounds were poorer and their economic statuses were lower. As for mental health and risk behaviors, the group with precocious puberty felt more sadness and despair and more frequently considered committing suicide and attempted suicide. The group with precocious puberty was more apt to regard themselves unhealthy, obese, and under very stressful surrounding. In the multivariate logistic regression model, the group with precocious puberty had more experiences of drinking, smoking, and taking inhalants, weight loss drugs, sleeping pills, and narcotic drugs. This group also had more experiences of sexual behaviors such as kissing or having sexual intercourses and undergoing or inflicting sexual violence.
Conclusions: In Korean female adolescents, precocious puberty is regarded as a factor that affects their sexual and risk behaviors. Additional prospective research to support this study's result is necessary.

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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 hypogonadotrophic hypogonadism (HH) is complex. To date several genes have been implicated; *FGFR1, FGF8, 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, FGF8, 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 muted. This or those genes are involved in hypogonadotropic hypogonadism without anosmia (GnRHR, GPR54, GnRH, 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-d1-760 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 i(Yp) appears to be the most uncommon. In the literature no data regarding the course of puberty in boys affected by i(Yp) is described.
Case report: We describe a 13 years old boy with monolateral gynaecomastia 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 enanthate (TE)replacement.
Conclusion: We described the course of puberty in an adolescent with i(Yp), 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 i(Yp) may contribute to our understanding of patho-physiology of hypothalamic-pituitary-gonadal axis.

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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 gilrs 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 three 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 hCG-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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Pubertal 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 gynecomastia, but ghrelin and pubertal gynecomastia relation didn't studied. So this is the first clinical trial that subjected ghrelin and pubertal gynecomastia relation.
Objectives: In this study we aimed to show the relations between pubertal gynecomastia with plasma ghrelin levels and insulin resistance.
Methods: For the study 54 nonobese pubertal boys diagnosed pubertal gynecomastia, 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 gynecomastia and boys in control group (340.25±122.31 pg/ml and 325.66±162.55 pg/ml, $p>0.05$). Boys with pubertal gynecomastia 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 gynecomastia and controls.
Conclusions: Ghrelin levels didn't relate to pubertal gynecomastia, adversely insulin resistance seemed to be related to it. Insulin resistance might play a role in pubertal gynecomastia.

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Risk of hyperprolactinemia and prolactin related sexual and endocrinological side effects in adolescents with psychiatric disorders using long-term prolactin elevating antipsychotic medication: a case control study

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Background: Antipsychotics (AP) are commonly and increasingly prescribed to children and adolescents with psychiatric disorders especially in autism spectrum disorders. AP may cause hyperprolactinemia by dopamine 2 blockade in the tuberoinfundibular pathway. The aim of the present study was to investigate the effect of long-term use of AP on prolactin level and prolactin related sexual and endocrinological side effects in adolescents with psychiatric disorders.
Method: Physical healthy 10-20 year old adolescents with psychiatric disorders chronically treated (mean 52 months, range 16-126 months) with (N=62 of whom 56 boys) or without (N=57 of whom 48 boys) AP were recruited for this case control study from child psychiatry outpatients clinics between October 2006 and November 2009. A morning non fasting serum prolactin was obtained and the prolactin related side effects were measured by questionnaires and a physical examination. In boys serum LH, FSH, testosterone, inhibin B and pubertal stage were assessed. Group differences were tested by Student's t-, Chi-square-, or Mann-Whitney tests and logistic regression analysis, according to the type and distribution of data.
Results: Hyperprolactinemia was present in 49% of cases treated with AP and in 3.5% of control cases ($p<0.0001$, odds ratio 26.6, 95% CI 6.0 -118.8). The current dose of AP predicted hyperprolactinemia. Gynecomastia and sexual dysfunction was present in respectively 41% and 13% of the AP cases compared to 21% and 0 % of the control cases ($p=0.02$ and $p=0.005$). The group of males with hyperprolactinemia had significant lower testosterone levels ($p=0.035$), with a linear negative relationship between prolactin and testosterone ($p=0.02$). There was no between group difference for LH, FSH, Inhibin B and pubertal stage.
Conclusions: Hyperprolactinemia is a common side effect in adolescents using long term prolactin elevating antipsychotic medication and is related to gynecomastia, sexual dysfunction and lower testosterone levels in males.

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Estrogen gene analysis in girls with central precocious puberty

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Background: Precocious puberty is characterized by early activation of the pituitary gonadal 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 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 were 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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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,

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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, p=0.035; 1,9±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(ICMA) at a cut-off level of 0.3 IU/L was found to be a significant risk coefficient for having an atypical course. 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.

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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 midline 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 dysmorphia 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, dilatated 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 mIU/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 between hypothalamus and hypophysis. Failure of inhibition in gonadotropic axis that is a probable case in midline brain defects can cause premature development. Genetic background for this regulation is complex and remains to be elucidated.

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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 yr (mean ± SD); 55% of the girls were from Asian ancestry. Weight and height SDS on arrival were -0.99 ± 0.85and -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.

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Changes in serum levels of hormones and neurotransmitters during sleep in girls wtih 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 difference 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 Gonadotropin-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/chronologial 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 haved 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.

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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, insulin, HOMA-IR, LDL cholesterol, leptin, NPY, and leptin/NPY ratio (L/N ratio) in precocious puberty group were significantly higher than that in control group. In precocious puberty, leptin was positively correlated to L/N ratio, amylin, TG, LDL, BMI. NPY was negatively correlated to BMI.
Conclusions: Precocious puberty was associated with diet regulating factors, and metabolic bio-markers. This result suggests that precocious puberty may associate with the risk of developing of metabolic syndrome.

P2-d2-770 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 age of 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-d2-771 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 LH-RH test. Bone age was assessed and MRI of the hypothalamic and pituitary region was performed.
Results: LH-RH 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 type1. However, the girl with R681X had very extensive cutaneous pigmentations, 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 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 hypertenstion 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 yrs, 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 CYP17A1 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-hydroxypregnenolone 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

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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-d2-773 Sex Differentiation 1

Novel heterozygous mutation in the StAR (Steroidogenic acute regulatory protein) gene in a 46,XY patient with congenital lipoid adrenal hyperplasia (CLAH)

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Background: StAR is required for adrenal steroidogenesis and male sexual differentiation. Recessive mutations cause classic and nonclassic CLAH. StAR acts on the outer mitochondrial membrane (OMM) prior to import and undergoes a structural transition to transport cholesterol.
Objective: We are reporting a 46,XY patient with ambiguous genitalia, and primary adrenal insufficiency.
Method and results: We found a novel heterozygous de novo IVS1-2A>G mutation in StAR gene and the pGly146Ala heterozygous polymorphism in SF1 gene. RT-PCR and sequence analysis of testicular StAR mRNA showed a 397bp transcript, corresponding to exon2 skipping, as well as the wild-type (WT) 511bp transcript. Functional analysis was performed in COS cell transfected with mutant and WT plasmids. Both the 37kDa precursor and 30kDa mature form were detected. Immunofluorescence showed almost no colocalization of mitochondria and mutant protein (delta22-59StAR). StAR activity was measured as pregnenolone production in COS cells cotransfected with the P450scc system. Delta22-59StAR activity was 65%±13 of WT. Cotransfection with WT and delta22-59StAR vectors reduce WT activity by 62%±13.9.
Conclusions: We identified a novel intronic heterozygous StAR mutation (IVS-2A>G) in a patient with CLAH. It produced a -exon2 mRNA resulting in the in-frame loss of aa 22 to 59 in the N-terminal mitochondrial targeting signal. It is reported that deletions of 62 N-terminal residues of StAR precluded the mitochondrial entry, but it did not affect its activity. Although delta22-59StAR did not localize to the mitochondria, it showed a reduced activity. We speculate that aberrant folding might compromise its activity. The delta22-59StAR might interfere with WT StAR by competing with cholesterol binding causing a dominant effect, explaining the clinical phenotype in heterozygosis. Finally, StAR requires interaction with several other proteins on the OMM. Mutations in some of them, contributing to the severe phenotype in our patient, could not be ruled out.

P2-d2-774 Sex Differentiation 1

Functional analysis of a hematopoieitic-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 skins 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

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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.

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 adenocarcinoma 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 orchidopexy. 2 boys originally had open orchidopexies 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 orchidopexies 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 adenocarcinoma 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.

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 life. Five patients were treated with Growth Hormone. The mean height velocity 1 year post 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.

P2-d2-778 Sex Differentiation 1

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

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Background: Steroid 5-α reductase type 2 isoenzyme (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 5-α reductase type 1 isoenzyme or exposure to environmental chemicals may affect clinical expression of the disorder.

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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 (DSD) 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 DSD, 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 clitoral enlargement; 14 patients had an uterus. AMH, LH, FSH, testosterone blood levels might be normal, especially in the first year 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. Genitoplastic 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 peripherical tubules like embryonic cords and a thin albuginea, 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-d2-780 Sex Differentiation 1

Prenatal choice of sex of rearing alleviates parental stress

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Background: Despite the advances in prenatal diagnosis by ultrasound techniques, the birth of a child with ambiguous genitalia and undeterminable sex of rearing remains a major source of anxiety and psychological discomfort.
Objective: Study the conditions and criteria (ultrasonography, gene analysis, measurement of hormones) allowing to choose bona fide before birth the sex of rearing of a child with ADS. Set the stage for a pilot study.
Patients and results: Fetus C was referred because of abnormal genitalia at 22 weeks' gestation. Fetal SRY sequence was negative in maternal plasma. Amniotic fluid revealed 17-OHP levels of 660 ng/ml, Delta4 of 465 ng/dl and testosterone of 35 ng/dl at 25 wk gestation. 21-hydroxylase sequencing showed that the patient was a composite heterozygous for Gln318stop/multiple mutations in exon 4, 6, 7, 8, 10. Diagnosis was announced to the parents. Female sex of rearing was immediately chosen at birth. Fetus E was identified as having abnormal genitalia at 27 weeks' gestation. Fetal SRY sequence was positive in maternal plasma. Amniotic fluid revealed normal 17-OHP levels and testosterone level of 30.4 ng/ml at 28 wk gestation. Androgen receptor sequencing showed a Pro390Ser mutation in the first exon. Diagnosis was announced to the parents. Female sex of rearing was prenatally chosen.
Conclusions: Following carefully planned prenatal evaluation, it has become possible to experts to make precise diagnoses that may allow the choice of the sex of rearing before birth, in order to protect the parents from the shock of giving birth to a child of undetermined gender.

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 <10pg/ml, Testosterone <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 Mullerian 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 multicyctic appeareance. Dominant follicule 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.

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P2-d2-782 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 ongoinig. 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-d2-783 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 (patient1) 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 plication. 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 situation in patient 1 and in scrotal situation 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 mUI/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-d2-784 Sex Differentiation 1

Ovotesticular disorder of sexual development and a rare 46,XX/47XXY 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 micropenis. Pelvic ultrasound revealed left inguinal hernia and the left testis could not be visualised. Pelvic MRI marked a suspicous gonad tissue solid structure in the right scrotum and a suspicious gonad cystic structure in the left inguinal canal. He underwent a diagnostic laporoscopy. Cytogenetic analysis of peripheric blood revealed 46,XX /47,XXY karyotype. Histopathologic examination of left side gonad showed ovarian tissue containing primordial follicules with ipsilateral undifferantiated tuba uterina. The right side gonad showed immature testis tissue. Both of the two gonad materials' cytogenetic analysis revealed 45,X/46,XX/47,XXY mosaicism.
Results: He underwent left gonadectomy, hypospadias repairing 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 occurence of malignancy, scrotally sited testicular tissue must be monitored for tumour development.

P2-d2-785 Sex Differentiation 1

17 A hydroxylase deficiency; an interesting case of primary amenorrhea with hypertensionα

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Background: Seventeen α hydroxylase deficiency (17OHD) is a rare form of congenital adrenal hyperplasia resulting from mutation in CYP 17 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 hypogonadism.
Methods: A 14 year girl presented with acute onset quadriparesis & hypertension. Parental consanguinity, primary amenorrhea and absent breast development were added informations. On examination BP was 150/100 mm Hg without 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 (513pg/ml) and high FSH (45mIU/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.

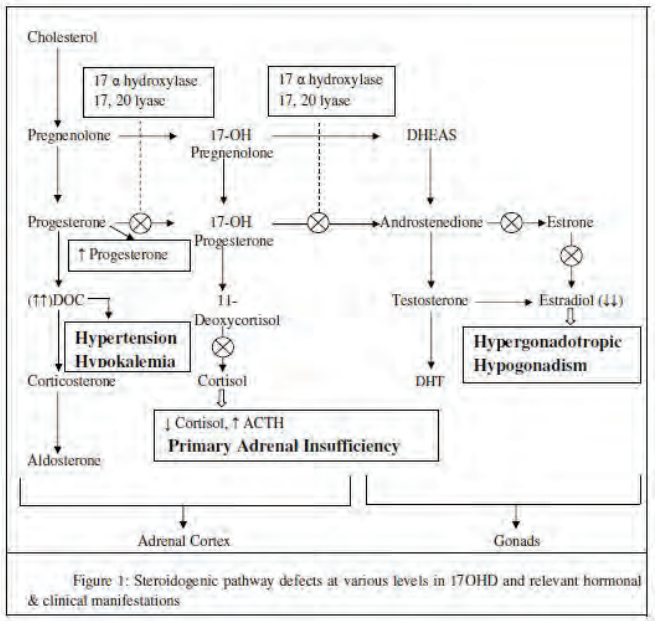

Figure 1: Steroidogenic pathway defects at various levels in 17OHD and relevant hormonal & clinical manifestations

P2-d1-786 Thyroid 1

Abnormal thyroid function tests in two mentally and motor disabled brothers: monocarboxylate transporter 8 deficiency

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Background: Monocarboxylate transporter 8 is a thyroid hormone transporter, defect of which underlies an X-linked disorder: Allan-Herndon-Dudley syndrome. The disease is characterized by severe developmental delay, and hypotonia in early life evolving to hypertonia in time with minimal craniofacial dysmorphic features and distinguishing thyroid hormone profile.
Objective and hypotheses: To present the clinical features and genetic analyses of two brothers with monocarboxylate transporter 8 deficiency.
Methods: A 16-month-old boy with a history of eventless term birth, marked developmental delay, and hypotonia was referred for further investigation of abnormal thyroid function test results [fT3 7.89 pg/mL (normal, 1.57-4.71), fT4 0.731 ng/dL (normal, 0.8-1.9), TSH 5.18 mUI/L (normal, 0.4-5)]. There was no history of prolonged jaundice or constipation. He was the second child of non-consanguineous and healthy parents. His older brother was clinically diagnosed as cerebral palsy due to birth asphyxia and their maternal uncle had similar problems attributed to birth trauma. Physical examination was unremarkable except followings: weight for height 78%, narrow/long face, asthenic build, hyperreflexia/clonus, and undescended testes.
Results: Thyrotropin releasing hormone test revealed normal TSH response. Diagnosis of Allan-Herndon-Dudley syndrome was made upon persistence of elevated fT3 and low fT4 levels despite gradually increased L-thyroxine treatment, recognizing that older brother had similar complaints, physical examination findings, and laboratory results, and history of similar situation in maternal uncle. Both of the brothers were found to have a novel hemizygous mutation (c.1494G>C; p. G495A), functional analysis of which is being planned.
Conclusions: Diagnosis of Allan-Herndon-Dudley syndrome can be made clinically with thyroid hormone profile, including free T3, in patients with developmental delay with an X-linked inheritance pattern. Although a curative treatment method does not currently exist, genetic counseling would be of benefit to parents.

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 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.
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 radioiodine or surgery, but what

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factors should be considered for the initial CMZ daily dose (ICDD)?
Objective: To determine the ICDD for children with GD to become euthyroid by 3 months, and whether it depends on biochemical, antibody and clinical status at diagnosis
Methods: The ICDD used to treat 108 patients (92 female; 85%) in our unit was grouped by age at diagnosis (<8y; 8-12y; >12y) and by the lowest thyroid hormone level reached within 3 months of treatment (BN=below normal fT4; N=normal fT4; AN=above normal fT4). Age, gender and baseline status (fT4; TSH receptor antibody (TRab); need for beta-blockers) were noted. Regression analyses were done to determine whether the ICDD used depended on these variables.
Results: Median (interquartile range; IQR) age at diagnosis was 12.2 (9.7-13.8) years. Median (IQR) ICDD used and the number of patients in each group are shown in the Table. Five patients (5%) remained biochemically hyperthyroid at 3 months. Regression analyses for all 108 patients identified age at diagnosis ($p<0.001$) and need for beta-blockers ($p=0.05$) as independent variables for the ICDD used, but not gender ($p=0.74$), baseline fT4 ($p=0.92$) and TRab ($p=0.90$). For the 57 patients (53%) who achieved the desired euthyroid state (group N), the only independent variable for the ICDD used was age at diagnosis ($p<0.001$).

Table	BN (below normal fT4); n=46	N (normal fT4); n=57	AN (above normal fT4); n=5
< 8 years old; n=14	20 mg (15 - 30); n=5	15 mg (10 - 15); n=7	10 mg (5 - 15); n=2
8 to 12 years old; n=39	23 mg (19 – 38); n=14	20 mg (20 - 30); n=24	30 mg (-); n=1
> 12 years old; n=55	30 mg (30 - 45); n=27	30 mg (25 - 40); n=26	33 mg (20 - 45); n=2

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 using body size to compute dose, but it is noteworthy that doses >30mg/day may be excessive. Non-compliance should be considered if the expected efficacy is not achieved. Using higher doses to treat children who need beta-blockers for symptomatic control may result in a hypothyroid state within 3 months.

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 de 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 fT3-to-fT4 ratio (as a proxy of deiodinase activity) with a metabolic profile [post load glucose, HbAc1, 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-fT4 ratio were associated with higher BMI, post load glucose, HbAc1, 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 HbAc1 ($\beta=-0.192$, $p<0.003$) and HMW-adiponectin ($\beta=0.245$, $p<0.0001$), while the fT3-to-fT4 ratio was independently associated with BMI ($\beta=0.367$, $p<0.0001$), HOMA-IR ($\beta=0.238$, $p<0.004$) and HMW-adiponectin ($\beta=-0.262$, $p<0.002$). No associations were found with placental weight or weights of the newborns.
Precise conclusions: In pregnant women without a history of thyroid dysfunction, decreasing concentrations of fT4 and increasing fT3-to-fT4 ratio are associated with a poorer metabolic phenotype. These findings are consistent with the known increased metabolic risk in subjects with a lower activity of the thyroid axis and suggest a higher conversion of fT4 to fT3 as a compensatory mechanism.

P2-d1-790 Thyroid 1

Dyshormonogenesis: phenotypic characteristics of 94 cases from a cohort of 757 children with congenital hypothyroidism (CH)

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Background: CH is the most common congenital endocrine disorder. Defects of thyroid hormone (TH) biosynthesis account for 10 to 15% of cases, are often recessively inherited and can be associated with goiter.
Objective and hypotheses: To describe the phenotype of children with dyshormonogenesis.
Methods: Sample comprised 94 children with dyshormonogenesis from a cohort of 757 children with CH detected by neonatal screening. The following parameters were collected: age at onset of treatment, presence of goiter and consanguinity, weight, height and body mass index (BMI) at 5 years of age; TSH, total T4 (TT4) and free T4 (FT4) pre-treatment and at diagnosis confirmation (3 years), thyroglobulin (TG), 131I thyroid scan; RAIU, perchlorate discharge test (PDT), salivary/serum iodine ratio (SSIR) and thyroid ultrasound.
Results: Seven patients were born from consanguineous parents. Treatment was initiated at a mean age of 29.3 days of life. Patients were divided into 2 groups according to RAIU: Group 1 (G1): RAIU≥15% and Group 2 (G2): RAIU≤15%. G1 included 62 patients (65.9%); mean TSH (mU/L), TT4 (µg/dL) and FT4 (ng/dL) initial values were 141.1, 3.6 and 0.5, respectively. TG was <2.5ng/mL in 10 cases (1 with high TSH) and high in 8 (mean 109ng/mL). PDT was positive in 17/30. In G2, mean TSH, TT4 and FT4 initial values were 210.6, 3.5 and 0.6, respectively. Two patients had low SSIR, one of them with goiter noted at first evaluation. Mean Z-scores for height and BMI were respectively 0.1 and 0.52.
Conclusions: a) clinical and laboratory findings are highly variable among patients with dyshormonogenesis; b) goiter is rare; c) in 17 patients, findings were suggestive of iodide organification disorder and in 2, defective iodide transport. Further studies, including evaluation of specific genes of TH biosynthesis, are necessary to elucidate the etiology of CH.

P2-d1-791 Thyroid 1

Serum thyroid hormone profile and trace elements in epileptic children receiving valproic acid therapy: a longitudinal controlled study

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Background: Alproic acid (VPA) may affect thyroid hormone profile, causing alteration in serum trace elements concentrations.
Objective and hypotheses: To prospectively investigate the relationship between serum thyroid hormone profile and trace elements in the epileptic children receiving VPA monotherapy.
Methods: Serum thyrotropin (TSH), free thyroxine (FT4), free triiodothyro-

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nine (FT3), thyroxine (T4), triiodothyronine (T3), thyroglobuline (TG), selenium (Se), zinc (Zn), and copper (Cu) levels were evaluated at baseline and at the 6th month in all patients and in the control group.
Results: Study was completed with 28 epileptic children and healthy matched controls. The mean Cu concentration in the 6th months of VPA therapy was significantly lower than that of the control group (114.81±1.34 vs 141.25±1.54 µg/dL). TSH level was significantly increased in patient group whereas FT4 was significantly decreased. The mean TSH level in the 6th month of VPA therapy was significantly higher than that of the control group, whereas mean T4 level was significantly lower (2.87±1.29 vs 2.38±0.78 µIU/L and 9.39±1.77 vs 10.07±1.19 µg/dL, respectively). The Cu level in the 6th months of VPA therapy was positively correlated with T4 level (r= .41, p = .01). Δ log Cu and Δ TSH were negatively correlated (r = -.36, p = .05).
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.

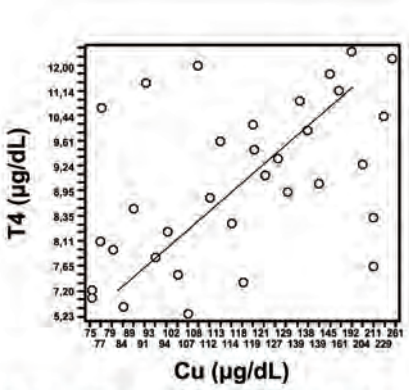

Figure 1. The positive correlation between serum Cu and T4 levels at 6 months of valproic acid therapy (r:.41, p:.01).

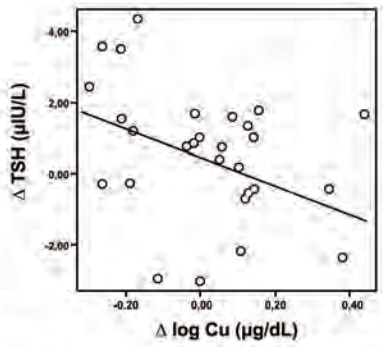

Figure 2. The negative correlation between Δ log Cu and Δ TSH (r:-.36, p:.05)

P2-d1-792 Thyroid 1

Gata4/5/6 are expressed in close proximity to the thyroid anlage during early stages of organogenesis

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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.
Method: 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.

P2-d1-793 Thyroid 1

Revaluation of thyroid hormone status in children and adolescents with autoimmune thyroiditis during follow up

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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-

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ered 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 unexplained
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.

Subsets of lymphocytes	Graves'disease	Hashimoto thyroiditis	p (Wilcoxon test)
APC CD1a+	1,2%	0,73%	0,65
T cells CD3+	17,79%	30,38%	<0,01
T helper cells CD4+	3,17%	0,93%	<0,01
T suppressor/cytotoxic cells CD8+	6,68%	20,54%	<0,01
B cells CD79 alpha +	22,89%	31,65%	<0,01

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 again 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 thyroids. 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 hyperthirotropinemia in obese Spanish children. To investigate the correlation between TSH levels and components of metabolic syndrome (MS).
Methods: Prospective study of a cohort of 439 obese pediatric patients (BMI> 2SD, Hernández-2004), 51% male, 74% Caucasian, mean age 11.03±2.7 years. TSH was determined in all subjects (nv 0.35-4.95) and when elevated, free thyroid hormones, antithyroid antibodies and thyroid ultrasounds were permormed. Antropometric, 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.

	TSH <4.95 (n=415)	TSH >= 4.95 (n=24)	p value
Age (yr)	11.04±2.7	10.99±2.9	NS
Gender (%,male)	52	42	NS
Ethnicity (%,Caucasian)	73	80	NS
BMI (SD)	3.87±1.3	3.71±0.9	NS
TSH (µUI/ml)	2.22±0.9	6.11±1.06	<0.001
TSH index	2.33±0.4	2.72±0.26	NS
TSH index (SD)	-0.55±0.6	0.03±.03	<0.001
HOMA IR	2.67±1.7	3.22±1.5	NS
Abnormal glucose metabolism (%)	7	17	NS
↑BP	18.8	29.2	NS
TG/HDLc (mg/dL)	83.03 ±48.9/46.1 ±10.9	81.2 ±31.1/49.8 ±12.5	NS
GPT/GGT (U/L)	23.0 ±15.4/17.5 ±7.4	27.6 ±19.1/24.4 ±23.7	NS

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.

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 the days on mechanical ventilation (MV). 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.

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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 (P50:1,3 months;IRQ: 0,7-1,8 months) were finally studied. Nine of them (29%; CI95%:16,1-46,6) meet the criteria for type 1 nonthyroidal illness syndrome (NTIS; low FT3 with normal TSH and T4); and 1 (3,2% CI-95:0,5%- 16,2%) for type 2 NTIS. FT3 values correlate inversely with days of admission in hospital (r=0,442; p=0,013) 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 clinical 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. However, children with chronic conditions like Down's syndrome and autoimmune illnesses like T1DM need periodic monitoring.

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 TIDM, 12 (19.4%), and hypocalcemia 13(21%). The duration of symptoms before diagnosis was 2 weeks to 7 years. Coun-

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selling 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 strenghtened to reverse this trend.

Socioeconomic class	No treatment offered	Difficulty in treating	No difficulty in treating	Total
1	1(1.6%)	0	7(11.3%)	8(12.9%)
2	2(3.2%)	8(12.9%)	11(17.7%)	21(33.9%)
3	1(1.6%)	8(12.9%)	13(21%)	22(35.5%)
4	2(3.2%)	6(9.7%)	2(3.2%)	10(16.1%)
5	0	1(1.6%)	0	1(1.6%)
	6(9.7%)	23(37.1%)	33(53.2%)	62 (100%)

P2-d2-800 Thyroid 2

Treatment with methimazole in a 3-year-old male with thyroid hormone resistance

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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-d2-801 Thyroid 2

Analysis of ROC curves of ghrelin and obestatin in children and adolescents with autoimmune thyroid diseases

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Background: Overweight and its related diseases appear to be an increasing problem in recent years, both among adults and children. Also thyroid diseases may lead to disturbances in maintaining normal weight. In hyperthyroidism, body weight is usually reduced whereas in hypothyroidism weight gain in observed. Recently, the role of peptides releases in the stomach, ghrelin and obstatin, in food intake has been emphasized. Recent data indicate that ghrelin may be involved in the regulation of body weight in hypothyroid patients. Both thyroid hormones and antibodies responsible for Hashimoto's thyroiditis exert an effect on the level of ghrelin in hypothyroid patients, causing its reduction as compared to healthy people. On the other hand obestatin induces an anorectic effect-appetite loss, decreased stomach emptying and attenuated jejunal contraction, which eventually leads to body weight loss.
Objective and hypotheses: The aim of the study was to analyze ROC curves of ghrelin and obestatin in young patients with untreated Graves' disease, subclinical Hashimoto' thyroiditis and in patients with appropriate treatment. The study group formed 78 patients of the Outpatient Endocrinology of the Department of Pediatrics, Endocrinology, Diabetology with Cardiology Division.
Methods: In all patients, ghrelin and obestatin levels were analyzed by RIA's method. The results were analyzed using Statisctia 9.0 programme.
Results: Analyzed ROC curves in children and adolescents with hyperthyroidism in Graves' disease we observe that ghrelin was more sensitive than obestatin. In group of children with Graves' disease after 4-6 months of methaimazole treatment both ghrelin and obestatin were similar sensitive and specific, too. On the other hand analyzed ROC curves in children and adolescents with untreated Hashimoto's thyroiditis we found- obestatin was more sensitive than ghrelin. After treatment l- thyroxine for 6-12 months both peptide hormones were similar sensitive and specific.
Conclusions: We suggested that more sensitive were: ghrelin in hyperthyroidism and obestatin in hypothyroidism.

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 makes 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 neurocognitive outcome of CH patients.
Population and methods: We studied 23children 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 5.3days. 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.

	General Quotient ≥ 88 (n=19)	General Quotient < 88 (n=4)	Test	p
Mean TSH at screening (µU/mL)	179.6	201.9	T-test (Significance level = 0.05)	p=0.699
Mean age at first normal serum free T4 (days)	25.7	50.3	T-test (Significance level = 0.05)	p=0.005
Mean age at first normal serum TSH (days)	82	88.5	T-test (Significance level = 0.05)	p=0.756
Etiology	9 agenesis/ hypoplasia; 7 ectopia; 3 dyshormonogenesis	2 agenesis/ hypoplasia; 1 ectopia; 1 dyshormonogenesis	Pearson Chi-Square (Significance level = 0.05)	p=0.861
Mean age at onset of treatment (days)	14	11.75	Independent Samples Mann-Whitney U Test (Significance level =0.05)	p=0.569

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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) ,heterogenicity 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), heterogenicity in thyroid parenchyma (n:14), thyromegaly (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 heterogenicity and thyroid nodule in both groups. Evaluation of risk factors leading to thyroid function disorder revealed that besides radiotherapy, alkylating agents and antimetabolites also increased the risk of thyroid disorder development.
Conclusions: The incidence of hypothyroidism, and nodule development increased in patients who received radiotherapy. Increased heterogenicity and increament 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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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 mU/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 dilation (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?

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Bacground: 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 concensus 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 control 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 Thyrotrophin-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 thyroidits with compensatory hypothyroidism showed pituitary thyrotroph cell hyperplasia.

Time	Groups	Number	Mean TSH levels (mIU/L)	Standard Deviation	95%CI Lower Bound	95% CI Upper Bound
0	Control	47	2.7	1.0	2.3	2.9
0	Pituitary hypothyroidism	25	1.5	0.9	1.1	1.9
0	Hypothalamic hypothyroidism	72	6.4	4.9	5.2	7.5
0	Hashimoto's thyroiditis with euthyroidism	19	3.1	1.5	2.4	3.8
0	Hashimoto's thyroiditis with compensatory hypothyroidism	31	26.3	14.7	13.2	34.3
0	Hashimoto's thyroiditis with hypothyroidism	17	51.3	45.4	17.9	84.6
20	Control	47	17.6	5.4	16.0	19.2
20	Pituitary hypothyroidism	25	8.14	4.46	6.3	9.9
20	Hypothalamic hypothyroidism	72	46.0	16.8	42.0	50.0

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20	Hashimoto's thyroiditis with euthyroidism	19	22.3	8.0	18.4	26.1
20	Hashimoto's thyroiditis with compensatory hypothyroidism	31	118.1	54.2	56.2	180.0
20	Hashimoto's thyroiditis with hypothyroidism	17	273.4	102.4	150.2	396.7
40	Control	47	15.2	4.7	13.9	16.6
40	Pituitary hypothyroidism	25	7.4	3.7	5.9	8.9
40	Hypothalamic hypothyroidism	72	42.0	17.6	37.9	46.2
40	Hashimoto's thyroiditis with euthyroidism	19	19.7	7.4	16.1	23.3
40	Hashimoto's thyroiditis with compensatory hypothyroidism	31	117.7	96.1	45.8	189.6
40	Hashimoto's thyroiditis with hypothyroidism	17	244.5	216.4	133.2	355.8
60	Control	47	11.9	4.6	10.6	13.3
60	Pituitary hypothyroidism	25	6.2	2.64	5.1	7.3
60	Hypothalamic hypothyroidism	72	33.4	17.9	29.2	37.6
60	Hashimoto's thyroiditis with euthyroidism	19	14.8	6.2	11.7	17.8
60	Hashimoto's thyroiditis with compensatory hypothyroidism	31	95.4	83.4	28.2	162.7
60	Hashimoto's thyroiditis with hypothyroidism	17	206.1	197.2	104.7	307.5

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-d2-806 Thyroid 2

Difficult treatment of consumptive hypothyroidism in a child with a massive parotidal infantile hemangioma

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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 lodge. 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 rT3 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-d2-807 Thyroid 2

Congenital hypothyroidism screening program in Turkey: cut-off level for TSH and evaluation of the factors affecting the time of treatment initiation

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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: 49785) 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 TSH levels between 15 and 20 mIU/L. If the cut-off level for investigation of CH was 20 mIU/L, recall rate would be decreased to 5.2% however 2 cases with thyroid dysgenesis and 11 cases requiring thyroxin treatment would be missed.
Conclusions: 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

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P2-d3-809 Thyroid 3

A case of primary hypothyroidism with stimulated pituitary adenoma associated with hyperprolactinaemia and irregular vaginal bleeding

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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, adynamia, severe headaches, delay of growth, reduced vision, indifference, constipation, icterus, dryness of the skin, edema of the whole body, especially of the face, irregular vaginal bleeding since the age of 10.8 ys; hight: -3,2 SDS, weight: -0,39 SDS, BMI: 23,5 kg/m². Sexual development: PT2, AT1, BT2. Retarded bone age of 6.6 years. Laboratory data: TSH >30 µIU/ml, FT4 0,54 ng/dl, Prolactin 1125 mU/L, LH <0,1 mIU/ml, Estradiol 15,7 pg/ml, Anti-TPO 8,2 IU/ml, Anti-TG 35,9 IU/ml, ACTH 13,9 pg/ml, cortisol 109,2 ng/ml. Cerebral MRI: pituitary adenoma growing intra- and supra-sellar. Neurosurgeon consultation: the patient needs to be operated on the pituitary gland. To get an euthyroid state of metabolism we started a treatment with Levothyroxine – 100 µg/day and with Potassium Iodine –100 µg/day. After 2 months of treatment edema and icterus were reduced, headaches stoped, and there was no constipation and no vaginal bleeding any more. Hight-SDS changed from – 3.2 to - 2.7. After 4 months of treatment the patient became more active and interested in different spheres. The tiredness had gone and vision had come to normal. After 1 year of treatment TSH normalized to 1,54 µIU/ml, also FT4 1,25 ng/dl, prolactin 11,88 ng/ml, H-SDS -1,7. On cerebral MRI the assumed "adenoma" had disappeared.
Conclusions: This case shows that severe hypothyroidism can mimick an adenoma in the pituitary gland by hypertrophy of prolactin secreting cells. After normalisation of thyroid hormones TRH and following prolactin decreases and the adenoma like formation disappears without operation.

P2-d3-810 Thyroid 3

Association of HLA alleles with autoimmune thyroid disease in Korean children

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Background: Data regarding differences in the genetic background of Hashimoto disease (HT) and Graves disease (GD) in Korean children are lacking.
Objective and hypotheses: The objective was to analyze HLA-A, -B, -C, and -DRB1 genotypes and allelic association with autoimmune thyroid disease (AITD) in Korean children.
Methods: Between March 2009 and February 2010, 73 patients with AITD (HT: 32, GD: 41) attending Seoul St. Mary's Hospital and Yeouido St. Mary's Hospital were recruited. We analyzed the polymorphism of HLA-A, -B, -C and -DRB1 alleles by PCR-SSP, and compared with those of 159 normal healthy control.
Results: There were significant increases in the allele frequencies of HLA-A*02, -B*46, -Cw*01, -DRB1*04 and -DRB1*08 and significant decreases in those of HLA-A*30, -B*07, -Cw*06, -Cw*07, -DRB1*01 and -DRB1*07 in Korean children with AITD. We categorized AITD as HT and GD for comparison with the control group. In HT, the allele frequencies of HLA-B*46, -Cw*01 and -DRB1*04 were higher and those of HLA-DRB1*01 and -Cw*07 were lower. In GD, the allele frequencies of HLA-A*02, -B*46, -Cw*01 and -DRB1*08 were higher and those of HLA-DRB1*07, and -Cw*07 were lower. For HLA-A*02, -B*46, -Cw*01, -Cw*07 and -DRB1*08, there were 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

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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 has 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 millitres of blood was collected from each of the enrollee 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±3.66 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 µLU/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

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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 HLA 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

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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 0,4% 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 promotor and p.Pro30Leu 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

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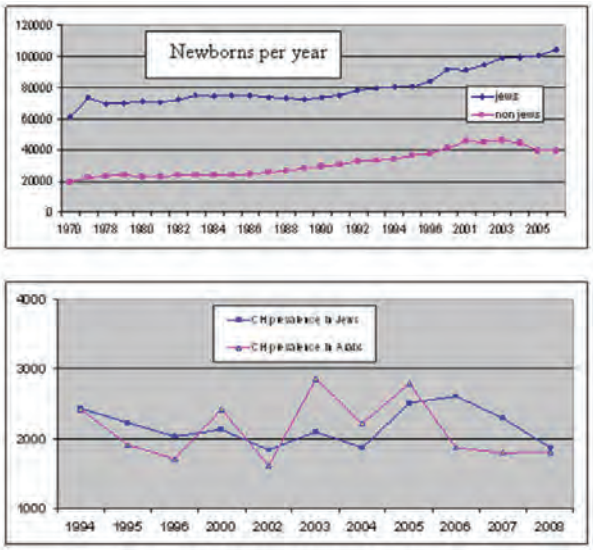
Background: A steady increase of Congenital Hypothyroidism (CH) among newborns has recently been reported in the USA. In Israel, a nationwide screening exists since 1978 covering 99% of the general population. The primary marker has been TT4 with a secondary TSH (above 40 mIU/L).
Objective and hypotheses: To study the prevalence of CH in the Israeli newborn 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

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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 thyroidectomy.
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 underwent total thyroidectomy (TT) , 4 TT + modified radical neck dissection (MRND), 2 TT+MRND+ thymusectomy and 1 right hemilobectomy- isthmusectomy and 1 right hemilobectomy -left 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

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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' 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 compared to the group of healthy children (19,37vs32,96ng/ml; p<0,02); after appropriate treatment in that group levels of nesfatin were higher compared to the group with hyperthyroidism, but lower compared to the group of healthy children (20,35vs32,96ng/ml;NS). On the other hand nesfatin levels were lower in children with untreated subclinical hypothyroidism in Hashimoto's thyroiditis compared to a group of healthy children (17,2vs32,96ng/ml; p<0,002). After treatment of l-thyroxine we found lower

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levels of nesfatin compared to a control group (14,5vs32,96ng/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

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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, that was noticed 9 months ago. On the examination we noticed a mass palpable bellow normal appearing thyroid gland, without enlarged lymph nodes. Biochemistry, bone marrow aspiration and tumor markers were not consistent with malignant disease. The thyroid function tests and calcitonin were in the normal range but thyroglobulin was elevated. US detected normal thyroid gland lifted up by mass spreading to the anterior mediastinum. Thyroid scintigraphy revealed normal thyroid gland, but no accumulation of technetium in the mass. NMR of the thoracic region showed, well defined mass with irregular margins, 8 x 4.4 x 9.5 cm. Since the biopsy showed thyroid tissue, we decided to perform a surgery to extirpate the mass and the thyroid gland if necessary. During the intervention the left thyroid lobectomy was done because mass was in a close contact with it. Patohistological finding were 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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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 hormone (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 peroxidise 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 and concern was raised regarding the possibility of a drug overdose. However, positive TSH receptor antibodies, TSH<0.01 and a FT4 of 67.5 and FT3 of 25.1 and a Technetium scan with an uptake of 13.6 % confirmed a diagnosis of Grave's disease. She was commenced on antithyroid medication which led to resolution of her symptoms.
Discussion: In summary, our patient developed hyperthyroidism 3 years after being hypothyroid. Though this phenomenon has been reported, (16 articles, 70 patients on Pub Med search on 'hyperthyroidism after hypothyroidism') most of the data related to adult patients with only 3 patients presenting with hyperthyroidism in the paediatric age group. Mechanism of conversion is still unknown though change in the properties of the TSH receptor antibodies from blocking to stimulating (with some studies showing the actual reversal) pregnancy and treatment with thyroxine have been implicated in different studies. The appearance of hyperthyroidism has been seen as early as 1 month or as late as 34 years after diagnosis of hypothyroidism.
Conclusion: Though, a rarity in the paediatric setting, it is important to be aware that hypothyroidism 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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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 -PC5/ CD152 -PE and CD8 -FITC/ CD28 -PC5/

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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 diagnosed only 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+152+ and CD8+152+ 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 (CD152) on the cell surface.

P2-d3-820 Thyroid 4

Thyroid hemiagenesis in two boys born small for gestational age-just only 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 of 5% of the general population. A suboptimal intrauterine environment may have a detrimental influence on disrupted 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 1460 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 dyshormonogenesis 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 dyshormonogenesis 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 dyshormonogenesis 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 dyshormonogenesis 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 durig its descend and unfold as a part of the thyroid gland. Eventhough it does not pose any threat to a patient, it is usually mistaken for a malignant tumor and is a cause of surgical intervetion. 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 occured 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 thymus 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 hiperechogenic 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.

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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 (44.2%). 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 thymic 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 hypothyroid patients detected before 2007 was 29/93 whereas this ratio was 19/82 in patients diagnosed after 2007(p: 0.3).

	<2007	>2007	p
N	93	82	
Median age of diagnosis (day)	25	20	0.60
TSH (mIU/ml)	45.3	31.7	0.07
T4 (mcg/dl)	5.1	8.1	<0.01
Free T4 (ng/ml)	0.68	0.99	<0.05

Conclusion: National neonatal screening operated by state, facilitated diagnosis of milder cases with congenital hypothyroidism and slightly decreased time to establish diagnoses.

P2-d3-826 Thyroid 4

Management of thyroid nodules in children and adolescents

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Background: Thyroid nodules in childhood and adolescence are less prevalent but more often malignant than in adulthood. Malignant nodules are predominantly papillary cancers; benign nodules are mostly solid colloid adenomas.
Objective: To determine a practical management of thyroid nodules in childhood and adolescence.
Population and methods: 21 children (10 girls, 11 boys, median age 11,9 yr (5-17,4yr) were admitted between 1997 and 2010 for thyroid nodules (median diameter 28,6 mm (16-62mm). Positive personal history of thyroid disease was found in 6/21: 2/6 Hashimoto thyroiditis and 4/6 dyshormonogenetic hypothyroidism. At diagnosis, 10/21 had a palpable goiter. Ultrasonography, needle aspiration biopsy of nodules, scintigraphy and thyrocalcitonin measurement were performed before lobectomy or total thyroidectomy.
Results: 6/21 were papillary cancer node-positive in 5 cases and an adrenal metastasis in one case. The needle aspiration biopsy was contributory in 50% of these cases. Ultrasonography found microcalcifications in 2/6. 2/6 had thyroiditis and 2/6 dyshormonogenetic hypothyroidism. All were boys with nodule diameter 34mm (16-53 mm), diagnostic delay was 1,8yr (1 month-5.25 yr). 11/21 were benign follicular adenomas and cysts. 2/21 were autonomously functioning nodules with activating Gs alpha mutation. 2/21 had an abscess complicating a cyst of the fourth pouch.
Conclusions: Given the high incidence of cancer, often with delayed diagnosis, thus metastases, and the limited reliability of exploratory investigations in children, our practical management of thyroid nodules is now almost systematically surgical.

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 and aim: 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,), mean aged 11,08±2,6 (3-21) years who presented with hypothyroidism or goitre were evaluated for their pubertal stage, thyroid functions, antithyroid antibodies and thyroid ultrasonographies. High titers of antithyroid antibodies and heterogenous 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

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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 determinated 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.

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 presence 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 M d. 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 both 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 ($p > 0.05$).
Conclusions: 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.

P2-d2-829 Turner Syndrome 1

Metabolic syndrome in Turner syndrome

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Background: Metabolic syndrome (MS) is a pathological condition that includes a combination of visceral adiposity, abnormalities in glucose metabolism, hypertension and dyslipidemia and increases the risk for developing diabetes mellitus and cardiovascular disease. An increased relative risk of diabetes, ischemic heart disease, atherosclerosis and hypertension have been reported in Turner syndrome (TS) patients. No data are currently available on the prevalence of MS in TS. The aim of this study was to evaluated the frequency of MS in TS patients according to obesity status
Methods: We evaluated 85 patients with TS (mean age 27.05 ± 11.17 yrs; karyotype 45,X in 45); TS were divided in obese (SDS-BMI ≥ 2) and non-obese. Sixty-two girls had been treated with GH, 64 with estroprogestin. According to the IDF, we defined subjects with MS as having central obesity and ≥ 2 of following parameters: high systolic BP or diastolic BP, high triglycerides, low HDL-cholesterol and impaired fasting glucose. HOMA-IR>2.5 was utilized as index of impaired insulin sensitivity (IIS). In all girls hepatic ultrasound was performed.
Results: 69 TS were normal-weight and 16 obese. The characteristics of the patients were reported in the table.
The overall prevalence of MS was 12.5% in obese and 4.3% in non-obeseTS (p=0.5). Significant association between MS and hepatosteatosis was found (p=0.03). MS is marginally associated with the presence of IIS (p=0.06). No difference in birthweight, karyotype and therapies was found in TS with or without MS.
Conclusions: MS occurred in 5.8% of the pts with TS and no clear relationship with obesity status and association with hepatosteatosis were found.

Characteristics	Obese TS (n=16)	Non obese TS	p
Age (yrs)	23.29±11.6	27.92±11.7	0.16
Karyotype 45,X (%)	62.6	50.7	0.56
BMI (Kg/m2)	28.54±4.56	21.75±4.35	<0.001
Waist circumference (cm)	84.05±11.5	71.04±11.17	<0.001
Pathological WC	96.9	23.1	<0.001
Triglycerides (mg/dl)	96.87±51.21	77.33±52.43	0.18
High triglycerides>95th(%)	12.5	5.8	0.69
HDL-cholesterol (mg/dl)	64.87±14.66	65.53±14.43	0.86
Low HDL-cholesterol (%)	12.5	13	0.72
Systolic pressure (mmHg)	115.31±14.31	114.63±14.27	0.86
Diastolic pressure (mmHg)	69.37±9.93	71.05±9.96	0.54
High blood pressure (%)	12.5	20	0.73
Fasting glucose (mg/dl)	81.62±13.2	75.63±6.7	0.01
Fasting insulin (µIU/ml)	7.41±5.87	5.07±1.16	0.002
Impaired fasting glucose (%)	12.5	2.8	0.31
HOMA-IR	1.57±1.2	0.95±1.16	0.005
HOMA-IR>2.5(%)	37.8	7.2	0.004
Hepatosteatosis	25	14.5	0.5

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 ethinyloestradiol at variable age.
Methods: Final AH data of TS girls responding to these inclusion criteria were retrieved from the database of the BSGPE. Height data are expresses 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 10.8 years (5.0-19.1), mean (SD) HSDS (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 lineer 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 lineer 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 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 and 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 chronological age (CA) difference and bone age (BA) difference were compared at the time of last control. The ratio in the transdermal estrogen patch treated group was significantly higher (p=0,008) suggesting slower bone age progression in the transdermal estrogen treated TS girls.
Conclusions: While providing adequate breast development, bone age advancement is less significiant with transdermal estrogen patches. These findings suggest a better height prognosis in patients treated by transdermal route.

P2-d2-832 Turner Syndrome 1

Improved accuracy of auxological screening for Turner syndrome based on height standard deviation score and target height

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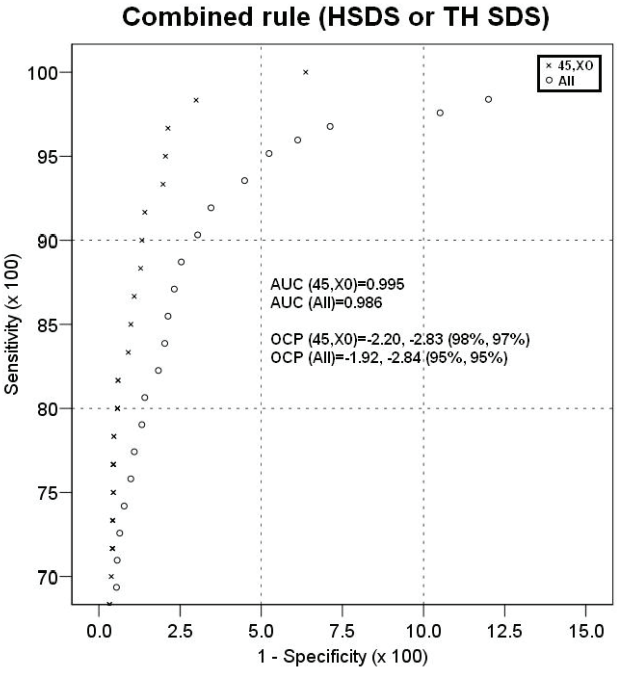
Background: Early detection of Turner syndrome (TS) is of paramount importance because of the associated morbidities, but currently however only approximately one third of the girls with TS are diagnosed by mid-childhood. Nevertheless, auxological screening of Turner syndrome in the general population 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. Analyzes 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.

Figure 1.
ROC curve representing combined growth screening rule [absolute height standard deviation score (HSDS) –rule or target height SDS (TH SDS) –rule] in the whole Turner syndrome (TS) population (n=124, circles) and in a subsample of TS girls with karyotype of 45,X0 (n=60, crosses). Areas under curves (AUC), optimal cut-off-points (OCP, maximum of sensitivity2+specificity2) with cut-off points for HSDS and age adjusted standardized HSDS difference from TH SDS and sensitivity-specificity pairs are shown separately for all TS girls and for 45,X0 TS girls.



P2-d2-833 Turner Syndrome 1

High blood pressure in Turner syndrome

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Background: Adults with Turner syndrome (TS) are at an increased risk of morbidity and mortality from cardiovascular disease. We investigated the prevalence of hypertension and its risk factors, and the relationship of high blood pressure (BP) and early marker of arterial stiffness in patients with TS.
Subjects and methods: Fifty three patients with TS (23.7±5.9 years; 37.7%, obese; 15.1%, type 2 diabetes mellitus; 26.4%, cardiac anomaly; and 33.3%, renal anomaly) underwent 24-hour ambulatory BP (ABP) monitoring. Abnormal 24-hour ABP was defined as having a blood pressure higher than 135/85 mmHg. Body fat was measured by using bio-impedance analyzer, and as a marker of arterial stiffness, we used cardio-ankle vascular index (CAVI) and pulse wave velocity (PWV).

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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 hyperglycemia 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.
Aims: 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 assessed.
Methods: Using a combination of two electronic databases, reporting, archiving and recording cardiology and cardiac, we identified girls with a diagnosis code 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 one other cardiac abnormality 52/138 (37.4%):These included bicuspid aortic valve(BAV):[27];BAV and ventricular septal defect(VSD):[6];VSD[5], aortic stenosis(AS)[2];AS and other abnormalities of valvular structure[12]. Forty five of 138 (32.6%) had karyotype performed. Five of 45 (11.1%) had a diagnosis of TS on karyotype. 40/45 girls were 46XX. Of the five girls with TS, karyotypes were: 45XO/XY[1], 45 X/46 Xp del[1] and Xq del[3}. Two girls with TS had coarctation in association with BAV; 3 had isolated coarctation with no other cardiac abnormalities.
Conclusions: Karyotype is not regularly or consistently analysed in girls who have coarctation of the aorta. True prevalence of Turner syndrome is unknown in this group. Due to the serious implications in Turner syndrome, for multiple lifetime risks, it is imperative that all girls with coarctation have karyotype performed. Factors leading clinicians to investigate girls presenting with coarctation of the aorta with karyotype analysis are unclear.

P2-d2-835 Turner Syndrome 1

SHOX dosage and final height (FH) in Turner syndrome (TS) treated with GH-therapy

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Background: Short stature is the most common feature of TS improved by long-term GH-therapy. SHOX haploinsufficiency appears to be the main cause of their growth failure.
Objectives: To assess whether SHOX dosage could influence the FH of TS pts treated with GH.
Methods: 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 or ratio in mosaic karyotype) and by MLPA analysis when the percentage of mosaic metaphasis 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-SA (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 in Group B, 153.3±4.5 Group C and 154.3±5.5 in Group D ($F=6.9$, $p=0.0002$). 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 haploinsufficient 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 diploidy: 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 follicular stock in the case of low % of X monosomy mosaicism.
Methods: 14 girls TS with a prenatal diagnosis underwent a neonatalevaluation: karyotype confirmation was done on juggal 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 juggal 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. Ultrasound of the ovaries is difficult at this age, follicles were visualized in only 6 cases of gp2.

Group	CA (months)/ Range	Height (cm)/SD	BMI (z score) /range	FSH (mUI/ml) /range	LH (mUI/ml) /range	Estradiol (pg/ml)	AMH (ng/ml /range
group1	8.5 ±8/1-21	61.8 ±9/-0.7 ±0.9	15.0 ±1.4/-0.16 ±0.8	42.8 ±32/3.3-82	1.7±1.5	0.5±0	0.04±0
group2	5.9 ±6.3/1-22	62.7 ±10/0.32 ±1	16.1 ±1/0.96 ±1.2	4.0 ±3.3/1-12	0.2±0	4.8±4.9	3.1 ±3/0.7-10

Conclusions: Early hormonal screening of FSH and AMH may assess follicular activity of the ovary. These early data does not predict the future formally puberty of these girls.

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P2-d2-837 Turner Syndrome 1

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.
Results: These four sisters were born from a first-cousin marriage. 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 news 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.

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