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Abstract

O01 A Homozygous NNT Gene Mutation Identified by Whole Exome Sequencing (WES) In a Boy with Familial Glucocorticoid Deficiency (FGD) Impairs Mitochondrial Oxidative Stress

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Introduction: FGD is a rare life threatening congenital condition frequently caused by mutations in ACTHR (type 1) and MRAP (type 2) genes or other known and yet unknown genes (type 3). In this study, our objective was to confirm the genotype-phenotype correlation in the novel homozygous p.G866D (c.2597G>A) NNT gene variant detected by WES in a boy with type 3 FGD.

Material and Methods: A 18-months old boy born to a consanguineous family presented with severe hypoglycemia, seizures, skin hyperpigmentation, undetectable plasma cortisol levels, elevation of ACTH (>1.250 pg/ml), normal Na/K and Renin Plasma Activity. Type 1 and 2 FGD were excluded by direct sequencing ACTHR and MRAP genes. Genomic DNA was submitted to WES and sequence readings were aligned to Hg19 and variant sequences screened by GATK and an in house sequenced protocol. Functional analysis included transient culture of mononuclear blood cells of the patient, heterozygous carriers and controls to analyze NNT mRNA expression and reactive oxidative species (ROS) under basal and after 5-hours stimulation with H2O2(100 uM). ROS levels were evaluated in flow cytometry by fluorescence intensity of the CM-H2DCFDA probe.

Results: WES analysis revealed few final candidate genetic variants, including a homozygous exon 17 transition (c.2597G>A; p.G866D) in NNT gene, which was confirmed by Sanger sequencing. Family pedigree analysis confirmed segregation of this homozygous variant with the phenotype and asymptomatic parents and his younger brother were heterozygous carriers. The pathogenicity of this novel missense was indicated by in silico tools. Functional analysis confirmed the NNT mRNA expression in mononuclear blood cells. In basal conditions, no ROS abnormalities were detected. However, after challenged with H2O2 cells carrying the homozygous NNT p.G866D variation presented higher ROS accumulation than heterozygous carriers or control wild-type (CM-H2DCFDA fluorescence intensity: 4.502 vs. 2.629 vs. 2.046).

Conclusion: Type 3 FGD was detected by WES in a boy carrying the novel homozygous mutation in NNT p.G866D mutation, highlighting the potential of the Next-Generation Sequencing in a clinical setting. In vitro analysis suggests that this mutation, in the homozygous state, impairs mitochondrial function by accumulating ROS under stress conditions.

O02 Cortisol – Cortisone Ratio and Metalloproteinase-9 Emerging as Risk Factors Associated with Pediatrics Hipertension

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Background: Paediatric hypertension is increasing and has been associated with obesity and insulin resistance. Recently, cortisol/cortisone ratio and the metalloproteinase 9 (MMP-9), which is a marker of vascular remodelling, have been syndicated as new risk factors associated with hypertension.

Objective: To analyse the association between paediatric hypertension with clinical, biochemical, inflammation, and vascular remodelling biomarkers.

Method: A Cross sectional study was designed. We selected 320 subjects (4 to 16 years old, female 49.4%), anthropometric parameters, serum aldosterone (SA), plasma renin activity (PRA), cortisol, cortisone, HOMA-IR, hsCRP, adiponectin, IL-6, TNF-α,
PAI-1, MMP-2 and MMP-9 activities were measured. We calculated SA/PRA ratio (ARR >10, as screening of hyperaldosteronism) and serum cortisol/cortisone ratio as 11β-HSD2 activity estimation. The systolic and diastolic blood pressure indexes were calculated (SBPi and DBPi = observed/50th percentile blood pressure).

Results: According the Fourth Report of Task Force and JNC7, 59 children were hypertensive. Cortisol and cortisol/cortisone ratio were higher in hypertensive (p < 0.001). No hyperaldosteronism was found. A positive linear correlation was observed between SBPi and DBPi with: BMI-SDS, HOMA-IR, cortisol/cortisone ratio and MMP-2, MMP-9 activities. However, correlations with SA, PRA and ARR were not significant. The variables associated with hypertension in the multivariate logistic model were: serum cortisol/cortisone ratio (OR: 4.73; CI = 2.32–9.65), BMI-SDS (OR: 3.74; CI = 1.91–7.32), MMP-9 (OR: 3.48; CI = 1.79–6.78) and HOMA-IR (OR: 2.20; CI = 1.10–4.38).

Conclusion: Novel biomarkers such serum cortisol/cortisone ratio and MMP-9 activity emerged associated with paediatric hypertension. Further studies are needed to know the role of these markers in hypertensive patients.

Supported by Fondecyt 1130427 and 1150437, CORFO 13CTI-21526-P1 and IMII P09/016-F (ICM) Chilean Grants.

003 Newborn Screening for Congenital Adrenal Hyperplasia (CAH): Improving the Effectiveness of the Neonatal 17OH-Progesterone (N17OHP) and Serum Confirmatory Tests

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Introduction: CAH newborn screening (NBS) programs, using N17OHP, present high capacity to detect the salt-wasters (SW). However, main concerns are high false-positive rate (FPR), low positive predictive value (PPV) of N17OHP levels and the heterogeneity of confirmatory methods. Considering the CAH-NBS implementation in our country, our objective is to optimize the best cutoff levels for the first screening and the confirmatory tests.

Materials and Methods: Data of 473,983 newborns were retrospectively evaluated. N17OHP was measured by IFMA assay (AutoDelfia) and cutoffs (99th percentile) adjusted according to birth-weight (BW1: <1,500 g; BW2: 1,500–2,000 g; BW3: 2,001–2,500 g; BW4: >2,500 g), and to age at sample collection (before or after 72 h of life). Confirmatory tests consisted in serum 17OHP measurement by RIA and/or mass spectrometry (MS). Entirety of newborns were diagnosed with classical forms (22 SW, 12 males), confirmed by molecular analysis. N17OHP levels ranged from 53–494 ng/ml (serum equivalence) in SW and from 36.5–52.8 ng/ml in simple virilizing (SV) newborns. Serum confirmatory tests were performed in 149 newborns. In affected newborns, serum 17OHP levels (MS) ranged from 56–668 ng/ml in SW and from 54–117 ng/ml in SV form. FPR persisted in the confirmatory tests in 70% using RIA and in only 13% by MS. Among these cases, molecular analysis identified 2 nonclassical newborns. PPV of MS methodology was significantly higher than RIA (52 vs. 27%).

Conclusions: N17OHP levels adjusted to P99.8th and to sample collection time improve the CAH-NBS by reducing the FPR rate without missing the classical form diagnosis. Although serum 17OHP measurement by RIA is widely used in our country, the MS significantly reduced the FPR in the confirmatory tests. Molecular analysis could be restricted for asymptomatic cases with persistently increased serum 17OHP levels.

004 Doppler Evaluation of the Uterine Artery for the Diagnosis and Follow-Up of Patients with Precocious Puberty

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Background: Pelvic ultrasound is used for the diagnosis and follow-up of girls with precocious puberty (PP). This tool could be imprecise, because during treatment some patients may persist with pubertal uterine and ovarian morphology. Estrogens decrease the resistance of uterine arteries, so Doppler evaluation of these vessels might be a useful complementary exam to determine the effects of treatment in these patients.

Objective: To evaluate the usefulness of uterine artery Doppler analysis in the diagnosis and follow-up of girls with PP.

Subjects and Methods: Fourteen girls with central PP (breast Tanner stage II–IV, <8 years, LH >6.0 IU/L after leuprolide stimulation, >3.5 cm uterus length) were treated with long acting triptorelin-pamoate 22.5 mg (6 months duration). A single operator performed a pelvic ultrasound at the time of diagnosis, and after 6 and 12 months of analog therapy, by measuring uterine size and ovarian volume; plus a Doppler color analysis of the uterine arteries. We described the blood flow velocity waveform: high resistance represents absence of puberty, whereas low and/or intermediate resistance indicates active puberty. These parameters were correlated with the LH levels observed in these patients at the time of diagnosis, and during treatment with triptorelin-pamoate 22.5 mg.

Results: All patients received one dose of triptorelin administered at time 0 and 6 months later, and completed one year of treatment. Mean age at time 0: 7.9 years ±1.3 (4.0–8.0), and LH peak before treatment: 34.0 IU/L ±23.0 (8.6–91.0). At baseline, 10 out of 12 patients (83%) had low or intermediate resistance with Doppler analysis, whereas 2 patients (17%) had high resistance. Mean peak
LH at 6 months of treatment was 2.2 IU/L ±0.8 (0.7–3.7), and 13 patients (93%) showed high resistance and 1 patient showed an intermediate pattern. All 14 patients (100%) showed high resistance blood flow velocity waveform at 12 months, which was associated with a mean peak LH of 1.8 IU/L ±1.0 (0.3–4.0).

Conclusions: Uterine artery Doppler color analysis is a valuable complementary tool for the diagnosis and management of girls with central PP. This technique shows a good correlation with LH levels, and may be particularly useful for patients with this condition during treatment.

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**O-1.2 Oral Session 1.2**

**005**

**Twenty Years Experience in Congenital Adrenal Hyperplasia: Clinical, Hormonal and Molecular Characteristics in a Large Cohort**

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**Background:** Most congenital adrenal hyperplasia (CAH) patients carry mutations derived from conversion events involving the pseudogene, and the remaining carry new mutations varying according to ethnicity. A good genotype-phenotype correlation is observed, allowing the use of molecular analysis in diagnostic confirmation and genetic counseling. Therefore, our objective is to review the molecular diagnosis in a large cohort of CAH patients and to evaluate the genotype-phenotype correlation.

**Materials and Methods:** DNA was extracted from peripheral leukocytes of 480 patients (158 SW, 116 SV, 206 NC). Fourteen point mutations were screened by allele-specific PCR and large gene rearrangements by Southern blotting/MLPA, CYP21A2 sequencing was performed in those with incomplete genotype. Gene founder effect was analyzed through microsatellite studies. Patients were divided into 4 genotypes, according to in vitro enzymatic activity (Null, A: <2%, B: 3–7%, C: >20%).

**Results:** Targeted methodologies identified mutations in both alleles in 88.6% of SW, 86.3% of SV and 80% of NC patients. CYP21A2 sequencing allowed genotype definition in 100% of classical and 87% of NC patients. The most frequent mutations in SW, SV and NC were I2 splice (21%), p.I172N (7.5%) and p.V281L (27%) of alleles in 88.6% of SW, 86.3% of SV and 80% of NC patients.

**Conclusions:** Considering the gene founder effect mutations, the addition of sequencing is essential to perform molecular diagnosis in our population and corroborates for a good genotype-phenotype correlation. Molecular studies could optimize the CAH hormonal diagnosis, especially in NC form, as well as indicate the 17OHP levels predictive of carriers’ status for severe mutations.

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**006**

**Differences in Insulin Receptor Isoforms (IR-A and IR-B) Expression in Human Term (T) and Preterm (PT) Placentas**

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**Introduction:** The insulin receptor (IR) is expressed as two different isoforms that differ in the presence (IR-B) or not (IR-A) of exon 11. The IR–B isoform mediates mostly the metabolic effects of insulin, whereas IR-A has potent mitogenic and anti-apoptotic functions and plays a key role in cell proliferation.

**Aim:** To determine the IR-A and IR-B mRNA expression in term (T-SGA and T-AGA) and preterm (PT-SGA and PT-AGA) human placentas; and to assess whether they are different according fetal growth.

**Methods:** We collected placentas from 32 T-SGA (birth weight (BW) = −1.74 ± 0.08 SDS), 29 T-AGA (BW = 0.11 ± 0.12 SDS), 20 PT-SGA (BW = −2.08 ± 0.14 SDS) and 27 PT-AGA (BW = −0.40 ± 0.13 SDS) newborns. We determined the mRNA expression by RT-PCR in the chorionic (CP) and basal (BP) plates of the placentas. Results are shown in the table as mean SEM: The differences were studied by Mann-Whitney.

**Conclusion:** We describe for the first time the expression of IR-A and IR-B in human placenta and the differences according gestational age and birth weight. The higher expression of IR-B in

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**Table 1. IR-A and IR-B mRNA Expression (for abstract O06)**

<table>
<thead>
<tr>
<th></th>
<th>T-SGA</th>
<th>T-AGA</th>
<th>PT-SGA</th>
<th>PT-AGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR-A (CP)</td>
<td>1.05±0.01*</td>
<td>1.20±0.05**</td>
<td>1.08±0.02</td>
<td>1.04±0.02</td>
</tr>
<tr>
<td>IR-A (BP)</td>
<td>1.08±0.02*</td>
<td>1.24±0.05**</td>
<td>1.07±0.01</td>
<td>1.06±0.01</td>
</tr>
<tr>
<td>IR-B (CP)</td>
<td>0.50±0.01**</td>
<td>0.33±0.01**</td>
<td>0.71±0.02*</td>
<td>0.55±0.01</td>
</tr>
<tr>
<td>IR-B (BP)</td>
<td>0.48±0.01**</td>
<td>0.33±0.02**</td>
<td>0.72±0.01*</td>
<td>0.56±0.01</td>
</tr>
</tbody>
</table>

* T-SGA vs T-AGA or PT-SGA vs PT-AGA; ** T-SGA vs PT-SGA or T-AGA vs PT-AGA.

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8 Horm Res Paediatr 2015;84(suppl 2):1–77

XXV Annual Meeting, SLEP
Puerto Varas, Chile
T-SGA and PT-SGA compared to T-AGA and PT-AGA placentas respectively suggest a possible placental compensatory mechanism in fetal IUGR.

O07

Co-Transporter NPT2a Defect: Pediatric Clinical and Biochemical Phenotype

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Background: Clinical and biochemical phenotype in type II sodium phosphate co-transporter (NPT2a) defects is scarcely known making it difficult for the physician to identify the etiology of hypophosphatemic patients and consequently to treat them properly.

Aim: To describe the clinical manifestation of NPT2a defect in two siblings during the first years of life.

Case Reports: Argentinean family composed by two siblings (boy and girl) with homozygous SLC34A1 (gene encoding the NPT2a) mutation c.1485G>A, p.Arg495His and non-consanguineous parents with SLC34A1 heterozygous mutation. Index case was diagnosed by whole exome sequencing (JCEM 2014;99(11):E2451–6). Main postnatal abnormalities in both patients were hypophosphatemia non detectable PTH with normal TRP associated to hypercalcemia, hypercalciuria and nephrocalcinosis. One had elevated 1.25(OH)2 vitamin D. Treatment with hyperhydration, glucocorticoids, biphosphonates and phosphate and calcium metabolism probably prevented further kidney damage.

Conclusions: The NPT2a defect found in this family leads to a severe transient hypercalcemia and to a hypophosphatemic disorder without neither renal phosphate leak nor rickets. This might be due to an increase in NPT2c expression leading to a compensatory mechanism that maintain circulating phosphate levels. The children’s phenotype is similar to that described in the KO Npt2a mouse. Early detection and proper treatment of this disorder of phosphate and calcium metabolism probably prevented further kidney damage.

O08

Mothers Vitamin D Level as the Main Factor to Predict Vitamin D Deficiency in Cord Blood

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Introduction: Several published studies show that insufficient vitamin D levels are common in the general population which has increased its clinical interest in the recent years. Vitamin D deficiency during pregnancy could cause serious consequences in newborn vitamin D levels as well as complications during the pregnancy. Vitamin D levels assessment in pregnant women may be useful to predict vitamin D deficiency in their children.

Methods: All mothers who delivered at the Integrated Health Organization Goierri-Alto Urola in Zumarraga (Basque Country), between August 2012 and July 2013, were invited to participate in the study from which 68.1% took part. Vitamin D levels were assessed in 561 pairs of mother and cord blood using chemiluminescence methods. Vitamin D deficiency was considered when serum levels of 25-hydroxy vitamin D were lower than 20 ng/ml. In the statistical analysis, Chi-square and T-student statistics were used first. Afterwards, a logistic regression analysis was applied to estimate the effect of vitamin D level in the mother to predict vitamin D deficiency in cord blood adjusted by other significant factors. Linear correlation between vitamin D level in mothers and cord blood was assessed using Pearson correlation coefficient.

Results: Pregnant women deficiency levels vary from 39.9% to 77.9% depending on whether they gave birth in summer or winter respectively. Overall vitamin D deficiency prevalence in cord blood was 41.4%. Linear correlation between vitamin D level in mothers and newborns was 0.87. The higher vitamin D level in the mother the lower the probability for vitamin D deficiency in cord blood (odds ratio 0.75 (0.72, 0.80)) adjusted by season, skin color, Spanish nationality and mother’s calcium level.

Conclusion: Vitamin D level in pregnant women adjusted by season, skin color, Spanish nationality and her calcium level can be used as a predictor for vitamin D deficiency in cord blood.
**Background:** SNPs of risk for type 2 diabetes (T2D) are not always identified in early-onset of the disease and there is insufficient information about its association with pre-diabetic disorders. The aim was to evaluate the association of SNPs of risk to T2D with the presence of the disease, b-cell function and insulin resistance in Mexican families with children and adolescents.

**Methods:** Case-control study. Families of pediatric patients with T2D (99 index cases, 57 diabetic parents, 99 non-diabetic parents and 101 non-diabetic siblings) and families without the disease (83 children and 137 parents) were included. Four SNPs were genotyped: SLC16A11 (rs13342232), TCF7L2 (rs7903146 and rs12255372) and ABCA1 (rs9282541). To test the association between SNPs and T2D, logistic regression was performed; and for quantitative glycemic traits (fasting glucose, 2 h glucose, fasting insulin, 2 h insulin, glycosylated hemoglobin A1c, C-peptide, quantitative glycemic traits (fasting glucose, 2 h glucose, fasting insulin, 2 h insulin, glycosylated hemoglobin A1c, C-peptide, HOMA-IR and HOMA-B) linear regression was used, adjusting by age, sex and cBMI, only rs7903146 and rs12255372 main-

**Results:** The rs13342232 was the only SNP associated with T2D in both adults (ORAdjusted1.73, 95% CI 1.06–2.79, p = 0.026) and children (ORAdjusted1.80, 95% CI 1.11–2.92, p = 0.016), with an increased risk homozygous (ORAdjusted4.11 95% CI 1.46–11.58 in adults and ORAdjusted3.07 95% CI 1.67–16.52 in children). The TCF7L2 and SLC16A11 SNPs were associated with fasting insulin (rs13342232 b = −1.04, p = 0.039; rs7903146 b = −1.4, p = 0.039), C-peptide (rs13342232 b = −0.25, p = 0.011; rs7903146 b = −0.26, p = 0.051), HOMA-IR (rs13342232 b = −0.24, p = 0.045; rs7903146 b = −0.33, p = 0.042) and HOMA-B (rs13342232 b = −13.34, p = 0.037; rs12255372 b = −22.21, p = 0.014); however, when were adjusted by age, sex and cBMI, only rs7903146 and rs12255372 maintained their association with levels of C-peptide (b = −0.22, p = 0.035) and HOMA-B (b = −23.35, p = 0.005) respectively.

**Conclusions:** The rs13342232 was identified as a risk for T2D in Mexican families of children and adolescents. Other SNPs previously associated with T2D, were not identified in these families, but were associated with b-cell function and insulin resistance. In some cases then association it lost when were adjusted by overweight and obesity, which points out the opportunity of preventing the development of disease in genetically susceptible individuals; while in others, the presence the early pancreatic function changes independently of cBMI suggest it’s probably a matter of time for individuals at risk to develop the disease.

**Introduction:** Type 1 diabetes (T1D) is an autoimmune disease characterized by the presence of susceptible HLA genotypes. At onset 91% patients have at least one positive diabetes autoantibody. Maturity-onset diabetes of the young (MODY) refers to a rare monogenic type of diabetes. Clinical diagnosis of MODY is difficult due to overlap with many clinical features of T1D and type 2 diabetes. In MODY patients appropriate molecular diagnosis is essential to improve glycemic control by modification of current drug treatment and to allow genetic counseling. Nevertheless, genetic analysis is expensive and laborious, so selection of candidates to undergo genetic study is crucial.

**Objective:** Determine whether HLA-DRB1 genotyping is an appropriate tool to detect patients who undergo MODY genetic study.

**Design:** In total 234 patients were typed at high resolution for HLA-DRB1 locus (PCR-SSO): 160 patients with a new onset of T1D (at least one positive diabetes autoantibody and mean age at diagnosis 8.8 ± 3.8 years) and 74 patients with a new onset of MODY (61 GCK-MODY and 13 HNF1A-MODY) and mean age at diagnosis 14.7 ± 6.5 years. Three HLA-genotype categories were considered: 0 risk alleles (no-DR3, no-DR4), 1 risk allele (DR3 or DR4) and 2 risk alleles (DR3/DR4 combinations). Statistical chi square test analysis was performed with software package SPSS (version 22) and Odd Ratio (OR, 95% CI) was calculated.

**Results:** Compared to T1D group, MODY patients carried significantly higher frequency of having 0 risk alleles [64.9% vs 7.5%; p < 0.0001; OR (95% CI) = 22.77 (10.7–48.6) and lower significant frequency of 2 risk alleles [5.4% vs 48.1%; p < 0.0001; OR (95% CI) = 0.06 (0.02–0.18)]. Although the presence of only 1 risk allele was statistically significant, the difference was not enough to distinguish MODY and T1D clinically [29.7% vs 44.4%; p = 0.03; OR (95% CI) = 0.53 (0.29–0.96)].

**Conclusion:** We suggest that molecular diagnosis should be performed in those patients with compatible clinical suspicion of MODY who have negative autoimmunity, family history of diabetes and presence of none or one risk HLA-DRB1 alleles. Diagnosis of MODY is less likely when two HLA-risk alleles are present.
Abstracts Horm Res Paediatr 2015;84(suppl 2):1–77

O-2.1 Oral Session 2.1

O11

Ambulatory Blood Pressure Monitoring in Children and Adolescents with Type-1 Diabetes Mellitus

Pietropaolo, G.; Ricci, J.; Lombardi, L.; Bresso, P.; Fasano, V.; Balbi, V.
Hospital de Niños de La Plata, La Plata, Argentina

Introduction: Type 1 Diabetes Mellitus (DM) is a risk factor for cardiovascular disease. The prevalence of hypertension (HT) is higher in these patients. The objective was to determine HT prevalence by ambulatory blood pressure monitoring (ABPM), in a group of DM normotensive children in a clinical setting.

Material and Methods: A prospective study of 31 DM patients (F:17, M:14) with one or more years of evolution was performed. Variables included: chronological age at DM debut (dCA), DM duration, familiar HT; metabolic control (mean annual HbA1C), BMI, age at ABPM and birth weight (BW). All patients underwent ABPM, retinal examination (RE), microalbuminuria (MA) and electrocardiogram (ECG).

Statistical analysis: Student’s t-test or Mann-Whitney. Spearman’s correlation coefficient was calculated between numerical variables.

Results: Mean dCA was 7.06±3.15 years, median DM duration was 3.19 years (2.16–5.41). Seven (22.6%) patients had familiar HT and there was no correlation with variables. Mean CA at ABPM was 10.91±2.63 years and median HbA1C was 8.49% (7.86–9.20). Mean BMI was 0.60±0.90 SDS. Three (9.7%) patients showed positive MA. ECG and RE were normal in all children. Significant differences were found in: 1-HbA1C between patients with normal versus pathological daytime diastolic blood pressure load (DPL) (p = 0.011), and between normal versus pathological nocturnal diastolic blood pressure (DBP) (p = 0.040). 2-Lower BW with nocturnal HT, nighttime systolic pressure load (SPL) and daytime loads (p = 0.01 and p = 0.005, respectively). ABPM results are shown in tables 1, 2.

Conclusions: 1-Although sample size was small, daytime and nighttime diastolic load were associated with poor metabolic control. 2- ABPM was useful to identify non dipper systolic pattern in 74.2% of patients and overnight changes in systolic and diastolic blood pressure. 3- It’s thought that lower BW and nocturnal hypertension are cardiovascular risk factors suggesting incipient nephropathy. Therefore, the use of ABPM in diabetic patients should be performed for early diagnosis.

Table 1. (for abstract O11)

<table>
<thead>
<tr>
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<th>SBP</th>
<th>DBP</th>
<th>SPL</th>
<th>DPL</th>
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<tr>
<td>Daytime (%)</td>
<td>6.5</td>
<td>6.5</td>
<td>16.1</td>
<td>16.1</td>
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<tr>
<td>Nighttime (%)</td>
<td>22.6</td>
<td>16.1</td>
<td>41.9</td>
<td>45.2</td>
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<tr>
<td></td>
<td>SBP systolic blood pressure</td>
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Table 2. (for abstract O11)

<table>
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<tr>
<th></th>
<th>Dipper revers</th>
<th>Non-dipper</th>
<th>Dipper</th>
<th>Hyper-dipper</th>
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</thead>
<tbody>
<tr>
<td>Systolic (%)</td>
<td>9.7</td>
<td>74.2</td>
<td>16.1</td>
<td>–</td>
</tr>
<tr>
<td>Diastolic (%)</td>
<td>3.2</td>
<td>25.8</td>
<td>51.6</td>
<td>19.4</td>
</tr>
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</table>

O12

Elevated AMH and Insulin Cord Levels in Daughters Born to Mothers with Type 2 Diabetes

Villaruel, C.; Solinas, A.; Lopez, P.; Rencoret, G.; Kohen, P.; Codner, E.

1IDIMI, Universidad de Chile, Santiago, Chile; 2IDIMI, Departamento Ginecología y Obstetricia Universidad de Chile Campus Centro, Santiago, Chile; 3Departamento Ginecología y Obstetricia Universidad de Chile Campus Centro, Santiago, Chile

Introduction: Effect sof diabetes on ovarian function of pregnant diabetic women and their female offspring are unknown.

Objective: To study the effect of maternal diabetes on ovarian function of female newborns (NB) and the relationship of NB hormonal findings with their mother hormonal profile during pregnancy.

Methodology: NB (n = 69) were recruited and classified as daughter of: woman with type 2 (dT2D n = 20), gestational DM (dGD n = 27), and physiologic pregnancy/without diabetes (dC, n = 22). Cord blood sample was drawn at delivery (TOD) to measure: sex steroids SHBG, insulin, glucose, IGF-1, IGFBP and AMH. HOMA-IR was calculated. Mothers (mT2D/mGD/mC) underwent clinical/hormonal evaluation at week 24–28/32–34 and TOD. The correlation of hormone levels in the NB and the mother was analyzed. Data analysis: ANOVA/LSD post-test and Pearson’s r correlation coefficient.

Results: NBs had similar gestational age and birth weight, but dT2D had a higher prevalence of macrosomy. Higher AMH levels were found in dT2D compared with dC. Likewise, higher HOMA-IR and IGF1 levels were observed in dT2D compared to dGD and dC. dT2D had higher cord insulin levels than dC. Similar cord glucose, androgens, SHBG and E2/T levels were observed in the three groups.

mT2D women had higher testosterone and insulin levels compared with mGD and mC at 32–34 weeks and at TOD. Maternal serum T levels had a positive correlation with cord insulin (r = 0.2; P = 0.04) and IGF-1 levels (r = 0.3; P = 0.01).

Conclusions: Daughters of mT2D appear to be more insulin resistant at birth compared with NB born to mGD and healthy women, which is related to elevated maternal testosterone levels during pregnancy. AMH levels were higher in newborns of T2D
mothers suggesting that pregestational diabetes affects ovarian function of the developing fetus during pregnancy. FONDECYT-No11.12146.

**O13**

**Reduced Humanin Levels in Children with Type-1 Diabetes Mellitus**

**Hernandez, M.**<sup>1</sup>; **Wan, J.**<sup>2</sup>; **Valdes, C.**<sup>1</sup>; **Avila, A.**<sup>3</sup>; **Codner, E.**<sup>1</sup>; **Cohen, P.**<sup>2</sup>

<sup>1</sup>Instituto de Investigaciones Materno Infantil, Facultad de Medicina, Universidad de Chile, Santiago, Chile; <sup>2</sup>USC Leonard Davis School of Gerontology, Los Angeles, California, USA; <sup>3</sup>Instituto de Investigaciones Materno Infantil, Universidad de Chile, HCSBA, Santiago, Chile

**Background:** Recent studies in multiple models of T1DM have demonstrated the role of mitochondrial abnormalities in the pathogenesis of this disease and its complications. Humanin is a potent cyto-protective and ‘metaboloprotective’ molecule in vitro and in vivo, including the protection of beta cells from apoptosis, improvements in insulin secretion and action, and both prevention and treatment of diabetes in the NOD mouse model, by ameliorating various aspects of the pathogenesis of the disease.

**Objective and Hypotheses:** We hypothesized that humanin levels are decreased in patients with T1DM and may be related to duration or severity of disease and evaluated humanin levels in T1DM and matched controls (C) as a function of HbA1c and microalbuminuria.

**Method:** Subjects with T1DM and age- and sex matched controls were recruited from the diabetes clinic. A complete physical exam including Tanner staging exam was performed. Early morning a blood sample was obtained for determination of HbA1c and humanin levels (in house ELISA, previously published).

**Results:** T1DM (n = 154) and C (n = 76), age 3–19 years old (T1DM mean 12.9, C mean 10.8), males 57% in DM1 vs 47% in C. New onset (<2 yr) of diabetes in 32.4% of T1D (n = 50). T1DM and C were divided according to Tanner stages (1–5). Humanin levels are lower in T1DM compared to C (974.6 ± 498.3 in T1DM vs 1241.2 ± 782.4 in C p = 0.0019). This difference is observed only in girls (T1DM 1327.4 ± 714.8 vs C 1997.4 ± 481 p < 0.01). Humanin levels are lower in Tanner I and III in T1DM compared with C (p < 0.05). Humanin levels increased throughout puberty in C children, but not in T1D adolescents. No association was observed between duration of T1D, albuminuria or HbA1c.

**Conclusion:** T1DM patients exhibit lower humanin levels, an observation that is especially pronounced in females and early Tanner stages. There is no correlation between the degree of metabolic control or disease duration and humanin levels. Future studies will address the impact of humanin levels on pathophysiology and metabolic control of diabetes.

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**Table 1.** (for abstract O12)

<table>
<thead>
<tr>
<th></th>
<th>T2D</th>
<th>gDM</th>
<th>C</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn (n)</td>
<td>20</td>
<td>27</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>37.7±0.4</td>
<td>37.9±0.4</td>
<td>39.0±0.3</td>
<td>P = 0.09</td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td>3,690±144.6</td>
<td>3,381±113.9</td>
<td>3,384±158.6</td>
<td>P = 0.2</td>
</tr>
<tr>
<td>Macrosomia (%)</td>
<td>25</td>
<td>15</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>AMH (ng/ml)</td>
<td>2.5±0.7*</td>
<td>2.2±0.9</td>
<td>0.6±0.3</td>
<td>P = 0.03</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>145.0±26*</td>
<td>88.0±13.9</td>
<td>84.2±9.8</td>
<td>P = 0.036</td>
</tr>
<tr>
<td>Insulin (μUI/ml)</td>
<td>11.6±5.7*</td>
<td>8.2±4.9</td>
<td>5.6±2.1</td>
<td>P = 0.03</td>
</tr>
<tr>
<td>Mothers (N)</td>
<td>20</td>
<td>27</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>32–34 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone (g/ml)</td>
<td>0.95±0.1</td>
<td>0.71±0.07</td>
<td>0.61±0.08</td>
<td>P = 0.02</td>
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<tr>
<td>Insulin (μUI/ml)</td>
<td>38.4±9.3</td>
<td>14.0±3.2</td>
<td>9.8±1.1</td>
<td>P = 0.03</td>
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<tr>
<td>TOD</td>
<td></td>
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</tr>
<tr>
<td>Testosterone (g/ml)</td>
<td>1.0±0.1</td>
<td>0.71±0.07</td>
<td>0.69±0.06</td>
<td>P = 0.003</td>
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<tr>
<td>Insulin (μUI/ml)</td>
<td>19.7±2.6</td>
<td>14.1±2.3</td>
<td>10.2±1.5</td>
<td>P = 0.04</td>
</tr>
</tbody>
</table>

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**O14**

**Timing of Pubertal Events in Boys with Type 1 Diabetes Mellitus (T1D)**

**Gaete, X.**<sup>1</sup>; **Vivanco, M.**<sup>2</sup>; **Romero, P.**<sup>2</sup>; **Lopez, P.**<sup>1</sup>; **Rocha, A.**<sup>3</sup>; **Codner, E.**<sup>1</sup>

<sup>1</sup>IDMI, Santiago, Chile; <sup>2</sup>Hospital Roberto del Río, Santiago, Chile; <sup>3</sup>Hospital Exequiel Gonzalez Cortés, Santiago, Chile

**Introduction:** T1D may affect the gonadal axis function. Recently, higher testosterone levels have been shown at the final stages of puberty in boys with T1D. However, the effects of type T1D on the timing of puberty of boys with modern insulin therapy are unknown.

**Objectives:** To evaluate the age of pubertal events in boys with T1D and determine whether duration of diabetes, metabolic control or insulin dose are associated with age of puberty in T1D boys.
Boys with T1D treated with modern insulin therapy appear to have a normal age of onset of pubertal development compared to a simultaneously studied group of healthy boys. However, T1D boys show at an earlier age the final stages of puberty in T1D.

**Results:**
Patients were 15 ± 2 years old, 3 ± 1 years post menarche and had attained final height. Results are shown as mean (basal/after 6 month on Dapagliflozin). BMI Z Score 1.42/0.75; weight (kg) 66.7/60.4; IMC (Kg/m²) 25.2/22.7; HbA1c (%) 8.13/8.10; insulin dose (U/day) 57.8/36.2; blood glucose (mg/dl) 191/175; blood glucose SD 92/85; hypoglycemia (n/week) 2.8/3.3. Capillary Beta-hydroxybutyrate was low or not detectable.

Polydipsia, polyuria and dry mouth were reported. One patient seemed to increase a hand tremor that was already present at the beginning of the study. In addition, two girls exhibited an unquantified reduction in body acne. Only one girl showed a reduction of Hba1c (8.3 to 7.7%) and all the adolescents reduced their body weight (3.9; 6.7 and 8 kg respectively). Interestingly blood glucose levels and fluctuation were reduced but overall metabolic control did not improved. We hypothesize that patients reduced insulin doses to attain their comfort glucose levels that may not be in the recommended target range. None of the girls wanted to suspend Dapagliflozin after the observation period.

**Conclusions:**
Dapagliflozin was effective to reduce insulin dose and body weight without metabolic deterioration in 3 adolescents with T1D. Randomized controlled trials are needed. Our findings provide hope that SGLT2 inhibition might be an effective adjuvant in insulin treatment in overweight adolescents with T1D.

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**Table 1. (for abstract O14)**

<table>
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<th>TD1 (years)</th>
<th>Controls (years)</th>
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<tr>
<td>Genital tanner 2</td>
<td>10.7 ± 1.0</td>
<td>10.7 ± 1.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Genital tanner 5</td>
<td>15.5 ± 1.2</td>
<td>16.9 ± 1.2</td>
<td>0.002*</td>
</tr>
<tr>
<td>Pubic hair tanner 2</td>
<td>11.1 ± 1.0</td>
<td>11.2 ± 1.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Pubic hair tanner 5</td>
<td>15.6 ± 1.2</td>
<td>16.1 ± 1.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Axillary hair (initial)</td>
<td>12.8 ± 1.1</td>
<td>13.2 ± 1.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Axillary hair (intermediate)</td>
<td>13.8 ± 1.1</td>
<td>14.5 ± 1.2</td>
<td>0.032*</td>
</tr>
<tr>
<td>Facial hair initial stages</td>
<td>13.2 ± 1.1</td>
<td>13.4 ± 1.1</td>
<td>0.6</td>
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</tbody>
</table>

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**O15**

**The Effect of SGLT2 Inhibitor Dapagliflozin on BMI in Female Adolescents with Type 1 Diabetes**

Roman, R.¹; Valdivia, N.²; Ruiz, S.³

¹Universidad de Antofagasta, Hospital Regional de Antofagasta, Antofagasta, Chile; ²Universidad de Antofagasta, Antofagasta, Chile; ³Hospital Regional de Antofagasta, Antofagasta, Chile

**Objective:**
Increased body weight is a main concern in female adolescents with Type 1 Diabetes (T1D). Dapagliflozin, an insulin-independent sodium-glucose cotransporter 2 (SGLT2) inhibitor, increases glucosuria and reduces hyperglycemia in individuals with type 2 diabetes. Whereas, it is not approved in T1D nor in children. The objective was to assess the effect of Dapagliflozin in combination with insulin on body weight.

**Research Design and Methods:**
A 6 months Dapagliflozin treatment (10 mg per day) was initiated in 3 overweight female adolescents with T1D in addition to their regular insulin treatment (2 on multiple daily injections, 1 on insulin pump). The insulin dose was proactively reduced to keep blood glucose levels in the target range. Capillary blood glucose was monitored as usual an capillary beta hydroxybutyrate was measured if blood glucose was over 300 mg/dl.

**Results:**
Body weight (kg) 66.7/60.4; IMC (Kg/m²) 25.2/22.7; HbA1c (%) 8.13/8.10; insulin dose (U/day) 57.8/36.2; blood glucose (mg/dl) 191/175; blood glucose SD 92/85; hypoglycemia (n/week) 2.8/3.3. Capillary Beta-hydroxybutyrate was low or not detectable.

Polydipsia, polyuria and dry mouth were reported. One patient seemed to increase a hand tremor that was already present at the beginning of the study. In addition, two girls exhibited an unquantified reduction in body acne. Only one girl showed a reduction of Hba1c (8.3 to 7.7%) and all the adolescents reduced their body weight (3.9; 6.7 and 8 kg respectively). Interestingly blood glucose levels and fluctuation were reduced but overall metabolic control did not improved. We hypothesize that patients reduced insulin doses to attain their comfort glucose levels that may not be in the recommended target range. None of the girls wanted to suspend Dapagliflozin after the observation period.

**Conclusions:**
Dapagliflozin was effective to reduce insulin dose and body weight without metabolic deterioration in 3 adolescents with T1D. Randomized controlled trials are needed. Our findings provide hope that SGLT2 inhibition might be an effective adjuvant in insulin treatment in overweight adolescents with T1D.

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**O16**

**46,XX Ovotesticular DSD in the Absence of SRY Gene Associated to SOX3 Duplication**

Grinspon, R.¹; Rey, R.¹; del Rey, G.¹; Nevado, J.²; Mori Alvarez, M.²; Chiesa, A.¹

¹CEDIE-CONICET-FEI-División de Endocrinología, Hospital de Niños R. Gutiérrez, Buenos Aires, Argentina; ²INGEMM-IdiPaz (Hospital la Paz) y CIBERER, Madrid, España

**Background:**
Ovotesticular DSD is a rare disorder defined by the presence of both ovarian and testicular tissue in the same individual. SRY is present in approximately 1/3 of patients with 46,XX ovotesticular DSD. In SRY-negative ovotesticular DSD, the mechanism responsible for the presence of testicular tissue is not yet understood.

**Case Presentation:**
A male patient was referred to us for hypoplasias and bilateral cryptorchidism at 2.5 years of age. He had a trophic phallus (32 mm x 13 mm) with coronal hypoplasias and hypoplastic scrotum. Right gonad was palpable in the inguinal region; no gonad was palpable on the left side. Basal AMH (216 pmol/L) and hCG-stimulated testosterone (30 ng/dl) were low, indicating that dysgenetic testicular tissue was present. Gonadotro-
in Xq27.1 chromosomal region encompassing SOX3 gene was evidenced. Metaphase FISH analysis using a BAC probe hybridizing on both X homologues demonstrated a tandem duplication of this region.

**Conclusion and Discussion:** This is the first case of SRY-negative 46,XX Ovotesticular DSD in whom a genetic association (SOX3 duplication) is reported. These results are in line with evidence in mice indicating that, in the absence of SRY, gain-of-function of SOX3 induces testis differentiation in the XX bipotential gonad. SOX3, as a surrogate of SRY, would act synergistically with SF1 to upregulate SOX9 expression and stimulate testicular organogenesis.

### O17

**Mutations in the DHX37 Gene Identified by Whole-Exome Sequencing are a Novel Cause of the Embryonic Testicular Regression Syndrome in Four Families with 46,XY DSD**

Silva, T.1; Ledário, A.1; Nishi, M.1; Funari, M.1; Dénes, F.2; Costa, E.1; Mendonca, B.1; Domenice, S.1

1Disciplina de Endocrinologia e Metabologia, LIM42, HC, Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil; 2Disciplina de Urologia, HC, Faculdade de Medicina da Universidade de São Paulo, Sao Paulo, Brazil

**Introduction:** The diagnosis of 46,XY DSD by abnormalities of gonadal development is established in less than 30% of the cases. Whole-exome sequencing (WES) is a promising tool in the investigation of these patients.

**Objective:** To establish the molecular diagnosis of patients with 46,XY DSD due to embryonic testicular regression syndrome (ETRS).

**Patients and Methods:** Two families were initially studied: F1 (2 affected, 2 unaffected members) and F2 (2 affected, one unaffected member). The four patients presented microopenis and absent or dysgenetic testes. WES by HiSeq2500 platform was used. The candidate gene variants identified by WES were confirmed by Sanger as well as the presence of variants in this gene was searched in 10 patients with sporadic ETRS. The mutated proteins was evaluated in silico by the Mutation Taster, Polyphen and SIFT tools.

**Results:** A novel heterozygous variant c.923G>A (p.Arg308Glu) in DHX37 was identified in the affected members of the two families by exome analysis. This variant was confirmed by Sanger in the four patients, in the F1 father and in the F2 mother, and in one of the 10 patients with sporadic ETRS. A second homozygous variant c.451C>T (p.Arg151Trp) was identified in another sporadic ETRS patient. Two of these allelic variants were not found in 194 controls studied and in 1000GENOME, ExAC and ESP6500 population databases. Both variants were considered damaging by in silico analysis.

**Discussion:** DHX37 gene (12q24.31) encodes a RNA helicase protein that belongs to the DEAH (Asp-Glu-Ala-His) family, and it is involved in the ribosome biogenesis. DHX37 is expressed in the seminiferous duct cells and we speculated if these variants could impair the maintenance of the testicular cells. A previous report of a 12q24.31-33 deletion, including DHX37 gene, in a syndromic patient, who had microopenis and cryptorchidism, reinforces the hypothesis that the DHX37 was involved in the etiology of ETRS.

**Conclusion:** The identification of deleterious variants in DHX37 in two familial and two sporadic cases of ETRS point out this gene as a novel and strong candidate to the etiology of 46,XY DSD by abnormality of the gonadal development.

**Financial Supported:** FAPESP 2013/02162-8.

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**O18**

**Lower Antimüllerian Hormone Levels (AMH) in Postmenarcheal Adolescents Conceived after Assisted Reproductive Techniques (AcART)**

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**Introduction:** A possible effects on children born after assisted reproductive techniques on gonadal function has been postulated. However, no data exists on ovarian reserve (OR) and morphology during adolescence in these girls. AMH, ovarian volume (OV) and follicle count (FC) have been used as indirect indicators of OR in women of reproductive age. The aim of the study is to evaluate AMH levels in AcART and compare them with adolescents that were spontaneously conceived (AcSP).

**Methods:** AcART (n = 8) and AcSP (n = 48) were studied during the first 2 years postmenarche. Hormonal profile and ultrasonographic study were performed during follicular phase.

**Table 1.** (for abstract O18)

<table>
<thead>
<tr>
<th></th>
<th>AcSP (n = 48)</th>
<th>AcART (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational-age (weeks)</td>
<td>39.2±1.5</td>
<td>38.1±1.5</td>
</tr>
<tr>
<td>Birthweight (gr)</td>
<td>3,490±485</td>
<td>3,120±742</td>
</tr>
<tr>
<td>Age-at-menarche (years)</td>
<td>11.9±1.1</td>
<td>12.0±0.9</td>
</tr>
<tr>
<td>Menstrual-cycle (days)</td>
<td>32.4±4.8</td>
<td>28.1±2.9*</td>
</tr>
<tr>
<td>BMI (Z-score)</td>
<td>0.77±0.77</td>
<td>0.70±0.61</td>
</tr>
<tr>
<td>FSH (mU/ml)</td>
<td>5.75±1.54</td>
<td>5.85±2.63</td>
</tr>
<tr>
<td>LH (mU/ml)</td>
<td>2.93±1.38</td>
<td>3.00±1.91</td>
</tr>
<tr>
<td>Estradiol (pg/ml)</td>
<td>43.25±14.99</td>
<td>41.73±16.27</td>
</tr>
<tr>
<td>OV-max (ml)</td>
<td>8.0±4.4</td>
<td>6.3±3.2</td>
</tr>
<tr>
<td>OV-mean (ml)</td>
<td>6.7±3.2</td>
<td>5.7±2.7</td>
</tr>
<tr>
<td>FC-max (n)</td>
<td>7.4±3.5</td>
<td>8.3±2.6</td>
</tr>
<tr>
<td>FC-mean (n)</td>
<td>6.4±3.0</td>
<td>6.9±2.4</td>
</tr>
</tbody>
</table>

* p < 0.05; ** p < 0.005.
**Results:** AcART have lower AMH levels vs AcSP (3.1 ± 1.6 and 6.0 ± 3.7 ng/ml, p = 0.002 respectively). Higher serum INHB levels were observed in AcART compared with AcSP (67.9 ± 30.7 and AcSP: 44.5 ± 27.5 pg/ml, respectively, p = 0.04). No differences in FSH, LH and estradiol between AcART and AcSP (table 1). Similar OV and total FC were observed in both groups (OV: 5.7 ± 2.7 and 6.7 ± 3.2 ml in AcART and AcSP, p = 0.61; FC: 6.9 ± 2.4 and 6.4 ± 3.0 follicles in AcART and AcSP, p = 0.42). No differences were observed between small follicles (SF; 2–5 mm, p = 0.79) and large follicles (LF; 6–9 mm, p = 0.95) between both groups. However, in AcART, INHB levels correlate with OV (r = 0.79, p = 0.036) and LF (r = 0.79, p = 0.033). Serum AMH levels show a tendency to correlate with SF (r = 0.75, p = 0.05). All AcART born at term with normal birthweight. AcART had a similar age at menarche vs AcSP (12.0 ± 0.9 vs 11.9 ± 1 years, p = 0.9), but shorter menstrual cycles (p = 0.03) (table 1).

**Conclusions:** These data suggest that adolescents born after assisted reproductive techniques have a lower number of small follicles, as inferred from the presence of lower serum levels of AMH compared with AcSP. Future studies should confirm whether these preliminary data represent a lower OR in adolescents AcTRA (Fondecyt Grant 1113024).

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**Table 1.** (for abstract O19)

<table>
<thead>
<tr>
<th>PCOM by</th>
<th>RC (+) (n = 34)</th>
<th>(-) (n = 69)</th>
<th>OV10 (+) (n = 21)</th>
<th>(-) (n = 82)</th>
<th>OV12 (+) (n = 10)</th>
<th>(-) (n = 93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHR</td>
<td>0.75±0.14</td>
<td>0.79±0.05</td>
<td>0.73±0.17</td>
<td>0.79±0.05**</td>
<td>0.69±0.23</td>
<td>0.79±0.06***</td>
</tr>
<tr>
<td>AMH (ng/ml)</td>
<td>8.80±4.6</td>
<td>4.30±2.5**</td>
<td>8.40±5.6</td>
<td>5.20±3.2*</td>
<td>9.90±5.7</td>
<td>5.50±3.6*</td>
</tr>
<tr>
<td>INHB (pg/ml)</td>
<td>64.5±31.6</td>
<td>57.8±27.9</td>
<td>69.8±34.6</td>
<td>57.6±27.4</td>
<td>89.3±34.7</td>
<td>57.4±27.3**</td>
</tr>
</tbody>
</table>

* p < 0.05, (+) vs. (-) PCOM; ** p < 0.01, (+) vs. (-) PCOM; *** p < 0.001, (+) vs. (-) PCOM.
Objective: To explore the interaction between the Wnt/beta-catenin pathway and the expression of a stem cell maintenance markers NANOG, STAT3, and OCT4 in ACTs.

Methods: Patients: 70 pediatric and 18 adults with ACTs; control adrenal tissues: 13 children and 13 adults. mRNA expression of DAX1, SF1, STAT3, NANOG and OCT4 evaluated by qPCR. Protein expression of SF1, DAX1, STAT3, NANOG and OCT4 evaluated by immunohistochemistry. Copy number variation of SF1 and DAX1 evaluated by MLPA. In vitro the effect of inhibition of the Wnt/beta-catenin pathway with PNU on NANOG expression was evaluated in H295 adrenal tumor cells.

Results: Decreased expression of SF1 mRNA was found in 84% of pediatric ACTs (P = 0.02) but not in adult ACTs (P = 0.49). Conversely, overexpression of DAX1 mRNA was found in 89% of adult ACTs (P < 0.01) but not in pediatric ACTs (P = 0.65). STAT3 mRNA expression among adult ACTs was higher in adenomas than in carcinomas (P < 0.01). p.S45P CTNNB1/beta-catenin mutated ACTs presented increased mRNA expression of NANOG (P < 0.01), which was dose-dependently reduced in vitro by inhibiting the Wnt/beta-catenin pathway with PNU (P < 0.01). At protein level, moderate or strong nuclear SF1 staining was found in 67% and 14% of pediatric and adult ACTs, respectively. Moderate to strong nuclear DAX1 staining was found in 45% of pediatric ACTs but not in adult ACTs, which only weak nuclear staining was present. Moderate or strong nuclear staining of OCT4 was associated with metastatic tumors in pediatric ACTs (P < 0.05) but not in adult ACTs (P = 0.52). MLPA analysis revealed SF1 gene amplification in 71% and 33% of pediatric and adult ACTs, respectively.

Conclusion: Post-translational mechanisms possibly regulate the overexpression of SF1 in pediatric ACTs, likely interacting with DAX1 through mutual activation in a synergistically manner. NANOG may play a role in Wnt/beta-catenin activation in ACTs, particularly in the presence of the p.S45P beta-catenin mutation. OCT4 immunostaining may be a marker of malignancy in pediatric ACTs.

P01

Serum Estrogen Activity (SEA) in Girls with Precocious Pubarche (PP)

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Introduction: PP has been considered a benign entity. However, advanced BA or increased metabolic risk has been observed in some of the girls with PP. A possible mechanism explaining advanced BA in girls with PP may be derangements in estrogen action. We postulate that girls with PP have overall elevated SEA.

Patients and Methods: Girls with PP (N = 10, age 8.1 ± 1.3 y) and healthy prepuberal girls without pubarche (C, N = 10, age: 7.0 ± 1.7 y) were studied. Inclusion criteria for PP girls included the presence of pubic terminal hair younger than eight years old, absence of obesity (three patients had BMIs ≤ p96th) and lack of other signs of pubertal development. Control girls had no signs of puberty, lack of medical chronic conditions and were younger than 8.5 years. A fasting blood sample was obtained for the measurement of testosterone, DHEA-S, 17(OH) progesterone, FSH, LH, and estradiol. Overall SEA was assessed with a modified in vitro bioassay, E-screen, which evaluates the proliferation of estrogen-sensitive MCF-7 BUS cells in response to blood serum. Proliferation was measured by fluorometry (CyQuant kit), SEA is shown compared to a serum pool (SP) obtained from healthy women.

Results: Both groups had similar age and anthropometric characteristics. PP had pubic hair Tanner stage 2. Axillary hair was absent. DHEAS and estradiol where significantly higher in PP compared to C, (110.3 ± 45.9 vs 33.6 ± 22.5 μg/dl and 43 ± 24.2 vs 18.7 ± 11.0 pg/ml, p = 0.002 and 0.03 respectively). FSH, LH, and 17(OH) progesterone levels were similar in both groups of girls. SEA was similar in PP and C girls (75.6 and 79.3% SP respectively, p = 0.57).

Conclusions: In this preliminary study, girls with PP have similar SEA compared to healthy prepubertal girls.

P02

Severe Hypertension in a Girl: Cushing Syndrome or Apparent Mineralocorticoid Excess Syndrome? Utility of Molecular Study

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Introduction: Apparent mineralocorticoids excess syndrome (AME) is an unusual cause of hypertension in childhood, caused by genetic mutation of type 2 11β-hidroxysteroid deshydrogenase (11BHSD2) enzime, which metabolizes cortisol to cortisone. Patients with AME born from consanguineous parents, are small for gestational age (SGA) and could have nephrocalcinosis, hypokalemia and high plasma cortisol/cortisone relation (F/E).

Clinical Case: 2-years old girl admitted to hospital for mild head trauma. During hospitalization she showed severe hypertension (197/133), requiring 4 drugs to control partially her blood pressure.

Clinical Background: Fullterm SGA newborn. Second daughter of normotensive parents who are first degree cousins; she has a normotensive sister. Past medical history: recurrent pneumonia and viral hypertrophic myocardiopathy.

Physical Exam: No characteristic facium; no Cushing signs were noted.

Hypertension Study: Renal US: bilateral nephrocalcinosis, mild pyelectasia, no arterial stenosis; normal renal function. Normal urine, except for a high calcium/creatinine index. Aldosterone: <1 (reference value (RV): 5–80) and plasmatic renin activity: <0.2 ng/ml/hr (RV 1.1–3.8), both were supressed. Urinary free cortisol in 24-hour (two samples) resulted elevated: 1413 y 262 ug/per
Diagnosis in this patient. Suggested hypercortisolism. AME is defined by normal levels of compatible with her medical history although the laboratory strongly level allows adrenal insufficiency diagnosis in most of these patients, so it should be systematically evaluated. 2) ACTH basal one member. The diagnosis of adrenal insufficiency (AI) and leucodystrophy in was to assess clinical and biochemical outcome of a family since transport of very long-chain fatty acids (VLCFA). The objective objective of this study was to evaluate adrenal insufficiency (AI) and leucodystrophy in one family.

**Material and Methods:** Familial screening was carried out in 12 family members with VLCFA (M: 11, F: 1), one pubertal and 11 prepubertal children, with a median age of 6.64 years (1.37–13.26). The following protocol was designed to evaluate AI according to ACTH (pg/ml) basal value: (i) ACTH <80 ruled out AI and it was repeated every six months, (ii) when ACTH was between 80 and 200 in two determinations, ACTH test was performed, (iii) when ACTH >200, AI was diagnosed.

**Results:** VLCFA were impaired in 7 patients (58.3%) with a median age of 7.02 years (1.64–10.09). Six children (85.7%) presented AI at a median age of 7.80 years (4.67–10.09). Three pre-sent signs and symptoms of AI. In all of them, AI was diagnosed with ACTH basal level >200. AI was ruled out in one patient who required ACTH test. Mean hydrocortisone dose used was 14.4 ± 4.2 mg/m²/day. Only one patient required mineralocorticoid replacement. Three patients had leucodystrophy. Bone marrow transplant (BMT) was performed only in 2 children, one of them died. The first patient could not be transplanted because of his advanced leucodystrophy.

**Conclusions:** 1) Adrenal insufficiency is frequent in these ALD patients, so it should be systematically evaluated. 2) ACTH basal level allows adrenal insufficiency diagnosis in most of these patients. 3) In this group, ACTH test was required only in one case. 4) BMT is useful to prevent neurological impairment if it is attempted in earlier stage of the disease. For this reason, ALD must be recognized as soon as possible in infancy.

**P04**

**Circadian Rhythm of Salivary Cortisol in Healthy Normal Weight and Obese Children and Adolescents**

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**Background:** Previous studies showed divergences regarding the impact of obesity on circadian rhythm (CR) of salivary cortisol (SAF) in children. Reference values of CR SAF are still lacking using ultrasensitive electrochemiluminescent immunoassay (ECLIA).

**Objective:** To test the influence of BMI, age, gender, attending school or during summer-break on CR of SAF in children.

**Methods:** Prospective-descriptive-cohort study. Saliva was collected by spitting into tubes at 8:00 AM (mSAF) and 11:00 PM (nSAF). Collection procedure was evaluated by a questionnaire. SAF was measured by ECLIA (Cobas411-Roche) in 103 healthy children (53 girls; 1.8–18 yr (median: 10 yr). Inclusion criteria: healthy children without acute or known chronic diseases at the time of the study. Exclusion criteria: corticosteroid therapy, incomplete sampling/erroneous time collection. Interindividual SAF variation (bCV%) and the decrease percentage of cortisol at night (D%) = ((mSAF-nSAF)/mSAF)x100 were calculated. Children were divided according to BMI-centile into Lean (L, n = 59), overweight (Ow, n = 12) or obese (Ob, n = 32). Obese children had no clinical signs of hypercortisolism.

**Results:** Eighty-four percentage of children referred no difficulties in salivary collection. SAF widely varied in children (bCV%: mSAF: 50% and nSAF: 42%) while D% variation was 27%. Multiple regression showed that SAF (nmol/L) was not associated to BMI (Median mSAF; 3rd-97thcentile range in L: 16; (3–35), Ow: 10; (8–20), Ob: 14; (4–47), p = 0.07; nSAF in L: 4; (1.4–8), Ow: 4; (2–7), Ob: 5; (1.2–9), p = 0.52]. Median mSAF concentration for the whole group of children was 14 nmol/L, 3rd-97thcentile range: 5–34 nmol/L. Age and attending school period were significantly associated to higher nSAF (r = 0.41, p < 0.01) and a lesser %D (r = –0.32, p < 0.001). Children older than 10 years of age had significantly higher nSAF compared to younger children (97thcentile: 8.0 vs 6.5 nmol/L, p = 0.001), whereas the proportion of children during summer-break was comparable between these two age groups (p = 0.97).

**Conclusion:** Obesity seems not to influence CR SAF in normal children and adolescents. Age should be taken into account when evaluating nocturnal free cortisol in saliva. Manufacturers do not provide morning or night SAF references for pediatric settings, hence, our cut-off values could be useful in children in whom abnormal secretion of cortisol is suspected.

**Abstracts**

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**P05**

**Testicular Tumors in Congenital Adrenal Hyperplasia Patients: Prevalence and Factors Associated to Its Development**


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**Introduction:** Testicular adrenal rest tumour (TART) is an important cause of infertility in men with Congenital Adrenal Hyperplasia (CAH). The aim of this study was to determine TART prevalence in CAH due to 21-hydroxylase deficiency (CAH-21) patients and to evaluate factors associated with its development.

**Patients and Methods:** A descriptive and analytical cross-section study evaluated thirty-eight male patients with CAH-21, aged from three to 27 years, 11 of them prepubertal, through testicular ultrasonography.

Medical records were retrospectively reviewed and the following data were obtained: anthropometry, prescribed glucocorticoids doses and serum 17-hydroxyprogesterone (17OHP), androstenedione (Andro), ACTH, renin and LH, in the period of six years preceding the ultrasonography and divided into three intervals of two-year. To evaluate the disease control the patients were divided in two groups for each one of the laboratory parameters: normal group (biannual median within the normal range for age/puberty stage) and increased group (increased values for age/puberty stage). We set up [-2/0] the last two years prior to the ultrasonography; [-4/-2] the period from four to two years and [-6/-4] that between six and four pre-assessment years. Three patients had monitoring period lower than six years: one of them with two years and two with four years.

**Results:** Nine patients, four of them prepubertal and the youngest aged five years, had TART. The mean age on ultrasonography was 15.2 ± 6.7 years. There was no significant difference between the groups with and without TART to prescribed glucocorticoid doses, 17OHP, Andro, ACTH, renin and LH serum levels in any of the determined periods. Statistical difference was found between groups of Andro levels in the two years period nearest ultrasonography. Half of patients with increased biannual Andro median in this period presented TART (p = 0.018 OR = 8.00 [95% CI 1.42 to 44.92]) versus only 16.7% in the normal Andro group. One of the determined periods. Statistical difference was found between groups of Andro levels in the two years period nearest ultrasonography. Half of patients with increased biannual Andro median in this period presented TART (p = 0.018 OR = 8.00 [95% CI 1.42 to 44.92]) versus only 16.7% in the normal Andro group.

**Conclusion:** TART prevalence was 23.7%. This study showed that disease control was one of the factors associated with TART development and that testicular lesions can occur in prepubertal patients. We suggested that active TART search should begin in early childhood.

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**P06**

**Peripheral Precocious Puberty in Girls with McCune-Albright Syndrome: Treatment and Outcomes**

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**Introduction:** Precocious pubertal development in McCune-Albright syndrome (MAS) is caused by gonadotropin-independent activation of ovaries, resulting in ovarian cyst formation and estradiol secretion. Therapeutic options include tamoxifen, progestational agents and aromatase inhibitors (AI) aiming to block sex steroid synthesis or action. Secondary gonadotropic axis activation generally occur after 8 years of age and GnRH analog (GnRHa) therapy must be added.

**Aim:** To describe the clinical follow-up of patients with MAS treated with distinct therapeutic agents in a single center.

**Patients and Methods:** 9 consecutive girls with MAS had their medical records’ data systematically revised.

**Results:** The chronological age at the diagnosis of gonadotropin-independent precocious puberty was 5.0 ± 1.8 (3.6 to 9.2 yr). Thelarche was the first manifestation in 7/9 patients whereas menarche firstly occurred in the remaining 2 girls, all of them before age of 3 years old. Fibrous dysplasia was identified in 7/9 patients and 5 of them were treated with pamidronate because they had bone pain and two had fractures. Tamoxifen (10 mg/day) was the first choice treatment in all patients but in one that used AI. Tamoxifen plus medroxiprogesterone (100–150 mg/mo) was used in 7 patients. AI (anastrozole 2 mg/day) was added in 4 girls who presented more advanced bone age. Seven patients presented secondary Central Precocious Puberty and were treated with GnRHa. The duration of the treatment was 5.3 ± 1.6 years (2.6 to 6.75 yr). One patient is still under treatment. Hypertricosis and uterine and ovarian enlargements were the main side effects of tamoxifen in 2 and 5 patients, respectively. Eight patients reached their adult height (155 ± 8.5 cm), three of them within the target height range. Five girls failed in reaching target height range even using all therapeutic options and GnRHa.

**Conclusion:** The treatment of precocious puberty of MAS remains a challenge even with distinct therapeutic agents available. The clinical and hormonal peculiarities in each patient have impact on short- and long-term follow-up of this condition.
Long-Term Evaluation of Patients with Testotoxicosis

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Introduction: Testotoxicosis or familial male-limited precocious puberty is a rare cause of peripheral precocious puberty in boys caused by germline constitutive activating mutations of the LHCG receptor gene. Affected patients develop rapid virilization, growth acceleration, and skeletal advancement with elevated levels of testosterone, despite prepubertal levels of LH. These patients have usually normal gonadotropin profile and fertility in the adult life.

Materials and Methods: Four unrelated boys (I-IV) with testotoxicosis were retrospectively analyzed. The time of follow up ranged from 5 to 24 years. Clinical and hormonal data were determined. Semen analysis was performed in two patients.

Results: Signs of progressive sexual development occurred from birth to three years. All patients had elevated serum levels of testosterone (164–623 ng/dL). Activating mutations were identified in all cases (p.Leu457Arg [1], p.Ala568Val [2] and pThr577Ile [1]). LH and FSH levels were prepubertal in three patients on the diagnosis occasion. Three patients (I, II, IV) were treated with cyproterone (70 mg/m2); and anastrazole (2 mg/day) was associated in one of these cases (I). One patient received medroxyprogesterone acetate only. In addition, two patients (II and IV) had secondary central precocious puberty and GnRH analogs (depot leuprolide) were introduced in these cases. Only one patient reached a target height (III). Patient I with severe testotoxicosis due to p.Leu457Arg mutation had short stature and persistently suppressed gonadotropin levels during his long-term follow-up (24 years). Despite his oligozoospermia, he fathered a girl. The biological paternity was confirmed by microsatellite analysis.

Conclusions: Normal final height was obtained only in one patient (I) with testotoxicosis who was early treated with cyproterone and anastrozole. We evidenced fertility in a patient who had severe testotoxicosis with persistently suppressed gonadotropin levels and oligozoospermia in adulthood. This case illustrates the potential role of high levels of intratesticular testosterone in the spermatogenesis.

GnRH Infusion in Females with Hypogonadotropic Hypogonadism

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Background: Hypogonadotropic hypogonadism (HH) in females is an uncommon and heterogeneous condition. There is little data regarding biochemical profile of gonadotropins to further substantiate the diagnosis.

Objective: To evaluate the gonadotropica secretion profile after GnRH infusion in a female cohort diagnosed with HH.

Patients and Methods: GnRH iv infusion test (0–120 min) were performed in 17 patients (17.5 ± 2.3 years) with suspicion of HH for pubertal delay or primary amenorrhea associated with: Group1 (G1)- acquired or congenital pituitary pathology (n = 7) or G2- hypo/anosmia (n = 6) or G3-lack of spontaneous pubertal progression after a brief estrogenic therapy or lack of pubertal clinical and biochemical progression for one year (n = 4). LH, FSH at 0, 15, 30, 45, 60 and 120 min (IFMA) and basal Estradiol (ECLIA) were determined. Basal pubertal cutoffs were defined as FSH >1.5 IU/L and basal LH >0.3 IU/L.

Results: Basal FSH <1.5 IU/L and LH <0.3 IU/L were found in 88% and 82% of patients, respectively. All patients had basal E2 <15 pg/ml. FSH peak occurred in all the patients at 120 minutes (maximum 8 IU/L), whereas the occurrence of the LH surge was variable (maximum 8.9 IU/L). Areas under the curve of both gonadotropins were compared among 3 groups and they did not show any significant difference. Peaks LH were: G1: 3.4 ± 2.5 IU/L, G2: 1.8 ± 0.42 IU/L and G3: 5.2 ± 3 IU/L. FSH peaks were: G1: 3.9 ± 2.4 IU/L, G2: 3 ± 1 IU/L, and G3: 4.9 ± 2.9 IU/L.

Conclusion: The occurrence of simultaneous basal FSH <1.5 IU/L, basal LH <0.3 IU/L and E2 <15 pg/ml, or peak values LH <8.9 or FSH <8 IU/L after the infusion of GnRH support the diagnosis of HH in females suspected of this condition. Patients with hypo/anosmia showed the lower gonadotropin profile variability.

Congenital Adrenal Hyperplasia Incidence in Minas Gerais State – Brazil, after Newborn Screening Implementation

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Introduction: Congenital adrenal hyperplasia (CAH) is suitable for newborn screening, as it is a common and potentially fatal disease, which can be easily screened by a simple hormonal measurement. Moreover, early recognition and presymptomatic treatment can prevent severe salt wasting and inadequate sexual assignation, reducing morbidity and mortality. The incidence of the disease varies according to the region, but it is estimated worldwide, based on neonatal screening, in approximately 1:15,000 live births.

Objective: To evaluate the incidence of CAH in Minas Gerais State/Brazil, after the implementation of Newborn Screening Program on May, 2013.

Materials and Methods: Screening for CAH has been included in the Newborn Screening Program of the State of Minas Gerais, which already comprised tests for five other diseases (phenylketonuria, congenital hypothyroidism, hemoglobinopathies, cystic fibrosis and biotinidase deficiency). This program covers 100% of the municipalities of the State, one of the biggest in Brazil. Heel-puncture blood samples are collected on filter paper on day 3rd to 5th after birth. Dried blood samples were analyzed for 17-OH-progesterone (17-OHP) by immunofluorescent assay.

Abstracts
(AutoDELFA® neonatal 17OHP). Threshold values for healthy children were established for 4 birth weight ranges (≥2.500 g, ≥2.000 g to 2.499 g, ≥1.500 g to 1.999 g, <1.500 g) according to 99th percentile for 17-OHP concentrations of the population evaluated in a preliminary trial. The incidence of CAH was calculated using the total number of children screened in the period studied and the number of children diagnosed with the disease. Children with positive results on the screening are followed-up in the pediatric endocrinology service of the University Hospital. The diagnosis was confirmed by clinical and hormonal assessment, based on the elevation of serum concentration of 17OHP and androgens.

**Results:** A total of 482,319 children were screened between May, 2013 and May, 2015, on the 5.64th (2–30) day after birth. Twenty-nine children were diagnosed with the classic form of the disease: 19 female and 10 male. The incidence calculated was 1:16,632 live births.

**Conclusion:** The incidence of CAH found in the State of Minas Gerais/Brazil was very similar to that one related in most countries, and in other Brazilian States.

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**P10**

**Reference Values for Serum 17α-Hydroxyprogesterone Levels in Neonates and Infants**

Tarifa, C.1; Ochetti, M.1; Cabral, M.1; Aguirre, M.1; Sobrero, G.1; Cabrera, N.2; Collet, I.1; Silvano, L.1; Testa, G.1; Inchauspe, M.2; de Elias, R.2; Kiener, O.2; Andrade, M.2; Martin, S.1; Miras, M.1; Muñoz, L.1

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**Introduction:** The measurement of 17α-hydroxyprogesterone (17OHP) is used for the diagnosis and monitoring of Congenital Adrenal Hyperplasia (CAH). Our previous date support the convenience of employing extractive procedures in the determination of 17OHP during the neonatal period and the first year of life to avoid the interferences observed during this stage. Since the degree of interference may vary between available assays, reference values for 17OHP should be method specific. Our aim is to analyze serum levels of direct 17OHP (17OHPd) and with previous extraction for 17OHP should be method specific. Our aim is to analyze serum levels of direct 17OHP (17OHPd) and with previous extraction procedures and requires adequate specificity and accuracy in the determination of 17OHP. The references values here obtained by the current commercially available method ensures its usefulness in the diagnosis and control of the evolution of CAH patients.

<table>
<thead>
<tr>
<th>AGE (days)</th>
<th>17 OHPd (ng/ml)</th>
<th>17 OHPe (ng/ml)</th>
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</thead>
<tbody>
<tr>
<td>1–7</td>
<td>11.00</td>
<td>2.36</td>
</tr>
<tr>
<td>8–14</td>
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<td>3.04</td>
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<tr>
<td>15–28</td>
<td>17.19</td>
<td>4.07</td>
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<tr>
<td>29–60</td>
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<tr>
<td>181–240</td>
<td>4.41</td>
<td>0.61</td>
</tr>
<tr>
<td>241–365</td>
<td>4.03</td>
<td>0.49</td>
</tr>
</tbody>
</table>

**Table 1. Reference values for 17OHPd and 17OHPe. Percentil of the frequency distribution P 98% (for abstract P10)**

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**P11**

**Hyperandrogenism and Influence of Steroid Therapy on Nutritional Status and Body Composition in Patients with Congenital Adrenal Hyperplasia**

Espinosa Reyes, T.1; Valdés Gómez, W.2; Munguía Salazar, V.1; Marín Julia, S.1; Perez Gesen, C.1; Navaquete Cabrera, J.1; Carvajal Martínez, F.1

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**Introduction:** Suppression therapy with cortisone into the CAH is limited and generally there are high levels of androgens so there is the risk of changes in body composition and nutritional status secondary to hyperandrogenism present in most of the patient and steroid treatment Objectives: To characterize the nutritional status and body composition of patients with CAH. Determining the ratio of these elements with the degree of hyperandrogenism and steroid dose used.

**Material and Methods:** A cross-sectional study of patients diagnosed with CAH treated at paediatric endocrinology consultation was conducted INEN. Were performed anthropometric measurements weight, height, waist circumference, abdominal and hip ratio and body mass, and abdominal/height was calculated. Body composition was determined by bioelectrical impedance equipment and data related to the therapeutic regimen were collected, the age of initiation of treatment and clinical forms.

**Results:** 32 patients diagnosed with CAH was study, belonging to the social female sex, 87.5% was classical forms predominated (11 losers of salt and 9 simple virilizing) to 62.5% and the remaining 37.5% non-classical. The mean age was 12.53 years, and the age at diagnosis of 4.04 years. Normoandrogéncicos was 68.8% and the average steroid used was 20 mg/day. According to BMI 46.9% were overweight or obese, the rest normal weight; which it was associated with a family history of obesity through the maternal line (p 0.028). Considering the ratio abdominal circumference/height 46.9% showed an increased abdominal adiposity. There was a predominance of patients with increased fat mass in 43.8% (10 very high fat and 4 high) determined by bioelectrical imped-
P12
Effectiveness of GnRH Analogues in 157 Girls with Early Puberty
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2Universidad EL Bosque, Bogota, Colombia

Objectives: GnRH analogs (GnRHa) is a common treatment in children, but its use is only recommended in precocious puberty according to the consensus published in 2008 based on little evidence and diverse results in older age patients. However, in our clinical experience, patients with early maturation shows a beneficial gain in final size and age of menarche.

Design: Retrospective study of 157 girls with height <135 cm at puberty onset (M2) and maturation index >1.10 and predicted height (PH) <1 SDS mean parental height (MPH), treated with GnRHa on average 2.174 years and followed to final height.

Results: Mean age 9.741 years (8.750 to 11.205), final age 14.035 years (10.120 to 17.975), average baseline height 133.1 cm (117 to 145.7), initial bone age 10.7 years (8.8–12.6), PH 151.4 cm (138.5 to 161.8), final height 157.2 cm (146.5 to 170.9).

Conclusions: We found a clear benefit of using GnRHa in patients with early puberty when the onset of puberty is presented with height <135 cm and maturational acceleration exceeding growth dynamics In our patients final height is close to MPH and average age of menarche for our population. Therefore, we propose to use a selection criterion not based on chronological age but auxological parameters.

P14
Missed Cases of CAH: Value of Neonatal Screening
Felipe, D.; Vargas, A.; Gomez, R.
LSU Health Sciences Center, New Orleans, USA

Introduction: This brief report describes siblings with nonclassic virilization CAH missed by the newborn screen and a review of the literature on false negatives.

Materials and Methods: Patient 1 was referred to our clinic due to ambiguous genitalia. She was born at 39 weeks with no complications. Parents are nonconsanguineous. On exam, no clitoromegaly and a small but patent vaginal opening. Newborn screen done at 1 day 23 hrs old – 17-oh progesterone (17OHP) 1,650 ng/dl (normal: <5,000 ng/dl by fluorometric assay). Upon return to clinic at 10 months of age, she was noted to have an enlarged clitoris measuring ~2 cm, clitoris width 1 cm, small vaginal opening, and posterior fusion of labia. Laboratory evaluation included 17OHP 1,650 ng/dl (<1) by high performance liquid chromatography, total testosterone 6.3 ng/dl (<2.5–10), DHEAS 20 μg/dl (<49), plasma renin activity 1,559 ng/dl/h (235–3,700). Bone age was 1 year 6 months at chronologic age 10 months. Chromosomes 46,XX.

Methods for measuring the 17OHP may be affected during the neonatal period by structurally similar steroids produced in the fetal zone of the adrenal gland. This zone produces high concentrations of 17-hydroxypregnenolone sulphate carrying immunoreactive epitopes similar to the 17OHP molecule. Numerous authors agree that these interferences could be removed efficiently by an organic solvent extraction process before measuring the 17OHP. The reference intervals (RI) should be specific to the method because the degree of interference may vary between the different commercially available assays.

The aim of our study was to verify the specified RI for the ELISA method, and correlate this with values obtained after organic solvent extraction.

Materials and Methods: Twenty three newborns were studied (16 boys and 7 girls, 3–30 days of life) who attended the hospital between December 2014 and June 2015. Samples were analyzed using an enzyme immunoassay (DRG Diagnostics), non-extracted (NE) and extracted (E) by a modified method of extraction (Make- la et al.).

Results: A significant difference between NE and E results (mean and range E: 1.39; 0.4 to 3.70 ng/ml; NE: 9.22; 3.05 to 27.5 ng/ml) was observed with a p < 0.001. The RI of the NE method in boys and girls until the month of life is 0 to 16.8 ng/ml. The 91.3% of the values were within the RI proposed by the manufacturer.

Conclusions: According to the NCCLS C28-A2 Guidelines, a result is satisfactory for verification of RI when less than 10% of the results are outside the range proposed by the manufacturer. In our case, 8.7% was obtained, by which we can conclude that the manufacturer RI for non-extraction technique can be used in children of both sexes up to one month of life.

A range of 0.4–3.70 ng/ml was observed In the case of values with extraction in the same group of patients. These values fall within the proposed RIA values, hence these could be used until reference values for the specific method can be established.
Her sister was born at 40 weeks of age with no complications. She was noted at birth to have clitoromegaly. Laboratory revealed a sodium 140, potassium 5.1, DHEA >1500 ug/dl. Prepubertal uterus on ultrasound and her newborn screen was also normal.

**Results:** At diagnosis both siblings had elevated 17OHP levels consistent with CAH, 1650 ng/dl and 1320 ng/dl, respectively for patient 1 and patient 2. Both girls had signs of virilization needing clitoroplasty. They are both currently taking physiological doses of hydrocortisone.

**Conclusions:** The early detection of CAH prevents life threatening adrenal crisis and decreases the number of virilized female infants initially identified as males. During our study period of 8 years, we have identified 4 female patients that have been missed by our newborn screening program. A possible explanation is that the newborn screen identifies the severe form of the disease rather than the milder simple virilizing or nonclassic form. Female infants seem to be missed more frequently than males due to higher 17OHP levels at birth. In conclusion, we should consider gender based cutoffs for 17OHP levels at birth and if any clinical suspicion arises for CAH, use mass spectrometry to confirm.

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### P15

**Clinical, Biochemical and Ultrasonographic Characteristics at Diagnosis in Adolescents with Polycystic Ovaries Seen at National Institute of Child Health between May 2012 and April 2015**

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**Introduction:** Polycystic ovary syndrome (PCOS) is the commonest cause of hyperandrogenism of peripubertal beginning, has a prevalence of 5 to 10% in the general population, however the prevalence of this disorder in adolescence is unknown.

**Material and Methods:** **Objective:** Describe the clinical, biochemical and ultrasonographic characteristics at diagnosis in adolescents with polycystic ovaries seen at National Institute of Child Health between May 2012 and April 2015. **Methods:** Retrospective clinical study of 235 medical records of adolescents with initial diagnosis of PCOS, finally 62 records with ultrasonographic diagnosis of polycystic ovaries were selected.

**Results:** The prevalence of PCOS in adolescents with polycystic ovaries was 53.2%. In this group of 62 adolescents with polycystic ovaries, media age was 14.39 ± 1.6 years, weight, 56.67 ± 11.11 kg, height, 1.55 ± 0.06 m, BMI (Body mass index), 23.5 ± 4.28 Kg/m². In the group of 33 adolescents with PCOS media age was 14.89 ± 1.57 years, media age of menarche was 11.21 ± 1.21 years, weight was 58.63 ± 10.02 kg, height, 1.57 ± 0.25 m, BMI, 23.94 ± 4.04 Kg/m². 30.3% had overweight and 21.2% had obesity. Abdominal circumference was 90.80 ± 5.89 cm, 9.1% had antecedent of precoce or early puberty. 21.2% had secondary amenorrhea, 55.6% has oligomenorrhea, 54.5% had hirsutism, 63.6% acne and 27.3% acanthosis, 20% had fasting hyperinsulinism and 41.7% dyslipidemia. HOMA was 2.37 ± 1.25. Total cholesterol was 157.62 ± 17.86 mg/dl, HDL-C 44.69 ± 9.16 mg/dl, LDL-C 91.77 ± 18.23 mg/dl, triglicerides 99.38 ± 46.89 mg/dl. Free testosterone 9.12 ± 18.33 ng/dl, DHEAS 7.20 ± 8.16 umol/l, the ratio LH/FSH was 1.44 ± 0.73. Ovarian right volume was 10.24 ± 4.67 cc and left volume 9.03 ± 4.68 cc.

**Conclusions:** The prevalence of PCOS in adolescents with polycystic ovaries was 52.8%. 30.3% had overweight and 21.2% had obesity, 21.2% had secondary amenorrhea, 55.6% has oligomenorrhea, 54.5% had hirsutism, 63.6% acne and 27.3% acanthosis. 20% had fasting hyperinsulinism and 41.7% dyslipidemia.

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### P16

**Becker’s Nevus Syndrome: Case Report and Review of the Literature**

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**Case Report:** An 11 year-old female patient consults with left breast hypoplasia. Has prior medical history of umbilical hernia surgical correction. Physical exam revealed a pigmented congenital skin lesion of 4 x 3 cm with irregular borders and hypertricosis found in the left mandibular area. In the thorax pectus excavatum was present, with right breast Tanner III-IV development, and left breast Tanner II development plus marked hypoplasia. Biopsy of the lesion was performed and revealed an increase in the number of hair follicles and melanophages, enlarged papilar crests with pigmentation in basal epidermis without signs of malignancy. Biopsy was compatible with Becker’s nevus. Renal ultrasonography, renal function, chest and spine X-ray were normal. Chest ultrasonography ruled out absence of mammary glands. Hormone levels (testosterone, prolactin, estradioil, FSH, LH, TSH) were normal. Due to the combination of Becker’s nevus, unilateral breast hypoplasia, umbilical hernia, and pectus excavatum, the diagnosis of Becker’s Nevus Syndrome was established. The patient responded to spironolactone therapy, with outstanding improvement in left breast development.

**Review of Literature:** Becker’s nevus syndrome is part of the Epidermal nevus syndromes (ENSs), and is described with a phenotype that includes: Becker’s nevus, ipsilateral breast hypoplasia and variable skeletal malformations. It is more frequent in males (testosterone, prolactine, estradiol, FSH, LH, TSH) were normal. However, to the combination of Becker’s nevus, unilateral breast hypoplasia, umbilical hernia, and pectus excavatum, the diagnosis of Becker’s Nevus Syndrome was established. The patient responded to spironolactone therapy, with outstanding improvement in left breast development.

**Conclusion:** When dealing with a congenital breast defect, a subjacent chest wall abnormality must be ruled out, because it is an ectodermic defect and most of the cases require integral management and surgical correction with aesthetic results.
Growth and Final Height in Congenital Adrenal Hyperplasia
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Introduction: Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency in its classical (C) and nonclassical (NC) forms as well as its treatment, can compromise growth and determine lower final height than target height (TH).

Material and Methods: We describe and analyze longitudinal growth and final height in a group of patients with CAH followed at a University Hospital. Retrospective anthropometric data of 13 patients (5 males) with C-CAH were analyzed from birth and 9 patients (5 males) NC-CAH since puberty to final height. The median age (range) at diagnosis was 25 days (7–61) and 9.4 (7–14.6) years, respectively.

Results: C-CAH: At diagnosis, first, third, sixth year and at onset of puberty they presented the following DS height data (mean ± SE): –0.76 ± 0.36, –1.84 ± 0.28, –1.34 ± 0.25, –0.68 ± 0.22 and 0.01 ± 0.28 respectively, reaching a final height of –0.77 ± 0.12 DS, not different from TH (p = 0.068, n = 6, paired t test). Growth impairment was significant between the baseline and the 1st year (–1.11 ± 0.43 DS, p = 0.026, paired t test). On the other hand the height gain between 1st year to puberty was 2.05 ± 0.27 DS, p = 0.0003, coinciding with decreasing doses of hydrocortisone (33.93 ± 1.82 at diagnosis, 17.21 ± 0.91 at 1st year, 11.79 ± 1.05 at sixth years of age and 11.25 ± 1.2 mg/m² at the onset of puberty).

NC-CAH: 8 patients started puberty at 10.36 years (8.5–12.8), with an average height of 1.28 ± 0.26 DS reaching a final height of –0.45 ± 0.24 DS, significantly below TH, p = 0.017, paired t test.

Conclusions: C-CAH impairment of height during the first year is followed by a significant recovery until pubertal onset. The decreasing doses of steroids may play a role. While patients with NC-CAH did not reach the target genetic height, patients with C-CAH reached it. However, more patients should be studied to corroborate our findings.

Van Wyk – Grumbach Syndrome: Report of a Case
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1Universidad Católica de Chile, Santiago, Chile; 2Complejo Asistencial Dr. Sótero del Río, Santiago, Chile

Introduction: Van Wyk Syndrome – Grumbach was first described in 1960. It consists of a precocious puberty with delayed bone age caused by severe hypothyroidism. Cases described in the literature are usually girls between 7–10 years, but there are also reports in males. It is important to suspect this syndrome because initiating thyroid hormone replacement completely resolves symptoms and hormone abnormalities, avoiding unnecessary investigations for malignancies or surgical intervention.

Case Report: A 6 years 10 months old girl was brought to Endocrinology Unit of Sotero del Río Hospital with history of two months of breast tenderness, whitish discharge per vagina and 6 days of vaginal bleeding. The child also had emotional lability and progressive loss of initiative and interest. Examination revealed a height of 120 cm (p50), weight 25.4 kg with BWI 17.4 (p88). Skin and thyroid was normal, breast was Tanner 3 with areola pigmentation, pubic and axillary hair was absent. External genitalia were strogenized and vaginal bleeding was present. No virilization features were noted. Abdominal examination did not reveal any mass. X-ray assessment showed bone age of 5 years 9 months. Laboratory exams showed serum free T4 <0.4 ng/dl, TSH >100 uUI/ml, LH <0.07 uUI/ml, FSH 3.92 uUI/ml, estradiol 107 pg/ml. A pelvic ultrasound scan found a pubertal uterus in size and appearance, and large, cystic ovaries with one big dominant cyst. Patient was diagnosed to have primary hypothyroidism and precocious puberty. Treatment with thyroid hormone replacement was started, initially with 50 ug/day, then 100 ug/day, with normalization of hypothyroidism. During follow up, thyroglobulin antibodies and peroxidase antibodies levels were 49.8 IU/ml (<4.11) and 76.4 IU/ml (<5.6), respectively. After three months a new pelvic ultrasound was done showing uterus and ovaries still pubertal but smaller. Examination revealed breast Tanner 1 with non strogenized genitalia. Vaginal bleeding has not recurred.

Conclusion: The association of primary hypothyroidism with cystic ovarian enlargement and precocious puberty is important to recognize. Gonadal or central nervous system tumors are the main differential diagnosis. Treatment with thyroid hormone generates regression of precocious puberty.
bone quantity, but also to bone quality. For child's bone evaluation, providing information relative not only to bone quantity, but also to bone quality.

**Objective**: To assess bone status of children and adolescents using QUS measurements.

**Materials and Methods**: Cross-sectional study of healthy children and adolescents who were randomly recruited at a public school. Participants didn’t use any medication and signed an informed consent form to be included. The study was approved by the Research Ethics Committee of UFMG. Daily intake of calcium (requirement estimated by Institute of Medicine), sun exposure and physical activity habits were evaluated by specific questionnaires. Serum levels of 25-OH vitamin D (ICMA: deficiency <20 ng/ml; insufficiency between 20–29 ng/ml and sufficiency ≥30 ng/ml), and PTH (ICMA; RV: 15–68 pg/ml) were assessed. AD-SoS (amplitude-dependent speed of sound) and BTT (bone transmission time), parameters of phalangeal QUS (DBM Sonic, IGEA), were measured in all participants. A SD score <−2 for age indicated low bone mineral status. Variables were expressed as mean ± SD or median (minimum-maximum), as appropriate. Diet-pro and SPSS softwares were used for data analysis.

**Results**: Among the 45 participants (12.2 ± 4.1 years old), only 42% had adequate calcium intake [median = 885 (222–2452) mg/day]. Most of the group (86.7%) had sufficient sun exposure [median = 13 (1–42) hours/week] and 83.3% were sedentary, with an average time of 3.5 ± 2 hours/day spent in indoor activities. Out of the participants, 17.8% were deficient, 46.7% insufficient and only 35.6% were vitamin D sufficient [median = 26 (11–38) ng/ml], PTH concentrations [43 (22–61) pg/ml] were within reference values. All participants showed adequate sonographic parameters for age: AD-SoS Z-score = 0.88 ± 1.23 and BTT = 0.40 ± 0.96.

Conclusions: The participants showed no evidence of bone mass disease at QUS assessment but demonstrated high-risk behaviors for bone health that, if maintained, may adversely affect bone growth and peak bone mass acquisition.

**P21**

**Hereditary Vitamin D-Resistant Rickets with Heterozygous Mutation in VDR Gene**

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**Introduction**: Vitamin D resistance is a rare autosomal recessive disease caused by vitamin D receptor mutations, where the mutant VDR gene leads to decreased intestinal absorption of calcium and phosphate, and decreased bone mineralization and rickets; some patients are associated with alopecia universals.

**Material and Methods**: A 6.5-year-old female patient with knee deformity, alopecia universalis, loss of eyelashes and eyebrows since age 3, no pathological background or consanguineous parents; with normal psychomotor development.

Examination showed: weight. 20.5 kg (25–50), height 101 cm (−3.5 SDS) imperfect dentogenesis, alopecia universalis, metaphyseal widening of her wrist and ankles, bowing of her lower extremities, waddling gait. Initial biochemistry revealed hypocalcaemia (7 mg/dl) elevated alkaline phosphatase (693 UI/L) and PTHi 274.8 pg/ml, normal phosphorus, 25(OH) D2: 15 ng/ml (15–65), 1.25 (OH)D 409 ng/ml. X-ray: cupping and frayed of metaphysis, and widening of the epiphysis, with genu valgus.

The patient was initially treated with calcitriol 25 ng/kg/day), with dose increasing to 66 ng/kg/day, and calcium adding to 50 mg/kg/day. Clinical, laboratory and radiological findings showed patient’s improvement; currently without drug side effects. Where-as orthopaedic management corrected genu valgus with improved gait, alopecia universalis persists; she is undergoing medical management with paediatric endocrinology, orthopaedic, dermatological and genetic counselling.

Sequencing analysis of VDR gene exhibits a nucleotide change 239 G>A (p.R80Q); in another allele shown c. 909 C>T (A303A). The bioinformatic analysis with Poliphen2 and SIFT showed the mutations are predicted to be probably damaging. Clinical, biochemical and VDR gene analyses in her parents and siblings were normal.

**Conclusion**: Vitamin D resistance is an autosomal recessive disease of which many mutations have been described. We present a girl with compound heterozygosity exhibited by the classical clinical pattern; diagnosis was made, albeit late. Universal alopecia has been associated with increased severity of rickets. Our girl presents favourable evolution upon calcium replenishing and high doses of calcitriol. Optimal treatment will call for permanent existence of multidisciplinary group.
Low Vitamin D Levels in Children and Adolescents with Growth Hormone Deficiency

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Introduction: Appropriate levels of vitamin D are critical for bone growth. High prevalence of hypovitaminosis D has been reported worldwide, and it could affect children with growth hormone deficiency (GHD). Objective: To evaluate serum 25-hydroxyvitamin D (25OHD) levels in GHD patients treated with recombinant growth hormone.

Material and Methods: Cross-sectional study of 36 GHD children and adolescents (up to 20 years old), in appropriate hormone replacement therapy, and 45 healthy subjects, matched for age and gender. Serum levels of 25OHD (deficiency: < 20 ng/ml; insufficiency: 20–29 ng/ml; sufficiency: ≥30 ng/ml), total calcium (RV: 8.8–10.8 mg/dl), phosphorus (RV: 3.7–5.8 mg/dl), and PTH (RV: 15.0–68.3 pg/ml) were assessed. Sun exposure was evaluated by a questionnaire and was appropriated if more than 2 hours/week. Quantitative variables were expressed as mean ± SD or median (p75–p25). T Student, Mann Whitney, Pearson’s chi-square and Spearman correlation tests were used. Statistical significance was defined as a p value <0.05. The study was approved by the Research Ethics Committee of UFMG. When indicated, vitamin D was supplied for the subjects.

Results: Both groups were similar regarding age (p = 0.939), gender (p = 0.221), ethnicity (p = 0.696), ZBMI (p = 0.107), pubertal stage (p = 0.198), and socioeconomic status (p = 0.159). Patients with GHD (75% male) were 12.3 ± 4.3 years old, had ZBMI = −0.04 ± 1.5 and 25OHD = 23.0 (11) ng/ml; 8 GHD patients (22.2%) were deficient, 18 (50%) insufficient and 10 (27.8%) were vitamin D sufficient. Similar proportions (17.8%, 46.7% and 35.6%, respectively) were found among the control group (p = 0.768). Calcium (9.95 ± 0.4 mg/dl), phosphorus (5.31 ± 0.5 mg/dl), and PTH [51.3 (23.2) pg/ml] levels were within reference ranges and were similar between groups (p = 0.146, 0.369 and 0.425, respectively). Sun exposure was adequate and similar in both groups (median of 13 hours/week; p = 0.527). There was a positive correlation between sun exposure (hours/week) and serum 25OHD among all participants of the study (r = 0.279; p = 0.012).

Conclusions: We found high prevalence of hypovitaminosis D in both groups. Further studies are needed in patients with GHD for better understanding this relationship and its implications for treatment outcomes.

Camurati-Engelmann Disease: Evaluation of a New Therapeutic Option in Two Patients

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Introduction: Camurati-Engelmann Disease (CED) is a rare disorder (approximately 250 reported cases in literature) caused by heterozygous activating mutations of transforming growth factor-β1 (TGF-β1) gene. TGF-β1 plays an important role in bone, specially stimulating bone formation. The disease is characterized clinically by generalized pain (more intense in limbs), muscle weakness, difficult to walk, poor quality of life and, frequently, depression. Radiologically there are thickening of cortical diaphyses of long bones and of skull.

Description of the Patients: We describe two patients evaluated due to severe chronic pain interfering with their daily activities, muscle weakness, reduced height and weight gain and pubertal delay. The radiologic evaluation suggested CED, and the disease was confirmed through molecular study, that identified the heterozygous mutation [p.Arg218Cys] in exon 4 of TGF-β1 in both patients (this is the most common mutation in CED). Their treatment with different analgesics (including anti-depressants) was not successful. Before the diagnosis the girl received 2 cycles of pamidronate. Following suggestion in the literature we decided to treat them with losartan, a drug capable to inhibit TGF-β1 signaling. They have been treated with 0.25 mg/kg/day and have showed a significant improvement of the pain (evaluated according to the visual pain-scale). At the beginning of treatment the girl showed hypotension, relieved after the reduction of dose to 0.25 mg/kg/day.

Conclusion: In our 2 patients with CED the treatment with losartan has improved significantly the chronic pain and the quality of life. Although this treatment is not yet well established, our results suggest that losartan has a promising role in patients with CED.

Evaluation of Bone Mineral Accretion and Bone Markers in Pediatric Patients with Osteogenesis Imperfecta Treated with Pamidronate Disodium

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Introduction: Patients with osteogenesis imperfecta (OI) may show reduced bone mineral accretion due to increased bone resorption. The treatment with pamidronate disodium (PD) aims to...
reduce osteoclast activity and increase bone mineral densitometry (BMD).

Patients and Methods: We evaluated 9 patients (6 boys) with OI (4 with type III, 4 type IV, 1 type I) treated with PD from 4.68–7.92 years (mean±SD: 6.75 ± 1.38 years). Intravenous PD was administered in a 1 mg/kg single daily dose for 3 sequential days at 4-month intervals. For each patient BMD was evaluated twice through dual-energy X-ray absorptiometry (DEXA-scan): the first DEXA-scan was performed before or up to 0.72 years after the beginning of treatment (mean age: 6.69 ± 1.11 years), and the second was performed 0.94–2.8 years after the first one (interval between the two DEXA-scans: 1.86 ± 0.64 years). We also evaluated the values of serum alkaline phosphatase (AP) and the relation calcium/cr(eatinine in urine (CaU/CrU, isolated sample) obtained at the first day of each cycle. Values of lumbar spine (L1-L4) BMD Z-score in the first DEXA-scan (Z1) and in the second (Z2) were compared through paired Student’s t-test. The correlation between AP and CaU/CrU was evaluated through Pearson’s correlation coefficient. We also compared the mean values of AP and CaU/CrU in the first and last cycle. For all studies p-values <0.05 were significant.

Results: The values of Z1 and Z2 ranged respectively between −2.8 and −7.9 (mean±SD: −5.12 ± 1.59) and between −1.76 and −5.1 (mean±SD: −3.44 ± 1.21). The mean of Z2 was significantly higher than that of Z1 (p = 0.0002). In all patients the values of Z2 were higher than values of Z1 and the difference Z2-Z1 varied between 0.6–2.8 (mean±SD: 1.680 ± 0.75). Lumbar BMD Z-score increased between 14–53% (mean±SD: 32.67 ± 12.02). There was a positive correlation between AP and CaU/CrU (r = 0.38; p < 0.01). Plasma AP reduced significantly between the first cycle (mean: 248.56 ± 57.96) and the last (207.78 ± 12.02). There was a positive correlation between AP and CaU/CrU (r = 0.38; p < 0.01). Plasma AP reduced significantly between the first cycle (mean: 248.56 ± 57.96) and the last (207.78 ± 12.02). There was a positive correlation between AP and CaU/CrU (r = 0.38; p < 0.01). Plasma AP reduced significantly between the first cycle (mean: 248.56 ± 57.96) and the last (207.78 ± 12.02).

Conclusions: The significant improvement of BMD in patients with OI treated with PD shows that this treatment increased bone mineral accretion efficiently. PD affects both osteoblast and osteo-clast activity, and this effect is as higher as more cycles of PD are administered.

P25
Bone Impact of Spinal Muscular Atrophy Without Treatment. HR-pQCT Use as a Method of Evaluation and Monitoring. Clinical Case
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Introduction: Patient of 13 years and 11 months diagnosed with spinal muscular atrophy. Consultation of 11 years to perform a pre-placement of plates fixing back-lumbar spine bone evaluation. This work demonstrates the deterioration of bone mass due to the underlying disease, not made the indicated treatment.

Material and Methods: X-rays of dorsal-lumbar spine and knee show radioluency of the vertebral bodies and long cortical bones. Given the presence of metallic elements in column it makes impossible bone mineral densitometry peripheral Computed Tomography (pQCT-HR) requested radio bone to patient evaluation.

Results: During the development of patient laboratory, one can observe an increased urinary deoxyxypiridinoline 24 h. compared with the basal requested in the first query (Desoxipir U/24 h basal (2008):28.2; (2010):63.8. The pQCT allows us to evaluate in three dimensions bone mass in this patient. appreciates a frank decrease of the parameters evaluated with loss of trabecular number, thickness thereof and decreased cortical enter the two studies compared with 11 months between them. Baseline values were: densitometric parameters: bulk density Total or integral (D100) (mgHA/ccm): 117.3, cortical density (D Cort) (mgHA/ccm): 486.2 and trabecular density (D Job) (mgHA/ccm): 66.4; and structural parameters: BV/TV (bone volume to total volume) (%): 0055, Tb.N (trabecular number) (1/mm): 1.46, Tb.Th (trabecular thickness) (mm): 0.038, Tb.Sp (trabecular spacing) (mm): 0.646 values at 11 months without antiresorptive therapy are: (D100): 78.6, lime (D Cort) and 424.7 (Job D): 28.9, BV/TV:0.024, Tb.N:0.92, Tb.Th:0.026, Tb.Sp:1.057. The patient has two fragility fracture within the evaluation period.

Conclusions: It shows the natural evolution of spinal muscular atrophy without making the prescribed treatment. Frank deterioration of bone mineral density loss of trabecular number, the thickness thereof, the increase of the disc space and decreased cortical observed. What determined new fragility fractures resulting in physical and psychological deterioration of the patient. HR-pQCT is an excellent method for assessing bone mass.
toms after two months of treatment. At diagnosis of metabolic disease, she had advanced bone age (three years), with significant reduced predicted final height. She was treated with GnRH agonist for two years. Orthopedic procedure, osteosintesis, was performed when she was 10.8 y. Her menarche took place at the age of 12 y and her current height (13.6 y) being of 149 cm (Z = –1.45) and Z score of the target height of 0.45.

Conclusion: We stress out the importance of early clinical and laboratory diagnosis of hypophosphatemic rickets associated with epidermal nevus syndrome and we also report the height evolution in a patient treated by a four-year period.

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**P27**

**Parathyroid Adenoma and Hungry Bone Syndrome in an Adolescent. Report of One Case with Overview**

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**Introduction:** The incidence of primary hyperparathyroidism (HPT 1°) in the pediatric population is still unknown. He has been reported an incidence of 1 in 200,000 to 300,000 children. The main causes are hyperplasia, adenomas and carcinomas. In adults the adenomas are the most common cause (75–85%), being the most frequent single adenoma located in the PT upper gland and less than 1% of cases corresponds to carcinoma. Ectopic glands can be seen in the 4–16%.

The patient has a good tolerance to the medication (shows only slight feverishness after the first infusion) and excellent improvement in bone mineral density in the first year of treatment (shows only slight feverishness after the first infusion) and excellent improvement in bone mineral density in the first year of treatment (48%) is observed, treatment continues until normal bone mass (Z score: –1.7). Traumatology you stop using the corset and normalizes the levels of deoxypyridinoline in 24 hours.

**Conclusion:** Use of zoledronic acid in the treatment of osteogenesis imperfect.
Hormonal Clinical Features and Response to Treatment of Patients with Precocious Puberty

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Introduction: Central precocious puberty (CPP) is a rare disease with female predominance, of idiopathic aetiology in most cases, in the past few years the first mutations in patients with CPP have been described. The prevalence of organic disease is notably lower among girls with CPP.

Objectives: To characterize the clinical and hormonally children with precocious puberty. Identify aetiology and describe the response to therapy.

Material and Methods: A longitudinal study that included all patients diagnosed with PP treated at a consultation of Endocrinology for the past decade was made. Clinical data were collected, hormonal therapy and some elements related developments.

Results: 30 patients with diagnosis of PP, 26 belonging to females (76.5%), the average age was 10.8 years and the average age at diagnosis was 6.06 years. The reasons most often motivated the consultation were increasing breast volume to 46.7% and the presence of sexual hair to 23.3%. At diagnosis showed a high stature growth rate was 5.8 cm and managed to stop pubertal development.

Conclusions: Puberty is a complex biological phenomenon and the causes for their advancement are not fully elucidated. The response to treatment in general is favourable and is related to the age of initiation of treatment.

P79

Prolactinomas: Three Pediatric Cases and Review of the Literature


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Prolactinomas accounts for 50% of pituitary tumors and 2% of all intracranial neoplasms in the pediatric age, the symptoms related to the disease differ from the symptoms of adult patients.

We present three patients with different features at the diagnosis.

Case 1: A 16 years old female, with primary amenorrhea, no neurological findings, no Tanner progression (stage III) and hypogonadotropic hypogonadism. Her prolactin value was 627 ng/ml. MRI shows a sellar lesion of 13.6x18.4x22.4 mm, with extension to the left cavernous sinus, compatible with pituitary adenoma. She received cabergoline and had a good clinical response, with later prolactin value of 1.4 ng/ml and a reduction in tumor size on control MRI.

Case 2: A 13 years old female, with progressive headache, impaired peripheral vision, Tanner breast Stage II, and pubic hair III. MRI reported a solid suprasellar, esphenoidal mass of 43 x 33 x 51 mm, with compression of optical chiasma. Prolactin values were 2000 ng/ml, and presented central hypothyroidism, hypocortisolism and hypogonadism.

She was treated with hidrocortisone, levothyroxine and cabergoline showing a decrease in prolactin levels to 329 ng/ml and achieving normal thyroid and adrenal function.

Case 3: A 17 years old male who presents bilateral galactorrhea and mild headache. Prolactine values were 204.4 ng/ml. MRI shows a sellar lesion of 11x11x7.4 mm compatible with pituitary adenoma, treated with cabergoline with decrease in the size of the lesion and prolactin levels.

Review: Macroadenomas are tumors larger than 1 centimeter and are considered the most common pituitary tumors. Prolactinomas represent 50% of pituitary tumors in children.

The clinical presentation includes pubertal arrestment, neurological abnormalities and panhypopituitarism secondary to mass effect. The concentrations of prolactin are related to the tumor size.

The treatment options includes pharmacological therapy, the first choice are the dopaminergic agonists with good clinical and paraclinical response.

The molecular tests are advisable to exclude MEN 1 and Familial isolated pituitary adenoma.

Conclusions: We present three cases of prolactinoma, with different symptoms at the diagnosis and values of prolactin in relation to tumor size, these patients showed a good response to pharmacological treatment with no indication of surgical resection until now.
O-3.1 Oral Session 3.1

O21
Self-Care and Optimal Glycaemic Control in Young Adolescents with Type 1-Diabetes: Role of a Coherent Support between Both Parents at Least for the Management of Diabetes and If Possible Also for Its Psychosocial Life

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Parental support plays an essential role in the development of adolescent’s self-care (SC). The challenge to develop autonomy in decision-making, and the need to integrate the identity of being a person with diabetes with other dimensions of one’s identity, can explain the difficulty of the adolescents to obtain an optimal diabetes control. Different parenting practices contribute differently to the development of adolescent SC, but the literature tends to focus exclusively on its medical dimension. Moreover, little is known about the impact of consistent parenting practices on SC in adolescents with diabetes (T1D).

Our study aimed to explore the association of adolescents’ HbA1c with consistency of parenting practices in supporting their adolescents’ management (i) of diabetes alone, (ii) of psychosocial life issues alone and (iii) of both issues. Moreover, we looked at the type of consistent parenting practices most frequently associated with optimal HbA1c.

During French AJD summer camps, we interviewed 31 adolescents with T1D, aged 13 to 15, and used mixed-methods design in order to code the different reported parental support practices, and to identify association between consistency in parenting practices and HbA1c by applying different statistical tests according to HbA1c level was used as continuous or categorical variable.

Our results show that HbA1c ≤7.5% was significantly associated with consistent reported parental support in the medical dimension of SC (Fischer Exact test p = 0.004), as well as across the medical and psychosocial dimensions of SC (Fischer Exact test p = 0.011). Moreover, optimal median HbA1c level (7.43%) was significantly associated with reported parenting consistency in both dimensions of SC (Kruskal-Wallis test p = 0.018). Concerning the type of support, only adolescents with HbA1c ≤7.5% reported a consistency in the Non-Directive Guidance type between the parents and across both dimensions of SC.

Our study supports the hypothesis that consistent parental support of SC is associated with better glycaemic control in young adolescents. We recommend that diabetes care include more systematically a dimension of family work in order to strengthen the parents’ capacity to effectively and adequately support their adolescents’ emerging SC capacity in its both dimensions.

O22
MODY 2, Report of New GCK Variants. Do They Have a Pathogenic Role?

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Introduction: The Maturity-onset diabetes of the young (MODY) is a monogenic disorder characterized by autosomal dominantly inherited non-insulin dependent form of diabetes. It begins in early adulthood and often in adolescence or childhood. MODY is a rare cause of Diabetes often confused with Type 1 or Type 2 Diabetes. The condition is due to a primary defect of pancreatic beta cells caused by mutations in one of the many genes involved in insulin secretion. The GCK-MODY (MODY 2) is one of the most frequent form of MODY. It is caused by heterozygous inactivating mutations in the Glucokinase (GCK) gene.

Objective: To report new GCK gene variants detected in children with incidental hyperglycemia and family history of first degree relatives with Diabetes type 2, Gestational diabetes or Glucose intolerance.

Material and Methods: 4 children, age 3 to 10 years, a GCK gene mutation analysis was requested due to incidental hyperglycemia and negative pancreatic islet autoantibodies. A direct sequencing was performed in the GCK gene, from exon 1a to 10. The Poliphpen-2 program, an automatic tool for prediction of possible impact of an amino acid substitution on the structure and function of a human protein, was applied to these variants.

Results: All patients were eutrophic and did not show signs of obesity or insulin resistance. Most of the relatives were treated with metformin. The following GCK new variants were detected, p.Phe260Ile in one patient, p.Glu237del in two non-related patients, and Gly44Arg in one patient. The program polyphen-2 suggests that these new GCK variants are probably involved in the pathogenesis of diabetes.

Conclusion: GCK enzyme regulates insulin secretion acting as glucose sensor of pancreatic β-cell. Heterozygote-inactivating mutations will cause mild subclinical hyperglycemia. In our patients new GCK gene variants were detected. These GCK gene variants could have some pathogenic role in the development of hyperglycemia in our patients and their parents. It has to be confirmed. Any children with incidental hyperglycemia and family history of any type of Diabetes or Glucose intolerance deserves to ruled out GCK-MODY in order to establish a correct diagnosis and management.
**O23**

**Report of a New GCK Gene Sequence Variant in 2 Children**

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**Introduction:** MODY (Maturity-onset diabetes of the young) are a heterogeneous group of diseases characterized by nonketotic diabetes mellitus, autosomal dominant inheritance and early onset. It begin in early adulthood, adolescence or childhood. It is a rare cause of diabetes. The condition is due to a primary defect of pancreatic β-cells caused by mutations in one of the many genes involved in insulin secretion. To date, 11 types of MODY have been described. GCK-MODY (MODY 2) is caused by a genetic defect in glucokinase (GCK). This enzyme, act as a glucose sensor in the β-cells. Heterozygote-inactivating mutations of the GCK gene cause mild subclinical non-progressive hyperglycemia. Objective: To report a new variant of the GCK gene in two non-related children, in whom the investigation was conducted due to incidental hyperglycemia.

**Method:** Molecular genetic analysis by direct sequencing of exons 1a to 10 of the GCK gene.

**Results:** The sequence variant detected in one of the alleles in these patients was the pGlut237del. This defect has not been reported before. The same defect was found in their parents. The father of one of the patients was diagnosed as Type 2 Diabetes and the mother of the other one had Gestational Diabetes. The PoliPhen-2 program predicts that this new variant in our patients is probably pathogenic.

**Conclusions:** GCK-MODY is an infrequent monogenic Diabetes that can be manifested by asymptomatic hyperglycemia since childhood. This sequence variant of the GCK gene is required to be present in a closer relatives with hyperglycemia or diabetes, since it is not enough to be present in the index case to have a pathogenic role. The presence of this new variant in our patients and their parents suggest its deleterous rol and its autosomal dominant inheritance.

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**O24**

**Metreleptin Use in Children with Congenital Generalized Lipodystrophy**

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Congenital generalized lipodystrophy (CGL), also known as Berardinelli-Seip syndrome, is an autosomal recessive disorder characterized by near total loss of fat. Affected individuals have hypertriglyceridemia, insulin resistance, and hepatomegaly due to hepatic steatosis. Other features include acanthosis nigricans, muscular appearance, umbilical hernia, and, in women, clitoromegaly, hirsutism, and PCOS. We describe the youngest subjects treated with metreleptin reported in the literature.

Patient 1 was evaluated for a sacral dimple and was noted to have a muscular appearance. Mother informed us she had an increased appetite and ‘this had always been her appearance’. At 2 years 2 months, height was at the 25–50th percentile, weight at 10–25th percentile, testosterone total <20 ng/dl, glucose 79 mg/dl, insulin level 1.7 (2.6–24.9 mcU/mL), c-peptide 0.8 (1.1–5.0 mg/ml), hemoglobin A1C 5.3 (4.0–6.0%), cholesterol 142 (0–169 mg/dl), HDL 38 mg/dl, LDL Cholesterol 89 mg/dl, triglycerides 75 mg/dl, ALT 27 U/L, AST 46 U/L. Metreleptin was initiated at a dose of 0.08 mg/kg/day and since, her appetite has decreased and she has lost 1 kg in a month.

Patient 2 is her sister product of a twin pregnancy (twin sister unaffected) born at 35 weeks, birth weight 1789 grams. At 11 months of age, during evaluation at the NIH, testosterone total was <20.0 ng/dl, insulin level 47.4 mcU/mL, c-peptide 6.7 ng/ml, glucose 84 mg/dl, hemoglobin A1C 5.4%, cholesterol 214 mg/dl, HDL 23 mg/dl, triglycerides 422 mg/dl, Alkaline Phosphatase. 281 U/L, ALT 35 U/L, AST 36 U/L. At 13 months of age, metreleptin was initiated at a dose of 0.07 mg/k/day. No adverse events have been noted for either patient.

Myalept (metreleptin) has been approved by the FDA for the treatment of congenital or acquired generalized lipodystrophy. Within 4 months of treatment, the requirement or need for lipid lowering agents and insulin decreases in patients with diabetes and dyslipidemia. There are some reported cases of metreleptin-associated lymphoma especially in acquired generalized lipodystrophy and others with neutralizing antibodies. The risks likely outweigh the benefits and the hope is that early intervention with metreleptin will prevent complications such as diabetes mellitus, hypertension, fatty liver and pancreatitis in these children.

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**O25**

**Challenged Diagnosis on Hypoglycemia: Hirata Disease X Factitious Hypoglycemia**


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**Introduction:** The Insulin Autoimmune Syndrome (IAS or Hirata Disease) is rare among children. Non-ketotic hyperinsulinemic hypoglycemia and the presence of insulin auto-antibody (IAA) are the conditions to diagnose the syndrome. The occurrence of hypoglycemia is due to the binding of the antibody to the insulin molecule at the immediate postprandial, followed by this binominal dissociation, which releases free insulin on serum and triggers symptomatic hypoglycemia.

**Case Report:** A 6-year-old boy was followed by symptomatic hypoglycemia. Seizures since 7 months old were treated and controlled with anticonvulsants until the age of five, when raised hypoglycemia symptoms. Several hospitalizations, some highlighted exams: random glycemia 21 mg/dl (1.16 mmol/l), insulin 34.7 μU/mL, other critical sample exams were negative, abdominal MRI was normal. No improvement after taken diazoxide, somatostatin,
hydrochlorothiazide and glucagon. As he did not improve, and there was still a suspect of exogenous insulin, new exams and a new hospitalization occurred: glycemia 26 mg/dl (1.44 mmol/l), insulin 686.7 μU/ml. Even though his mother was kept away from him, the insulin level increased to >1000 μU/ml, c-peptide was 5.1 ng/ml (1.1–4.4), sulphonylurea dosage was negative, and two extended OGTT were performed, ranging insulin 407–1000 μU/ml, C-peptide 1.5–5.2 ng/ml and glycemia 21–112 mg/dl (1.16–6.2 mmol/l). Insulin antibody was found, associated to the insulin molecule, which resumes the syndrome. As soon as dietary and physical activities recommendations were followed, there had been less hypoglycemic episodes.

**Conclusion:** To exclude factitious hypoglycemia, four hospitalizations and judicial separation of mother and child were necessary to prove the mother was not giving inadvertently insulin to his child. Only when IAA was performed, which set the presence of autoantibodies bound to native human insulin, the diagnosis was elucidated. As IAS is usually related to previous exposure to drugs, this case is considered a novel insight into clinical practice.

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**O-3.2 Oral Session 3.2**

**O26**

**Higher Expression of the Oncogene YAP1, a WNT/ß-Catenin Target, Is Associated with Poor Outcome in Pediatric Patients with Adrenocortical Tumors**


**Background:** Overexpression of the oncogene Yes-Associated-Protein-1 (YAP1), a Hippo pathway target, associates with increased cell proliferation in some human cancers. There is not data on adrenocortical tumors (ACT). YAP1 is a potential target of Wnt/beta-catenin pathway, which plays an important role in ACTs.

**Objectives:** To evaluate the role of YAP1 and its interaction with the Wnt/beta-catenin pathway in ACT.

**Patients and Methods:** association between YAP1 mRNA and protein expression and clinical, biochemical, pathological and patient’s outcome data was evaluated in 42 pediatric patients with ACT (81% females; median age: 31 months [5–185]). The expression data was compared to 21 normal pediatric adrenal cortices and 32 normal fetal adrenal cortices. In addition, in vitro experiments blocking the TCF/beta-catenin complex with PNU-74654 showed YAP1 protein expression by 44%, 58% and 81% after 48 h with 50, 100 and 200 μM PNU-74654, respectively.

**Conclusion:** Higher expression of the oncogene YAP1 appears to be a marker of poor prognosis and lower survival rates in pediatric patients with ACT. These original data highlight YAP1 as a potential target to treat patients with invasive or recurrent adrenal tumors.

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**O27**

**VHL-P138R and VHL-L163R Novel Variants: Mechanisms of VHL Pathogenicity Involving Only HIF-Dependent Functions?**

Mathó, C.; Liu, X.; Vieites, A.; Barontini, M.; Sansó, G.; Jonasch, E.; Pennisi, P.

Introduction: von Hippel Lindau disease is an autosomal dominant cancer syndrome caused by mutations in the VHL tumor suppressor gene. VHL protein (pVHL) forms a complex (VBC) with elongins B-C, Culin2 and Rbx1. The most described function of pVHL is to recognize and target hypoxia inducible factor (HIF) degradation. We found new VHL variants in VHL families that need to be functionally characterized to determine their pathogenicity.

**Aim:** Perform the in vitro functional characterization of L163R and P138R variants of pVHL. Materials and methods: VHL variants were generated using the VHL-wt-Venus plasmid as a template to create 786-0 stable cell lines expressing Venus, VHL-wt-Venus, VHL-P138R-Venus and VHL-L163R-Venus. Western blots were performed to evaluate pVHL and HIF-2α levels. VHL, EPAS1 and VEGFA expression was quantified by qPCR. VHL protein half-life was determined by cycloheximide treatment. VBC complex formation was evaluated by immunoprecipitation (IP) using GFP-Trap beads followed by western blot.

**Results:** Stable cell lines showed similar mRNA VHL expression of variant and wild type VHL. However there was a marked
difference in half-life of wt pVHL and P138R and L163R variants as early as 1 h after treatment with cycloheximide indicating these are less stable than wt pVHL. HIF-2α levels decreased when wt pVHL was reintroduced, and intermediate levels were observed in the presence of the variants. To assess HIF-2α activity we performed qPCR of EPAS1 and VEGFA (a downstream target of HIF-2α) in 20% oxygen and observed no differences in their expression in wt pVHL and VHL variants. VBC complex formation assessed by IP revealed complex formation was decreased for P138R and L163R variants compared to wt pVHL.

**Conclusions:** Striking differences were observed in P138R and L163R half-lives. We also observed decreased VBC complex formation with P138R and L163R, although HIF-2α target gene expression was not different between wt pVHL and VHL variants under normoxic conditions. Taken together, our results suggest that P138R and L163R pathogenic mechanisms may involve HIF dependent mechanisms, but the reduced half life of VHL mutant proteins could impact HIF independent VHL functions as well.

**O28**

**VHL Type I and II: Clinical Presentation and Follow-Up According to Age**

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**Introduction:** von Hippel Lindau disease (VHL) is an inherited syndrome caused by mutations of the vhl gene. It predisposes to the development of retinal and CNS hemangiomas, renal or pancreatic cysts/tumors, endolymphatic sac tumors and pheochromocytomas (pheo). 

**Aim:** To characterize the clinical presentation of patients with the VHL disease according to age.

**Patients and Methods:** We evaluated 190 individuals belonging to 33 families by genetic screening of vhl gene. We described the clinical presentation and the outcome of 67 patients. They were divided into 2 groups according to age: group 1, <21 y (n = 36/5/36VHL1 and 31VHL2) and group 2, aged ≥21 y (n = 31/36VHL1, 23/31VHL2). Genomic DNA was extracted from peripheral blood leukocytes. Complete genetic analysis of vhl gene was performed using PCR and automatic sequencing for the study of gross deletions.

**Results:** The initial manifestation of VHL in group 1 was pheo in 28/36 patients (78%). During follow-up 17/28 pheo patients remained free of disease (median: 4 y, 0–30 y) but the time of follow up was shorter than the group 1. Three patients died due to VHL in this group. During follow up the remaining 11 patients presented hemangioblastoma of CNS (4), renal carcinoma (3), retinal hemangioma (2), neuroendocrine tumor of the pancreas (1) and pheo (1).

**Conclusions:** Our results confirmed that pheo is the predominant initial event in VHL in the pediatric group while in the other group CNS hemangioblastoma and pheo appeared in similar frequency.

Comorbid pathology can appear after a long disease-free period, lifelong surveillance is mandatory in both groups.

**O29**

**Metastatic Paraganglioma: A New Mutation in SDHB**


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**Objective:** Report of a metastatic paraganglioma with a mutation not described in SDHB.

**Design:** Case report.

**Introduction:** Paragangliomas are neuroendocrine tumors derived from the embryonic neural crest. The majority of paragangliomas are sporadic. However, about 40% of these develop from germlinal mutations in genes susceptible to the tumor, SDG2 genes (10.3%), SDHD (8.9%), VHL (7.3%), RET (6.3%) and NF1 (13.3%). In pediatric population the SDHB mutation is a risk factor for malignancy and metastasis, with an overall incidence of 17% and a 13% prevalence.

**Case Report:** Masculine, 9 years old, preterm with perinatal asphyxia. Seeks Medical attention for headache and palpitations. Physical examination reveals tachycardia and hypertensive crisis, treated with prazosin and enalapril. Brain CT: Without alteration. Abdominal CT angiography reports: Renal Ectopia and a retroperitoneal mass (6 x 5.5 x 6.4 cm) which invades the pelvic cavity, and neoplastic appearance.

Surgical removal was performed by the oncology surgical team on 17.06.14.

Due to the persistence of symptoms (headache and occasional palpitations) a PET/CT 68 GAD-DOTA-TOC 2.4 mCi was made: Hipermetabolic areas were not observed. Plasma Metanephrines and metaiodobenzyl were reported positive. In November 2014 he was hospitalized for persistent headache with a BP above the 99 percentile. Simple and contrasted abdominal CT was performed revealing a left paravertebral mass. According to clinical and labora-
tory data, a new surgery was performed on 19.01.15 with resection of the left paravertebral tumor and adrenalectomy. Histopathological report: Paraganglioma with periaortic, paraaortic, and intercavo aortic ganglia with histosinusul hyperplasia. No neoplastic cells found.

**Conclusions:** SDHB mutation in pediatric population has a metastasis risk of 50–97%, mainly to lymph nodes, bone, liver and lungs. The molecular study reported in this case is heterozygotic Deletion of 4 nucleotides in the area (c. 200 + 3_200 + 6del-GACT) Sitemap giver of the splicing of intron 2 gene SDHB, a new mutation not described in the literature, with high risk of metastasis.

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**O30**

**Follow-Up of Reproductive Health and Ovarian Reserve (OR) in Young Women after Childhood Acute Lymphoblastic Leukemia (ALL)**


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**Introduction:** Advances in treatment of cancer have improved survival of patients with LLA. There is some concern about the long term effects on reproductive health and fertility. Anti müllerian hormone (AMH), a marker of OR might help to predict ovarian impairment in these patients.

**Objectives:** To evaluate the reproductive function and AMH levels of ALL survivors after cancer treatment in a previously cohort evaluated at our institution.

**Patients and Methods:** We initially evaluated 33 patients treated for ALL according to local protocols in childhood (diagnosed at 5.3 ± 3.6 years), and followed 18 of these patients several years later. They were studied with a menstrual and pregnancy history, and we obtained a blood sample for hormonal profile in the follicular phase (AMH, gonadotropins and estradiol). In women on oral contraception (OCP) only AMH was studied.

**Results:** Age at initial and subsequent evaluation was 20.6 ± 3.6 and 23.8 ± 3.7 years respectively. The period elapsed from the first to the second evaluation was 3.2 ± 0.8 years. The age at menarche was 12.8 ± 1.6 years, 11.1% of them with late menarche (after 15 years of age). According to the standard definition, 33.3% had oligomenorrhea and 27.7% had amenorrhea during the last year prior to evaluation. 77.7% are sexualy active and 13 are on OCP. Six patients have tried to become pregnant, but only 33.3% have been successful, whereas one (16%) required fertility assistance. Serum AMH levels decreased from the initial to the second evaluation (5.2 ± 2.7 vs 3.9 ± 2.4 ng/ml respectively, p = 0.015 (Wilcoxon). No differences in gonadotrophins were observed (p = 0.53). AMH levels correlated with the current age (r = –0.7, p = 0.005 Spearman).

**Conclusions:** AMH levels decreased during follow up in our cohort of ALL patients, which may indicate evolving gonadal failure. A longer follow up may help to understand if this finding is related to ALL treatment or advancing age.

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**O41 Oral Session 4.1**

**O31**

**Molecular Study of Rasopathies in Patients with Isolated Cryptorchidism**


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**Introduction:** Cryptorchidism is a frequent finding in patients with molecular confirmed RA Sopathies. Furthermore, analysis of the recently developed Cryptorchidism-Gene-Atlas discloses a strong association between cryptorchidism and the Ras/MAPK pathway genes. Our aim was to determine whether monosymtomatic patients, who present with a clinical picture characterized by cryptorchidism, exhibit molecular alterations in the genes of the Ras/MAPK pathway.

**Methods:** Seventy seven patients with cryptorchidism were recruited and classified into three study groups, according to their height and presence of a phenotype suggestive of RA Sopathy. Genomic DNA was extracted for molecular analysis of PTEN11, SOS1, KRAS, NRAS, HRAS, RAF1, BRAF, MAP2K1 and MAP2K2 genes. The molecular analysis was performed by screening the exons most frequently mutated according to the literature. The screening was achieved through High Resolution Melting (HRM).

**Results:** Fifty nine patients were classified as isolated cryptorchidism (G1) [Age (years): 5.9 ± 0.4; height (SDS): 0.28 ± 0.15], 8 as cryptorchidism, short stature and normal phenotype (G2) [Age (years): 5.7 ± 1.6; height (SDS): –1.69 ± 0.21] and 10 as cryptorchidism and phenotype suggestive of RA Sopathy (G3) [Age (years): 6 ± 1.0; height (SDS): –2.16 ± 0.21]. Molecular analysis of G1 showed one missense substitution (SOS1_p.P655L), two synonymous substitution (SOS1_p.Q410Q, SOS1_p.P651P and BRAF_p.Q456Q), and a HRAS intrinsic deletion. Group 2 analyses showed one synonymous substitution (SOS1_p.Q410Q) and an unreported intronic SNP in SOS1. Finally, G3 analysis showed two pathogenic mutations PTEN11_p.F285L and SOS1_p.R552G and three intronic SNPs with unknown consequence in KRAS, MAP2K1 and MAP2K2. The missense substitution (SOS1_p.P655L) had been previously reported as not associated with RA Sopathies. Analysis of the synonymous substitution SOS1_c.1953A>G and

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**Abstracts**

Horn Res Paediatri 2015;84(suppl 2):1–77 33
Whole Exome Sequencing Identifies Genetic Causes of Disproportional Short Stature

Vasques, G. 1; Funari, M. 1; Learrio, A. 1; Freire, B. 1; Shinjo, S. 2; Marie, S. 2; Arnhold, I. 1; Jorge, A. 1
1Disciplina de Endocrinologia da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brasil; 2Departamento de Neurologia Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brasil

Introduction: Disproportional short stature is the most frequent clinical presentation of skeletal dysplasias. Skeletal dysplasias are a heterogeneous group of more than 450 disorders. Skeletal survey is a very important tool to establish the diagnosis and to guide the genetic test, but has several limitations, especially in mild and atypical cases.

Objective: To investigate the genetic causes of disproportionate short stature by exome sequencing.

Subjects and Methods: We selected six patients with disproportionate short stature without a definitive classification into a skeletal dysplasia category. Whole exome sequencing of six affected individuals and their affected (n = 6) and unaffected (n = 5) available relatives was performed using Agilent SureSelect kits for library preparation and exome capture. The samples were sequenced in Illumina HiSeq sequencer.

Results: We obtained an average on target coverage of 170x (99.6% target region with ≥10x coverage). Each patient has an average of 65,490 allelic variants. All cases had an autosomal dominant pattern of inheritance. By focusing on variants of interest (i.e. heterozygous stop codon gains, frameshift, non-synonymous or splice-site variants absent in controls) that segregated with disproportional short stature phenotype in the families, we identified a causative defect in 3 patients. All mutations were predicted as pathogenic by multiple lines of evidence. Case 1 with height SD score of –2.0, has a novel heterozygous mutation in *NPR2* gene (c.2905G>C/p. V969L). Heterozygous mutations in *NPR2* are a cause of short stature without a distinct phenotype. Case 2 (height SDS of –4.5) has a heterozygous mutation in *BRAF* (c.1368.G>A/p. V969L). Heterozygous mutations in *BRAF* cause several skeletal disorders with highly variable phenotype.

Conclusions: We report the first study of molecular RASopathies in a cohort of patients with isolated cryptorchidism. We found pathogenic mutations in the group of patients with cryptorchidism associated with a suggestive phenotype. This suggests that a careful clinical exam looking for subtle dysmorphic features of RASopathy should be performed in patients with cryptorchidism.

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Identification of a Novel Mutation in STAT3 Gene by Exome Sequencing in a Patient with Neonatal Diabetes and Early Onset-Autoimmune Disease

Velayos, T.1; Martínez, R.1; Aguayo, A.1; García-Etxebarria, K.1; Alonso, M.1; Barrio, R.2; Castaño Gonzalez, L.1

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Abstract: Neonatal diabetes mellitus (NDM) is a rare monogenic form of diabetes characterized by the onset of hyperglycemia within the first six months of life. NDM is genetically heterogeneous, with at least 20 different causal genes identified to date. The most frequent causes involve mutations in KCNJ11, ABCC8 and insulin genes and isolated diabetes. However, NDM sometimes appears in association with other pathological conditions and genetic causes, including genes related with early onset-autoimmune diseases, as FOXP3 and the recently described STAT3. Despite the advances in understanding the molecular pathogenesis of NDM, 20% of patients remain undiagnosed.

Aims: The aim of the study is to use Whole Exome Sequencing (WES) to characterize patients with NDM to whom mutations in KCNJ11, ABCC8 and INS genes had been previously excluded.

Methods: We have carried out an exome enrichment in 8 trios (index case and parents) followed by high-throughput sequencing using the Nextera Expanded Exome Sequencing kit and the Whole-Exome sequencing Pipeline web tool (WEP) for data analysis. The mutation found in STAT3 gene (NM_139276.2) was confirmed by Sanger sequencing.

Results: WES identified a novel de novo mutation in STAT3 gene (c.988C>T; p.Pro330Ser) in one of the patients. This mutation was confirmed by Sanger sequencing in the index case. The altered residue is highly conserved and due to prediction softwares (SIFT, PolyPhen-2, MutationTaster) is pathogenic. The patient presents permanent NDM (with negative autoantibodies), neonatal hypothyroidism with positive autoantibodies, gastritis and collagenous colitis and short stature, even she had a good glycemic and thyroid control.

Conclusions: Our results agree with the recent findings about the association between activating mutations in STAT3 gene and neonatal diabetes mellitus. The STAT3 mutation is a good candidate to be responsible for the clinical features of our patient. Our results support WES as a complete and cost-efficient method for further molecular diagnosis of NDM cases, negatives for frequent genes alterations.

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Importance of the Molecular Investigation for the Etiological Diagnosis of Short Stature: A Case Report of Wolf-Hirschhorn Syndrome by Chromosomal Microarray Analysis

Machado Pinto, R.; Plaza Pinto, I.; Bernardes Minasi, L.; Da Cruz E. Cunha, D.; Ribeiro, C.; Da Silva, C.; Da Cruz, A.

Abstract: Growth is a complex process influenced by several genetic factors both pre and postnatal, in which 80% of the height variation is explained by genetic factors. Nevertheless, the standard medical evaluation of short stature (SS) relies upon physical examination and laboratory parameters and identifies a pathological cause of SS in 1–40% of individuals. Recent advances in genetic diagnosis are revolutionizing the clinician’s ability to obtain a molecular diagnosis for patients with growth disorders. The Wolf-Hirschhorn Syndrome (MIM194190) is a complex genetic disorder caused by loss of genomic material from the short arm of chromosome 4 (4p16.3 region), including LETM1 and WHSC1 genes.

We report a female patient, 1 year old, presented with severe SS (~4.36 Z-Score), IUGR, neonatal jaundice, syndromic facies (microcephaly, prominent glabella, high arched eyebrow, broad nasal bridge and hypertelorism, short filtrum, mouth turned down, micrognathia, malformed ears), delayed psychomotor development, intra-atrial communication and seizures. She had a female karyotype, without any suggestion of chromosome alterations. We performed the Chromosomal Microarray Analysis (CMA) on the proband and her parents. The array used was Affymetrix’s GeneChip CytoScan™ HD SNP array. CMA detected four de novo genomic imbalances, corresponding to a 3.86 Mb microdeletion at 4p16.3, a 1.55 Mb microdeletion at 4p16.3, a 320 kbp microduplication at 5p13.2 and a 4.21 Mb microduplication at 9p24.3. The CMA showed that the microdeletion at 4p was harboring several genes, including LETM1, WHSC1, WHSC2, MSX1 that have been described and related to the Wolf-Hirschhorn Syndrome.

These findings allowed identification of genomic cause for the clinical features of the proband. Molecular diagnosis is important because it can end the diagnostic workup for the patient, it may alert the clinician to other medical comorbidities for which the patient is at risk, and it is extremely valuable for the genetic counselling.
Introduction: Congenital hyperinsulinism (CH) is the most frequent cause of persistent hypoglycemia in infancy, due to unregulated insulin secretion. Severe recessive mutations and milder dominant mutations have been described in the ABCC8 and KCNJ11 genes encoding SUR1 and Kir6.2 subunits of the beta-cell ATP-sensitive K⁺ channel.

Material and Methods: We report the case of a term boy who presented the first episode of hypoglycemia around 36 hours of life. Most subsequent hypoglycemas occur after a short fasting period (between 4 and 5 hours). Also presented two seizure episodes associated with hypoglycemia. He received high glucose infusions and with the presumption of hyperinsulinic hypoglycemia (hypoglycemia with dosable insulin, negative ketonuria and low beta hydroxybutyrate and NEFA) began treatment with diazoxide. Under this treatment, he repeated hypoglycemia in the self-monitoring at home, that were controlled with frequent feeding with formula milk with added polymers and cornstarch. For the purpose of defining the focal or diffuse involvement of the pancreas to define surgical resolution strategies, 18F-L-DOPA PET/CT Scan was done and also genetic study was conducted.

Results: Genetic study was conducted showing a heterozygous mutation in the gene ABCC8 c.4133 G>A. (Athena Labs). This mutation was not found in either parent assuming as a de novo mutation. This mutation has not been described but mutations in the same codon have been described as pathogenic significance. However functional studies need to be performed. 18F-L-DOPA PET/CT Scan (University Medicine Greifswald, Berlin, Germany) revealed diffuse involvement of the pancreas and watchful waiting was suggested. During follow-up he stopped diazoxide and presented few hypoglycemic episodes when prolonged periods of fasting and isolated seizure incidents. He presents adequate growth and development milestones.

Conclusion: Early diagnosis and appropriate treatment of CH are essential to prevent morbidity and mortality. New mutations and complementary studies may provide an understanding of the prognosis and treatment of the disease. In addition, the data will be useful for genetic counseling.

Temporal Trend of Newly Diagnosed Type 1 Diabetes Cases According to Age Range in a Brazilian Institution

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Introduction: The incidence of Type 1 Diabetes (DM1) is increasing worldwide, although there is a large variation in the incidence rates among countries. Increased incidence in DM1 has also been related in the age range between 0 and 5 years of age.

Objective: To evaluate the temporal trend of newly diagnosed DM1 cases and its distribution according to age in a Brazilian pediatric endocrinology service.

Methods: Data was obtained from the Pediatric Diabetes Group of the University Hospital. We analyzed all medical charts from children diagnosed with DM1 who attended the service between 1990 and 2014. Children were divided into three groups according to age at diagnosis (≤4 y, 5–9 y and ≥10 y). Temporal trends were analyzed in 5-year intervals (1990–1994, 1995–1999, 2000–2004, 2005–2009 and 2010–2014).

Results: 420 children diagnosed with DM1 attended the University hospital during the studied period. The youngest child presenting the disease was a 4 months old baby and the eldest were 17 years old adolescents. 135 of the patients were diagnosed between 0 and 4 years of age (35.95%); 160 children between 5 and 9 years (38.09%) and 109 adolescents were diagnosed between 10 and 17 years (25.95%). There was a progressive decrease in the proportion of children diagnosed between 0 and 4 years old (63.8% in 1990–1995 and 20.37% in 2010–2014; p < 0.05) and, an increase in the proportion of children diagnosed after 10 years old (5.55% in 1990–1995 and 53.70% in 2010–2014; p < 0.05). The proportion of children diagnosed between 5 and 9 years maintained stable.

Conclusions: In the studied population the diagnosis of DM1 in infants and toddlers seems to be decreasing throughout the years while in the age group older than 10 years, it seems to be increasing. Although data are inadequate to estimate the true incidence of DM1 in children in this city, it should be taken into consideration that this University hospital is the regional main public reference center for specialized care of DM1 children. Therefore, it’s intriguing to verify the reasons of these different results compared to the literature. More studies are needed to confirm and clarify this information.
Abstracts

O38

A Homozygous Point Mutation in the GH1 Promoter (-161T>C) Leads to Reduced GH Expression in Siblings with Isolated GH Deficiency (IGHD)
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Introduction: Mutations in the GH1 promoter are a rare cause of IGHD. In order to find the molecular cause of short stature due to IGHD, 3 siblings (2 M) born to consanguineous parents without mutations in the GHRHR and GH1 coding regions were screened for mutations in the GH1 promoter and locus control region. All patients harbored 2 variants (c.-123T>C and –161C>T) in homozygous state in the GH1 promoter, not found in 100 controls. The parents and a brother with normal stature were carriers. Patients presented proportionate short stature (height SDS from –4.1 to –5.8) and normal pituitary at MRI. At first evaluation, low IGF-1 and IGFBP-3 levels, in addition to decreased GH peak at hypoglycemia test (4.8 ng/ml by RIA), were found in all siblings. At adulthood IGF-1 and IGFBP-3 were low as well as GH peak at hypoglycemia tests (2.5 to 2.8 ng/ml – IFMA). Nucleotides –123T and –161C are within a highly conserved region among species and for –161 position (–161MUT).

Methods: DNA-protein interaction was evaluated by EMSA. In order to perform transient transfection and dual luciferase reporter assay, 3 plasmids were constructed containing both positions wild type (WTWT) or mutated (MUTMUT) or only mutated for –161 position (–161MUT).

Results: EMSA demonstrated less affinity of GH3 nuclear extract to –161C>T variant and normal affinity of POU1F1 protein and GH3 nuclear extract for –123T>C variant. The transfected WTWT mean values were significantly higher compared to MUTMUT (20.2 ± 2.24 vs 11.1 ± 2.7, p < 0.01), and to –161MUT (11.3 ± 2.1 vs 5.2 ± 0.8, p < 0.01).

Conclusion: To our knowledge, c.-161C>T is the first point mutation in the GH1 promoter that leads to short stature due to IGHD.

O39

Components of the Insulin-Like Growth Factor (IGF) System in Paediatric Gliomas Upon Diagnosis According to WHO 2007 Grading
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Background: Gliomas are the most common central nervous system tumours in children. Histologic grading is a means of predicting the biological behavior of these tumours and survival is strongly correlated with tumour gradation. The insulin-like growth factor (IGF) system of ligands and receptors are known to play an important role in both normal and neoplastic cellular growth. Information about the association of IGF-1, IGF-2, Insulin Receptor (IR) isoforms and IGF-1 receptor intracellular localization with tumour grading in paediatric gliomas is lacking.

Objective: To perform a quantitative assessment of IGF system components and to characterize intracellular localization of the IGF-IR in glial tumours from paediatric patients according to WHO 2007 grading.

Patients and Methods: In this prospective study we included 37 patients (20 males, age range 0.87–18.2), with gliomas without previous medical treatment. Total RNA was extracted from frozen tumour samples and IGF-1, IGF-2, IR and IR expression was quantified by qPCR. IR isoforms were assessed by PCR. Formalin-fixed tumour tissue sections were immunostained for IGF-1Rβ. IGF-1R expression and intracellular localization were scored as positive, negative, nuclear or cytoplasmic. Contingency tables were analyzed using Pearson’s χ² test to assess relationships between IGF-1R and tumor grade (Low grade I-II; High grade III-IV).

Results: IGF-1R staining was positive in 25/30 (83.3%) low grade and in 7/7 (100%) high grade gliomas. Low grade tumours showed cytoplasmic localization of IGF-1R in 22/25 cases, while in high grade tumours IGF-1R localization was mainly nuclear (p < 0.05). No differences were found between groups in total IR or IGF-1R. IR isoform A was present and predominant in all gliomas. IGF-1 expression was higher in high grade tumours, while IGF-2 expression was higher in low grade tumours (p < 0.05, Mann Whitney Test).

Conclusions: Our results would indicate that the amount of IGF-1R and IR expression are similar in all gliomas. However, IGF-2/IR components seems to have a role in low grade gliomas while IGF-1R intracellular localization and IGF-1 expression are associated with high grade gliomas, suggesting that an intratumoral IGF1/IGF-1R circuit may be involved in the biological behavior of this particular type of paediatric tumours.
De Novo Germline STAT3 Mutations Associated with Severe IGF-I Deficiency and Multi-Organ Autoimmune Disease in Two Unrelated Patients


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Background: Primary IGF-I deficiency with immune dysfunction has been associated to STAT5B inactivating mutations. More recently, activating mutations in the STAT3 gene have been described in children with severe growth failure associated with a spectrum of early-onset autoimmune disease.

Objective and Hypothesis: Whole Exome Sequencing (WES) approach was used to identify the affected gene, presumably a member of the GH-signaling cascade, in two unrelated patients (P1 and P2) presenting GH insensitivity associated to immune dysfunction and autoimmune disease.

Methods: In P1, no STAT5B mutation was identified by Sanger sequencing. WES was performed in both patients, and parents and sister of P1, using Illumina HiSeq 1500. WES findings were confirmed by Sanger sequencing in both patients.

Results: P1, a 3.6 year old girl, born at term with normal weight (3155 g), presented congenital hypothyroidism, desmastic eczema, chronic diarrhea, recurrent candidiasis and severe respiratory infections. At 3 years, she presented height –6.0 SD, lymphocytic interstitial pneumonia with non-necrotizing granulomas. She had normal IgG and IgM with elevated IgA and non-detectable IgE levels. Lymphocyte subset, FOXP3 and Treg CD127 were normal, but Th17 were low. She presented elevated GH (20 ng/ml), prolactin (30.6 ng/ml) levels. After 17 months of rhGH treatment, IGF-I levels increased (240 ng/ml) with a partial recovery of height (–4.8 SD). P2, a 3 year old male (height –5.36 SD), had a history of thyroiditis (no Graves disease). He also presented low IGF-I (57 ng/ml), normal IGFBP-3 (2.2 μg/ml) and elevated prolactin (30.6 ng/ml) levels. After 17 months of rhGH treatment, IGF-I levels increased (240 ng/ml) with a partial recovery of height (–4.8 SD). In P2, variant c.1276T>C (p.Cys426Arg) in STAT3 was identified. The patients’ phenotypes suggest that the identified STAT3 variants could be activating mutations.

Conclusion: Activating STAT3 mutations represent a novel monogenic defect presenting multi-organ autoimmune disease associated with severe growth retardation as the result of marked IGF-I deficiency. In contrast to STAT5b deficiency, patients carrying activating STAT3 mutations appear to preserve partial GH responsiveness.
P32

Clinical Features and Course of Pediatric Patients with Type 1 and Type 2 Diabetes Mellitus

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Background: Differences in clinical features and complications related to diabetes in pediatric patients are described, complications that present shortly after the onset of illness and whose frequency varies according to the type of diabetes. Objective: To describe the clinical features and course of patients with T1DM compared to T2DM.

Methods: 74 patients aged <18 years diagnosed with T1DM (54) and T2DM (20) were retrospectively evaluated with a longer follow-up of 1 year. A data collection chart was designed to collect clinical and biochemical information at diagnosis as well as the annual clinical course.

Results: T1DM patients at diagnosis have an average age of 7.72 (±2.86), 53.7% were male, 78.7% pre-pubertal with BMI average: 0.16 (±1.12), height: –0.24 (±1.07); 60% had ketoacidosis at diagnosis with classic symptoms such as polyuria, polydipsia, polyphagia and weight loss in 95.5% of patients, HbA1c: 10.39 (±2.76), C-peptide: 0.57 (±0.74). Whereas patients with T2DM have an average age of 12.59 (±2.32), 50% were male, 93.3% pubertal with BMI average: 1.28 (±1.40) height: –0.07 (±1.23); 23.5% had ketoacidosis with classic symptoms in 84.2% of patients, 61.3% showed acanthosis nigricans, HbA1c: 9.56 (±1.87), C-peptide: 1.58 (±1.15). The average follow-up time was for T1DM: 5.71 (±2.73) and T2DM: 3.72 (±2.37) years. Pre hypertension and overt hypertension was found in 27.6% of T1DM and 34.47% of T2DM; dyslipidemia in 62.4% and 72.43% respectively. Microalbuminuria was found in 27.6% of T1DM and 34.47% of T2DM; dyslipidemia. During the evolution similar frequencies for pre hypertension and overt hypertension and dyslipidemia were found; as well as higher frequencies of microalbuminuria in patients with T2DM despite having a shorter disease.

Conclusions: T2DM patients compared with T1DM are older, have higher BMI and C-peptide. During the evolution similar frequencies for pre hypertension and overt hypertension and dyslipidemia were found; as well as higher frequencies of microalbuminuria in patients with T2DM despite having a shorter disease.

P33

Associated Autoimmune Disease in Children with Recent Onset Type 1 Diabetes in a Cordoba Population

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Background: There is wide variation in the prevalence of pancreatic and other major autoantibodies in different population of children with Type 1 Diabetes (T1DM). The frequency data of associated autoimmunity in children with T1DM in our population is limited. The aim of this study was to describe the frequency of specific beta-cell, thyroid and celiac auto antibodies in a caucasian population of children at the clinical presentation with T1DM, from Cordoba Argentina between 2011 and 2015.

Patients and Methods: We studied 126 children with T1DM aged ranged between 1.3–14.0 years (Female n = 61, Male n = 65) and mean BMI of 15.1 (13.7–28.2). We determined anti-GAD65, anti-IA2, anti Insuline (AI) antibodies by IRMA-Beckman Coulter, anti-TPO and anti-Tg by Elecsys-Roche, and anti-tTGA antibody by Elisa-Orgentec.

Results: Anti-GAD65, anti-IA2 and anti-AI antibodies were positive in 67%, 62%, 36% respectively. The 15.5% of the patients presented the three autoantibodies positives and the 18.3% all negatives. Anti-TPO and anti-Tg were positive in 8% and 12%, respectively, with variation in the follow up. All of them were without treatment for the thyroid condition in this stage. Anti-tTGA antibody was positive in 15% for all the group of patients and not shown modification in the follow up of T1DM. We not observed significant difference in the prevalence of the analyzed antibodies by sex.

Conclusions: Our patient cohort exhibited higher prevalence of beta-cell autoimmunity compared with other populations. The knowledge of the presence of the autoantibodies and their behavior could contribute to the diagnosis and follow up the different associated autoimmune diseases in children with T1DM.

P34

Novel Mutation of Gene ABCC8 Causing Hyperinsulinism in an Infant

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Introduction: Hyperinsulinism is a heterogeneous condition which can be genetic or caused by a congenital abnormality of glycosylation. Genetic alterations which are found affect the genes of glutamic dehydrogenase (GHD), Glucokinase (GK) and L-3 Hydroxyacil Coa dehydrogenasa of short chain (SCHAD) as well
as genes of K channel, ATP dependent of the cell, which is composed of two proteins: the sulphonylurea (SUR) and subunit kir 6. Structural damage of the last three proteins and the hyperfunction of the first two determine a state of permanent depolarization of the cell and insulin hypersecretion unresponsive to glucose concentration.

Objective: To present a patient with hyperinsulinism caused to novel double mutation of gene ABCC8.

Material and Methods: We describe one patient with hypoglycemia (below 20 mg/dl) caused by hyperinsulinism from 52 weeks of age who was treated with parenteral fluids, diazoxido and subtotal pancreatectomy. We found a heterozygous missense mutation of exon 5 pGly228Asp (Pg228GD) and c.683 G>A of gene ABC8.

Analysis and Conclusions: Mutation of gene c683G>A has not been described previously. It is believed that it may associated with lesions and its detection may avoid pancreatectomy and improved the quality of life. We are standing patients parents.

P35
Factors Associated with Good Glycemic Control Among Pediatric Patients with Type 2 Diabetes Mellitus
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Introduction: Clearly, an improvement in glycemic control is likely to reduce risk of diabetic complications. In clinical practice, the recommended glycemic control target is very difficult to achieve. It is important, therefore, to identify factors that influence the outcomes of glycemia in order to improve the quality of diabetic management. The aim of the present study was to determine the status of glycemic control and identify factors associated with good glycemic control among diabetic children and adolescents treated at referral hospital.

Materials and Methods: Cross-sectional analytical study that included 47 patients aged 8–17 years diagnosed with type 2 diabetes. Data were collected from patient’s medication records, glycemic control tests and structured questionnaires. Logistic regression analysis was carried out to predict factors associated with good glycemic control.

Results: Of the patients included in the study, 29.8% had good glycemic control based on the recommendations of the American Diabetes Association (ADA). Those with poor control were in early pubertal stages, had higher concentrations of HbA1c. Variables associated with good glycemic control included age and duration of diabetes. Compared with the patients who were receiving monotherapy (metformin or insulin) and a combination of metformin plus insulin, there was no significant differences. In the present study, the proportion of patients with good glycemic control was higher than in other published study.

Conclusions: The goals of glycemic control in diabetic patients may be improved. Patient’s level of knowledge of metabolic control is related with educational level, but is very low. Patients need to be educated in metabolic control which would probably result in an improvement of such control.

P36
Clinical Characteristics of Urinary Tract Infections in Children and Adolescents with Type 1 Diabetes
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Introduction: In diabetic patients, the risk for systemic infections is higher, urinary tract represent the most common site of infection and Escherichia coli, the bacteria most frequently isolated in uroculture.

Objective of Study: To determine the clinical characteristics of urinary tract infections (UTI) in pediatric patients with type 1 diabetes.

Material and Methods: Study of patients under 15 years of age with type 1 diabetes and diagnosis of UTI. Variables studied: Age, sex, pubertal development and body mass index (BMI) of patients; duration of diabetes, level of glycosylated hemoglobin (HbA1c), insulin therapy scheme, symptoms of UTI, identified bacteria and antibiotic sensitivity. Exclusion criteria: Duration of diabetes less than three months, urinary malformation, vesicoureteral reflux, antibiotics in the last trimester; irregular checkups.

Results: Universe investigated: 41 patients; studied: 27. Age: 9 ± 4.8 years. Sex: 18 women (66.7%). Pubertal development: Tanner I, 16 (59%). BMI between percentiles 10–85, 23 patients (85.2%). Diabetes duration: 3–12 months, 11 cases (40.7%). HbA1c: 8.1 ± 3.1%, range 6.7–11.8%. Insulin: NPH and Regular, 15 patients (56%); glargine and glulisine, 12 (44%). Identified Bacteria: Escherichia coli, 22 patients (81.5%). Clinical features: asymptomatic episode, 11 cases (40.7%); lumbar or abdominal pain, 10 (37%). Susceptibility to Escherichia coli (22 patients): Sensitive to amikacin and ceftriaxone, 21 cases (95.45%); cefotaxime and gentamicin, 20 patients (90.91%).

Conclusions: Most patients were female, with poorly controlled diabetes, asymptomatic infection or causing lumbar and abdominal pain; Escherichia coli was the most common etiologic agent, being sensitive to ceftriaxone, cefotaxime, amikacin and gentamicin.

The clinical presentation, epidemiology and therapy bacterial UTI in diabetic patients are similar to those evident in the general population.

P37
Self-Care in Adolescent with Type 1-Diabetes: A Process Supported by Five Pillars: Disease Management, Parental Coherence, Conciliation of Identities, Autonomy of Decision and Attachment
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The adolescence, during which glycemic control is more precarious, is characterized by the development of the autonomy, which concerns the decision-making and the realization of behav-
behavior in all life’s dimensions. It is the stake in the construction of the self-care in adolescents with diabetes (DT1). In the field of the pediatric diabetology, the definition of the SC is often reduced to the autonomous behavior in management of the disease, not taking enough account of the other essential dimensions in the adolescent’s life, as the psychosocial life and the development’s needs.

We realized two successive studies: (1) a qualitative study to explore the signification of self-care in youth with DT1, and (2) a study by mixed methods, with adolescents from 13 to 15 years old, to verify the existence of links between the glycemic control and (a) the declared self-care, and (b) the parental support.

The results of the study 1 show that the behavior of self-care managed by the youth is always supported by the parents and are described in a perspective of health promotion by responding to three purposes of take care: the psychosocial life, the physical health and the diabetes. The results of the study 2 show that in adolescents with an optimal HbA1c, the importance of a salutogène perspective to take care of its psychosocial life. Our results underline the importance of a coherent support between the parents and adapted to the adolescent needs at least for the management of the diabetes and if possible also for its psychosocial life.

In conclusion, the self-care in adolescent with DT1 is a complex process supported by five pillars: disease management, parental coherence, conciliation of identities, autonomy of decision and attachment. It is important that, as health professionals, we considered them to support the process of self-care during our medical and educational support of the adolescents with DT1 and their two parents.

P39

**Mauriac Syndrome: A Case Report**

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**Case Report:** We report a 19-year-old diabetic patient, who presented at 8 y with moderate ketoacidosis (pH 7.2), initially managed with NPH and regular insulin. He achieved good metabolic control (HbA1c 6.5%) until nine years old, when he started with several decompensation episodes due to lack of adherence to insulin and food intake (HbA1c 12%). At 12 years old the insulin schedule was changed to glargine and aspartic insulin, but there was no improvement in his metabolic control. After four months, he started a progressive slowdown in his growth, reaching less than the 3rd percentile at the age of 14 y, with flattening of the growth curve and retarded pubertal development (10cc tests, VP T-III GT III). Hepatomegaly appeared with abnormal liver function (AST 84, ALT 84) and abdominal ultrasound showed hepatic steatosis. High digestive endoscopy with prepyloric congestive gastropathy, finding that suggested diabetic neuropathy and gastropathy. Actually the patient’s height is –3.45 SD and his BMI is 21.4 kg/m² (–0.1 SD).

**Discussion:** The Mauriac syndrome is an uncommon illness which is seen very occasionally, it develops in adolescents and young adults. Its incidence is unknown. It is distinguished by the presence of hepatomegaly, Cushing’s signs and growth failure with delayed puberty. Its pathophysiological mechanisms are not fully clarified but it could be a combination of factors: IGF1 and glucocorticogenesis alteration and increased cortisol levels. Its diagnosis is essentially clinical, but the laboratory and images helps, and it is directly related to a poor metabolic control.
P40
Cystic Fibrosis-Related Diabetes in Childhood. A Two Cases Report
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Introduction: Diabetes is a frequent co-morbidity in cystic fibrosis (CF). Cystic fibrosis-related diabetes (CFRD) has been associated with a worse prognosis in affected patients because of a higher frequency of infections, decline of pulmonary function, weight loss and growth impairment, occurrence of microvascular complications and mortality. However, CFRD development is mostly asymptomatic and thereby early diagnosis is difficult.

Methodology: Two cases with the recent diagnosis of CFRD are presented in order to expose the differential characteristics of the disease at clinical presentation.

Results: A 10.4 years old girl with the diagnose of CF at 3 months of age had been suffering weight loss, growth impairment and a worsening of respiratory function in the last 4 months. Two oral glucose tolerance tests (OGTT) were performed according to World Health Organization guidelines, in which hyperglycemia was presented. The second case is a male adolescent (18 years old) with a CF diagnosed at the age of 5 months that was admitted with weight loss, fatigue, polydipsia, and polyuria for about 3 months. Random plasma glucose was dramatically elevated and two fasting glucose tests confirmed the diagnosis of CFRD. Both patients showed ΔF508 genetic mutation, low insulinemia and C-peptide levels, normal hemoglobin A1c, as well as an impaired Shwachman score.

Conclusions: CFRD has different forms of clinical presentation in which unspecific manifestations may delay the correct diagnose. The early recognition of this entity in pediatric practice is vital for improve the clinical prognosis in CF patients.

P41
Gender Identity Prediction in Adulthood by HTP Test (House-Tree-Person) in 46,XY DSD Patients
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Introduction: Patients with 46,XY DSD present conflicts related to gender identity and change to male social sex in patients registered in the female social sex is not rare. The HTP test is a projective psychological test, which assesses aspects related to sexual identification, social aspects and psychodynamic aspects. GI in this test is defined as female (F), male (M) or ambiguous.

Methods: We used the HTP test in 96 subjects with 46,XY DSD before and after treatment. The first HTP test (HTP1) was performed on 90/96 patients (33.3% < 16 yo and 66.7% > 16 yo). The second HTP (HTP2 – performed after treatment) was applied in 81/96 (all >16 years). For analysis, we considered concordant when gender identity agreed with the social sex and discordant when gender identity was different from social sex (opposite or ambiguous).

Results: In our cohort, 20 patients changed social sex and 76 kept the social sex (56/76 = 73.68% in female social sex and 20/76 = 26.31% in male social sex). In the group that changed the social sex all patients (18 F to M and 2 M to F) showed discordant HTP results before treatment. In these, the HTP2 was consistent with the final social sex in all of them. Among those who maintained the female social sex, the HTP1 was concordant in 67.8% and discordant in 32.2%. After treatment, the HTP2 showed 81.1% of concordance in female social sex and discordant in 18.9%. In the group that kept male social sex, HTP1 was discordant in 50% (10/20). After treatment, the HTP2 was discordant in 80% (16/20) and discordant in 20%.

Conclusion: In 46,XY DSD patients who changed social sex the HTP test was able to identify a discordant gender identity before treatment in 100% of cases. Among those who kept the social sex, discordant gender identity was found in approximately one third of female social sex and in half of male social sex. After multidisciplinary approach the social sex adequacy had a marked improvement. The HTP test proved to be a usefull tool for diagnosis and treatment of patients with 46,XY DSD.

P42
Prevalence of Micropenis in Isolated Congenital Hypogonadotropic Hypogonadism and Treatment Outcome after Testosterone Replacement Therapy
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Introduction: Micropenis (defined as normal penis length ≤–2.5 SD) is an early manifestation of congenital isolated hypogonadotropic hypogonadism (IHH). Previous studies described a low prevalence of micropenis in congenital IHH (28%) and an association of this phenotype with mutations in TAC3/TACR3 genes. We evaluated the prevalence of micropenis and cryptorchidism in patients with congenital HHI according to the molecular defect and the impact of testosterone replacement therapy (TRT) in penile length in adulthood.

Materials and Methods: Phenotypic and genotypic data of 82 men with congenital IHH (43 Kallmann Syndrome [KS] and 39 normosmic IHH [nIHH]) followed at the Endocrinology Outpatient Clinic of HCFMUSP were retrospectively collected. Data of 55 patients were available before and after TRT. The penile length was measured with flacid penis under traction and compared to international tables. Genes classically associated with congenital IHH had been previously screened for mutations (GNRH/GNRHR, KISS1/KISS1R, TAC3/TACR3 in nIHH, KAL1 in SK and FGF8/FGFR1, PROK2/PROKR2 in both groups).

Results: Mean age at diagnosis and TRT initiation was 19 years (18–41). The median serum baseline LH was 0.65 U/L (<0.6–2.3 U/L) and testosterone 33 ng/dL (<11–232 ng/dL). Cryptorchidism was present in 48.7% of patients with KS and 30.7% with

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Puerto Varas, Chile
nIHH. All patients evaluated before TRT had micropenis (n = 65), with median penile length, 5.8 cm (Z-4.6) in SK and 6.5 cm (Z-4.2) in nIHH. Median post-treatment penile length (n = 70) was 10.2 cm (Z-1.93) in SK 10.6 cm (Z-1.68) in nIHH. In 53 patients assessed before and after TRT, the average increase in penile length was 3.92 cm. Seventeen patients remained with micropenis despite TRT. Twenty five patients (30.5%) harbored deleterious mutations: 12 KS (3 FGFR1, 6 KAL1, 3 PROK2) and 13 nIHH (9 GNRH, 1 FGFR1, 2 TACR3, 1 PROKR2). No phenotypic difference was observed between patients with and without mutations except for cryptorchidism, present in all patients with mutations in KAL1.

**Conclusion:** All patients with congenital IHH had micropenis at diagnosis regardless of molecular diagnostics. The TRT resulted in penile growth enough to allow sexual activity, although 23.9% remained with micropenis.

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**P43**

**Characterization of Mutations in the Androgen Receptor (AR) Identified in 38 Brazilian Families with Complete or Partial Androgen Insensitivity Syndrome (AIS)**

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**Background:** Androgen insensitivity syndrome (AIS) is a genetic disease X-linked, caused by functional abnormalities of the androgen receptor (AR). Mutations in the AR are associated with broad phenotypic spectrum from partial insensitivity (PAIS) to complete insensitivity (CAIS).

**Methods:** PCR amplification of the coding and promoter regions of the AR gene, followed by direct sequencing. The mutations were searched in the literature, genomic sites and the novel mutations were evaluated by prediction sites. We classify mutations according to the type (missense and nonsense), exomic location, functional domain (NTD, LDB, DBD, Hinge) and phenotype (CAIS and PAIS).

**Results:** We identified 17 different mutations in the AR in 22 families with PAIS (37 patients) and in 13 families with CAIS (n = 23 patients). Of these, 6 (CAIS) and 8 (PAIS) have not been described. These novel variants are not found in either 1000 Genomes and ESP-6500 database but all of them were considered deleterious. Missense mutations were identified in 90.5% of PAIS and in 83% of CAIS and nonsense in 9.5% of PAIS and 17% in CAIS. The frequency of mutations in each exon differ between CAIS and PAIS, being more frequent in exons 5 and 7 (18% and 17%) in PAIS and in exons 1 and 4 (27% and 21%) in CAIS. In functional domains, there was a lower frequency of mutations in the DBD domain (12.5% in CAIS and 20% in PAIS) followed by the NTD domain (25% in CAIS and 20% in PAIS) and by the LBD (62.5% CAIS and 60% PAIS). We describe for the first time, a large deletion in the promoter region of the AR gene in a PAIS family, whose exonic region was normal. Mutations in AR were not identified in 18.2% of families with PAIS (4/22) and 6.25% of the families with CAIS (1/16).

**Abstracts**

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**P44**

**Polycystic Ovarian Syndrome (PCOS) in Adolescents with and Without History of Central Precocious Puberty (CPP)**

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**Introduction:** The heterogeneity in clinical phenotype in PCOS has been recognized recently. The long-term consequences of PCOS on metabolic dysfunction may be related to androgens excess. Girls with CPP have an increased prevalence of PCOS. Whether these patients present a different clinical or metabolic phenotype remains unknown.

**Objective:** To evaluate if differences in clinical or biochemical features of PCO girls with or without history of CPP may have a differential impact on their metabolic profile at diagnosis.

**Patients and Methods:** A retrospective study was performed in 65 adolescents with PCOS (16.2 ± 2.6 years, gynecological age 4.6 ± 2.2 years) diagnosed according to Androgen–Excess–Society criteria. Patients were divided into: History of CPP (GA, n = 24), and without history of CPP or premature pubarche (GB, n = 41). Menstrual disorders, BMI-SDS, clinical signs of hyperandrogenism, serum gonadotropins and androgens levels, ovarian ultrasound pattern (PCOM), and HOMA-IR and G/I ratio at diagnosis were assessed.

**Results:** Menstrual abnormalities were present in 84% of patients in GA and 100% in GB. The gynecological-age and BMI-SDS were not different between groups (5.2 ± 2.2 vs 4.2 ± 2.1; 0.9 ± 0.8 vs 0.6 ± 1.1, p=ns, respectively). Clinical hyperandrogenism was found in 75% in GA and 100% in GB. GA presented a significantly lower prevalence of PCOM (20%, 5/24) than GB (46%, 19/41, p = 0.03). Basal LH levels (mUI/ml) and the ratio LH/FSH were significantly lower in GA (8.5 ± 5.0 vs 12.2 ± 6.2; p = 0.03; 1.6 ± 1.1 vs 2.2 ± 1.1 p = 0.01 respectively). Testosterone and Androstenedione (ng/ml) levels were also significantly lower in GA (0.5 ± 0.3 vs 2.2 ± 1.1 p = 0.004; 2.4 ± 1.0 vs 3.8 ± 1.5 p=<0.0001, respectively). Neither HOMA-IR (2.6 ± 1.0 vs 2.4 ± 1.6, p=ns) nor the G/I ratio (7.6 ± 3.1 vs 11.5 ± 8.4, p=ns) were different between groups.

**Conclusions:** The fact of a less severe clinical and biochemical phenotype in PCO girls with history of CPP compared with those without CPP history appears not to be associated to difference in their metabolic profile at diagnosis. A careful follow up should be performed to determine whether the phenotypic differences found could be long term implications on metabolic risk.

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Mutations in NR5A1 Associated with a Wide 46XY Phenotypic Range

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Introduction: Steroidogenic factor (SF-1) is a nuclear receptor that plays a crucial role in the transcription of multiple genes involved in adrenal and gonadal development, steroidogenesis and reproduction. Mutations of the NR5A1 gene, encoding SF-1, have been reported in association with a wide spectrum of 46XY DSD phenotypes, including individuals with normal adrenal function, but also those with isolated anorchia, variable degree of hypospadias, adult male infertility or in 46XX individuals with primary ovarian insufficiency.

Patients and Methods: Molecular analysis of the NR5A1 gene was performed by PCR and direct sequencing in five 46XY patients with a wide phenotypic spectrum and without evidence of adrenal insufficiency.

Results:

Patient 1: 46XY boy diagnosed with complete gonadal dysgenesis, presenting with primary amenorrhea and hypoplastic uterus. She carried in heterozygosis the previously described p. His24Leu mutation.

Patient 2: 46XY girl harbouring primary amenorrhea, virilization, clitoral hypertrophy, hypoplastic uterus and without evidence of gonads. Mutational analysis revealed a novel heterozygous p. Cys301Tyr (c.902G>A) alteration, located in exon 5 at the ligand-binding domain of the gene. Her asymptomatic mother presented the variation as a possible mosaicism. In silico analysis with prediction software classified the variation as pathogenic.

Patient 3: 46XY boy presenting with micropenis, scrotal hypospadias, bilateral cryptorchidism and bifid scrotum. He carried in heterozygosis the previously described p. Gly146Ala polymorphism.

Patient 4: 46XY boy with micropenis and bilateral anorchia presented in heterozygosis the already reported disease-associated p. Gly146Ala polymorphism.

Patient 5: 46XY boy presenting with scrotal hypospadias, unilateral cryptorchidism and bifid scrotum presented in homozygosis the p. Gly146Ala polymorphism.

Conclusions: Our findings support the previously described complex phenotype expressivity, penetrance and variable inheritance pattern of NR5A1 mutations, especially in heterozygosis, ranging from severe DSD phenotypes to completely asymptomatic carriers. Establishment of phenotype-genotype correlations remains unclear, and the search for modulating factors that could explain the spectrum of clinical manifestations continues.

Ovarian Morphology and Serum IGF-I Levels in Postmenarcheal Hyperandrogenic Oligomenorrheic Girls

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Background: There is evidence that the insulin-like growth factors (IGFs) play an important role in the human ovary and IGF1 has a central role in the selection of the dominant follicle. Acromegalic women show evidence of an increase in polycystic ovarian morphology.

Objective and Hypotheses: We evaluated IGF-1 levels and its relationship with ovarian morphology in postmenarcheal hyperandrogenic and control girls. We hypothesized that IGF-1 levels are increased in girls with higher ovarian volumes (OV) and with the number of follicles (NF).

Method: Girls with hyperandrogenism and oligomenorrhea (HO, n = 18) and normal girls (C, n = 36) were evaluated at our institution after a complete physical exam. An early morning blood sample was obtained for determination of IGF-1, and a gynecological ultrasound was performed in the follicular phase.

Results: Age 11.4–19.9 years old (HO 15.3 ± 2.0, C 14.7 ± 1.7 p = NS).

We documented a higher follicular number in HO girls, but we did not observe any correlation between IGF-1 levels and OV or NF in the HO girls, or in the controls.

Conclusion: HO girls show a higher number of follicles compared to C, but there is no correlation between serum IGF-1 levels and OV or NF. Future studies will address the impact of IGF-1 levels on pathophysiology and metabolic changes in HO patients.

Supported by: FONDECYT 11121427 and 11130240.

Table 1. Characteristics of HO and C (mean ± SDS) (for abstract P46)

<table>
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<th>HO (n = 18)</th>
<th>C (n = 36)</th>
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<td>Gynecological age (y)</td>
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<td>2.6±1.5</td>
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<td>Height (z-score)</td>
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<td>0.2±0.9</td>
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<td>BMI (z-score)</td>
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<td>OVMean (ml)</td>
<td>9.7±2.4</td>
<td>5.9±2.3</td>
<td>0.99</td>
</tr>
<tr>
<td>NFMax (n)</td>
<td>14.8±7.7</td>
<td>7.0±3.8</td>
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<tr>
<td>NFMean (n)</td>
<td>12.2±5.5</td>
<td>6.3±3.2</td>
<td>0.002</td>
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<tr>
<td>IGF-1 (ng/ml)</td>
<td>248±52.2</td>
<td>259±48.1</td>
<td>0.57</td>
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</table>
Evaluation of 47XXY Syndrome in Disorder of Sex Development (DSD) Multidisciplinary Clinic: Lessons Learned

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Introduction: The Y chromosome polisomy or 47XXY syndrome is an aneuploidy which incidence is estimated to be in 1/1000 male births. It is caused by a meiosis II dysfunction ending in an extra Y chromosome. Most of the patients have usually a normal clinical phenotype with minor anomalies in external genitalia, male assignment, increase stature, learning and language disabilities.

Material and Methods: We report the case of a 6 month-old toddler with bilateral cryptorchidism and micropenis. Firstborn of a 19 year-old mother and a 20 year-old father, without pathological background or consanguinity. His prenatal and perinatal periods were uneventful. Male assignation and psychomotor development were normal. Examination revealed stature and weight in + 1.75 SDS (exceeding the midparental target height), normal head circumference, asymmetric external genitalia was found: hypoplastic left scrotum, 24 mm microphallus, left cryptorchidism, right testis descended to the scrotum and his penis showed significant growth (35 mm); Karyotype 47XYY: number of metaphases count 100, band level 650. The patient was found to have bilateral inguinal hernia and underwent surgical repair.

Result: The hCG stimulation test (500 UI/d IM for 3 days) showed, FSH 14.94 UI/mL, LH 3.88 UI/mL, AMH 8.67 ng/mL, testosterone 1.23 ng/ml and a post-hCG testosterone collected 24 h after 6.58 ng/ml. The child had elevated gonadotropins and low AMH markers of Sertoli malfunction, and elevated testosterone level. Erections were frequently seen during hCG test; the left testicle descended to the scrotum and his penis showed significant growth (35 mm); Karyotype 47XYY: number of metaphases counted 100, band level 650 Karyotype 47XXY. The patient was found to have bilateral inguinal hernia and underwent surgical repair.

Conclusion: The 47XXY should be suspected in children who present with unilateral cryptorchidism, micropenis and increase stature. The natural history of testicular cells in 47XYY has not been well documented. Evaluation by multidisciplinary team is recommended in order to rightfully assess social competence, behavioral and cognitive problems usually associated with DSD patients.
Results: We found a total of 4 cases, in whom we saw an early onset of symptoms. The most common symptom was seizure associated with hypoglycemia. Hyperinsulinemia was shown in all patients (level insulin/glucose >0.3). All received medical treatment with octreotide and diazoxide, without improvement, so the need for pancreatectomy was in the 4 patients, with subtotal resection (80–95% pancreas) in 3 patients, and almost complete (98% pancreas) in a patient. The pathology in all cases was reported as nesidioblastosis. Genetic testing to patients and their parents was conducted: in 3 patients a mutation of gen ABCC8 was found, and in one patient no one genetic mutation was found in blood, but in pancreatic tissue was found partial segmental loss of the maternal allele in the region of chromosome 11 that encompasses the KCNJ11 and ABCC8 genes; in one patient was homozygous mutation, which is associated with a diffuse involvement, so needed an almost total pancreatectomy; and the others were heterozygous mutation. Their evolution was: 1 euglycemic without treatment, 1 had hyperglycemia, required insulin, currently euglycemic, 1 in treatment with diazoxide, and 1 died post-second pancreatectomy. The three survivors have delay psychomotor development.

Conclusions: The clinical evolution and complications observed in our patients is similar to that described in other studies, highlighting the importance of genetic testing in the diagnostic classification and management. It is necessary to do an early diagnostic and treatment to minimize the development of neurological sequelae.

P50
Prevalence of Polycystic Ovary Syndrome in Obese Adolescents
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Background: Polycystic Ovary Syndrome (PCOS) is the most common endocrine disorder in women on childbearing age (5–10%) and the leading cause of female infertility. The prevalence of PCOS in obese adolescents is not well established and its diagnosis can be masked by pubertal physiological changes. Childhood obesity may increase PCOS prevalence and severity in adolescence. We aimed to determine the prevalence of PCOS in obese adolescents, according to different diagnostic criteria.

Methods: We performed a cross-sectional study, which included 47 adolescents between 10–18 years of age, with overweight or obesity. They were evaluated according to Rotterdam, AES, and NIH criteria that included clinical and biochemical signs of hyperandrogenism, signs of chronic anovulation and/or polycystic ovaries/increased ovarian volume. We divided the patients in 2 groups (obese adolescents with or without PCOS) for further analysis.

Results: The prevalence of PCOS by the Rotterdam criteria was 40.4% (n = 19; 95% CI 26.7 to 55.7); by AES, the same 19 adolescents were diagnosed with PCOS; and by NIH, 36.2% (n = 17; 95% CI 23.1 to 51.5) of the girls were diagnosed with PCOS, all previously fulfilling the Rotterdam and AES criteria. Free androgen index (FAI) was the only biochemical sign of hyperandrogenism significantly different between the two groups according to all three criteria. The prevalence of subclinical PCOS (biochemical hyperandrogenism, associated with the presence of LH/FSH ratio >2 or ovaries >10 mL) were 17% (95% CI 8.1–31.3) by the AES, 19.1% (95% CI 9.6–33.7) by the Rotterdam and 12.8% (95% CI 5.3–26.4) by the NIH criteria.

Conclusion: PCOS prevalence among obese adolescents is high (36.2–40.4%). FAI seems to be a useful endpoint for biochemical hyperandrogenism in obese adolescents. PCOS screening in all obese adolescents may avoid its under-diagnosis and allow an early treatment.

P51
Sirolimus Therapy in Infant with Congenital Hyperinsulinemic Hypoglycemia Unresponsive to Diazoxide
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Background: Congenital Hyperinsulinemic hypoglycemia (CHH) is the most common cause of severe, persistent neonatal hypoglycemia. Treatment of diffuse forms that do not respond to diazoxide and octreotide is near total pancreatectomy.

Clinical Case: Preterm male (33 weeks) born from non-consangunineous parents. Birth weight: 3030 g (>p90), length 44.5 cm (p50). Apgar: 8–9. He was non-dysmorphic and systemic examination was unremarkable. At 5 hours of life he was trembling (glycemia 20 mg/dl, insulin 36 uU/ml, negative ketone bodies). He was treated with i.v. glucose infusion up to 19 mg/kg/minute and glucon 8 ug/kg/hour. Hyperinsulinism was suspected. Gallium 68 PET/CT showed a diffuse compromise of pancreas. Sequence analysis for the ABCCS and KCNJ11 gene showed no mutation. Diazoxide was started (with hydrochlorothiazide). There was no response despite the increase of dose (5 to 20 mg/k/day) and Octreotide was added, with a good response with dose of 25 ug/kg/day.

At 1 month of life the patient presented acute cholecystitis, a possible side effect of Octreotide and it was suspended. At 2 months of age, before pancreatectomy, he entered in a treatment protocol with Sirolimus, an Mtor pathway inhibitor with progressive doses from 0.5 a 1 mg per square meter p.o, to achieve serum level of 5–15 ng/ml. One month later we could stop glucose and glucagon infusion and the patient was discharged to home with enteric feeding every four hours. He is now 6 months old and doesn’t present hypoglycemia.

Conclusions: We present a case of a newborn with CHH due to a diffuse compromise of pancreas. The patient didn’t respond to maximal dose of Diaxoside and had a mayor adverse effect with Octreotide. Before to perform a near total pancreatectomy we decided to use oral Sirolimus. The patients had a good glycemic response to this drug. There were no adverse events during 4 months of follow-up.
Multinodular Goiter in Pediatrics: How Frequent and Dangerous?

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Introduction: In a recent report we have identified multinodular goiter (MNG) as a condition with an increased risk for thyroid malignancy in children and adolescents.

Objective: To report the prevalence and characterization of a prospectively and uniformly followed cohort of pediatric patients with MNG and to retrospectively analyze the differences between prospectively and uniformly followed cohort of pediatric patients.

Material and Methods: We studied 32/104 patients under 19 years of age referred to the Division of Endocrinology for thyroid nodules between 2008 and 2015, who presented MNG and reached a final diagnosis (benign vs. malignant) by surgery (n = 24) or by at least 1 year (range: 1.5–6.5) of clinical follow up (n = 8). Initial evaluation included clinical data, thyroid function, Doppler ultrasound and US-FNAB cytology categorized with the Bethesda System for Reporting Thyroid Cytopathology.

Results: Upon admission mean age was 13.6 years, 75% were females, 69% pubertal. Papillary thyroid carcinoma (PTC) was found in 8 patients (25%). Risk factors, present in 5/32 [(dyshormonogenesis (n = 3), Lhermitte-Duclos Syndrome (n = 1) and iodine deficiency (n = 1)], were not associated with malignancy. All patients with familiar MNG (n = 6) had a benign diagnosis. Younger age (10.4 vs. 14.8 years), prepubertal status (5/8 vs. 5/24,) and pathologic lymphadenopathies (4/8 vs. 1/24) were significantly associated with malignancy. All malignant nodules were associated with malignancy (p < 0.05). All malignant nodules were solid (8/8 vs. 12/24, p < 0.05). Conversely, the finding of mixed/cystic nodules on US was always associated with a benign diagnosis (p < 0.05). Although within the normal range median TSH concentration was higher in patients with PTC (3.5 vs. 1.4 mIU/L, p < 0.05) and the likelihood of PTC increased with rising TSH levels. Malignancy risk in Bethesda categories I, II, III, V and VI was 0%, 7.7%, 0%, 75% and 100% respectively. PPV and NPV for Bethesda V–VI FNAB results were 86% and 96% respectively.

Conclusions: MNG represented 31% of our thyroid nodule population. PTC incidence was 25%, similar to that reported in pediatric thyroid nodules. Younger age, prepubertal status, higher TSH concentrations, solid nodules and pathologic lymphadenopathies were significantly associated with malignancy. These findings should be considered when facing the therapeutic approach for these patients.
**O43**

**Ontogeny of the Synchronization of Adrenal Clock Genes, Adrenal Steroidogenesis and the Circadian Rhythm of the HPA Axis in Rats**

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**Introduction:** The circadian rhythmicity of the hypothalamic-pituitary-adrenal (HPA) axis depends on the synchronization of the clock molecular systems in the suprachiasmatic nucleus and in the adrenals. When and how this process occurs in the adrenal is unknown.

**Objective:** To assess the ontogeny of daily variation of the expression of the adrenal clock genes (*Clock, Arntl, Per1, Per2, Per3, Cry1, Cry2, Rora, and Nrl1D*) and plasma corticosterone (B) and *Mc2r* mRNA expressions from P1. Since P3, adrenal clock gene expression, adrenal steroidogenesis, and adrenal steroid concentrations were observed from P3, with a progressively stronger nocturnal increase of B concentrations, with peak at P6 and reversal of these parameters from P14, reaching adult patterns at P24. Synchronization between the expression of the clock genes and adrenal steroidogenesis was observed from P3, when the mRNA expression pattern of *Per2, Per3, Cry1* genes became concordant with B concentrations since neonatal period.

**Results:** It was identified diurnal variation in plasma B concentrations from P1. Since P14 until P24 there was a progressive nocturnal increase of B concentrations, with peak at ZT20 and nadir at ZT0 (P < 0.01), characterizing the well known adult rat circadian rhythm of the HPA axis. There was a daily variation in the mRNA expression of *Clock, Arntl, Per2, Per3, Cry1, Nrl1D, Mc2r* and *Star* since P3 (P < 0.05), with attenuation between nadir and peak at P6 and reversal of these parameters from P14, reaching adult patterns at P24. Synchronization between the expression of the clock genes and adrenal steroidogenesis was observed from P3, when the mRNA expression pattern of *Per2, Per3, Cry1* genes became concordant with the B concentrations since neonatal period.

**Conclusions:** In the adrenal, there is a gradual synchronization of the molecular mechanisms modulating the ontogeny of the HPA axis circadian rhythm. From P14, this synchronization is maintained in spite of the reversal of the temporal pattern in the expression of both the adrenal clock genes and the genes involved in adrenal steroidogenesis, resulting in the appearance of the adult circadian rhythm of the HPA axis.

**Financial support:** FAPESP.

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**O44**

**Differences in Sertoli Cell Markers between Boys with Hypogonadotrophic Hypogonadism and Constitutional Delay of Puberty**

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**Introduction:** We hypothesised that Sertoli cell function is impaired in boys with absence of puberty due to hypogonadotrophic hypogonadism (HH), but not in constitutional delay of puberty (CDP). No long-term follow-up prospective study with an ascertained final diagnosis of CDP or HH has studied Sertoli cell markers.

**Subjects and Methods:** In a multinational prospective study, all boys referred for absence of puberty (testicular <4 ml) at ≥13 years between 2008 and 2014 were followed until age ≥18 yr, when they were classified as CDP (testicular volume ≥15 ml) or HH (<15 ml). Serum AMH and inhibin B were compared between groups; we also compared testosterone (T) and basal and post-stimulation LH and FSH. Data are shown as median (range). Mann-Whitney test was used for comparisons between continuous variables and Fisher exact test for categorical variables.

**Results:** To present, 28 patients had an appropriate follow-up, which allow reaching a final diagnosis: CDP was ascertained in 14 and HH in 14. Clinical differences between groups included the history of micropenis and/or cryptorchidism at birth in 64.3% of HH vs none in CDP, and the existence of at least one testis of 3 ml at referral in 85.7% of CDP vs 28.6% of HH, p = 0.0063. We found significant differences (HH vs CDP) in serum AMH 211 pmol/l (26–462) vs 340 (136–1115), p < 0.0001, basal LH 0.10 IU/l (0.05–1.47) vs 1.20 (0.10–3.28), p = 0.014, basal FSH 0.57 IU/l (0.30–11.30), p = 0.0029, post-stimulation LH 1.3 IU/l (0.3–11.1) vs 19.6 (3.8–37.4), p = 0.0008 and post-stimulation FSH 3.2 IU/l (0.2–7.3) vs 11.1 (4.8–23.1), p = 0.0006. No differences were found in serum T (p = 0.104), the lag between chronological and bone age (p = 0.264) and parental history of pubertal delay (p = 0.41).

**Conclusions:** Lower levels of Sertoli cell markers (AMH and inhibin B) are more frequently found in boys with HH whereas at least one testis of 3 ml was more prevalent in CDP. These preliminary results suggest that Sertoli cell markers may be useful to differentiate these overlapping clinical conditions.
HESX1 Mutations Cause Hypopituitarism with Different Clinical Features

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Introduction: Developmental defects in pituitary gland cause hypopituitarism. HESX1 is a transcriptional factor expressed during the development of the forebrain and Rathke’s pouch, a pituitary primordium, in vertebrates. Mutations in this gene are associated with septo-optic dysplasia (SOD), isolated growth hormone deficiency (IGHD) or combined pituitary hormone deficiency (CPHD). The inheritance is recessive or dominant with incomplete penetrance.

Materials and Methods: Four patients with CPHD and no midline defects or SOD from 3 unrelated families were approached by exome sequencing and candidate gene screening.

Results: Using Sanger sequencing we identified a homozygous mutation, HESX1 p.R160C, in two siblings from a consanguinous family who presented with ACTH, TSH and GH deficiencies. Magnetic Resonance Image (MRI) revealed severe anterior pituitary hypoplasia (APH) or pituitary aplasia (PA) and topic posterior pituitary (TPP) in both siblings. The oldest had hydrocephalus and required pubertal induction. The youngest, with 6 years of age, is too young to assess spontaneous puberty. The p.R160C mutation, in the homeodomain (HD), impairs DNA binding and was previously described associated to SOD, ectopic posterior pituitary (EPP), and hypoplasia of the corpus callosum, optic nerve, and anterior pituitary. Using exome sequencing, we identified a homozygous p.I26T mutation in a patient born to consanguineous parents. She presented evolving CPHD, except ACTH and MRI revealed APH and TPP. These clinical features contrast with another Brazilian patient, born to consanguineous parents, homozygous for the same mutation who presented with evolving CPHD and EPP. Finally, we used exome sequencing to analyze a male newborn infant with PA, born from non consanguineous parents, who developed hypoglycemic convulsions at 8 hours of age. This diagnosis was anticipated because of autopsy in an older female sibling who died of hypoglycemia revealed PA. Diagnostic studies confirmed TSH, GH and prolactin deficiencies. We identified compound heterozygote mutations in the HD with p.R160H, previously described in the literature in homozygous state in a patient, from consanguineous parents, with CPHD, EPP, APH and a novel change, p.R159W.

Conclusion: Our observations demonstrate marked phenotypic variability associated with these HESX1 mutations, implying a potential role for modifier genes or environmental factors that impact the phenotype.

Leptin Status Is Associated with Academic Performance in Chilean Adolescents Transitioning to Young Adulthood

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Introduction: Leptin is associated with learning abilities and memory performance via brain receptors distributed in the brain, especially in the hippocampus. In the hippocampus, leptin facilitates the induction of synaptic plasticity by converting short-term potentiation into long-term potentiation, a process regarded as part of the neurophysiological basis of learning and memory formation. Because leptin modulates the cellular processes underlying hippocampus-dependent learning and memory, and because memory skills are good predictors of learning outcomes, we hypothesized that leptin resistance would compromise the ability of adolescents to perform in school and, thus, would be associated with worse academic results.

Objective: To study the association of leptin resistance with academic performance in adolescents transitioning to young adulthood of middle-to low SES from Santiago (Chile).

Methods: We measured serum leptin concentration in 562 Chilean students, aged 16.8 (0.26 SD), using an enzyme-linked immunoabsorbent assay (ELISA). Cutoffs from the HELENA Study for 16 years olds were used for diagnosis of leptin resistance in males and females. Academic performance was measured by final high school grade point average (GPA), transformed into standardized score values. Scores ≥75th percentile in our sample were considered good academic performance. A series of models explored the impact of leptin resistance on academic performance, after controlling for potential confounders, including sex, quality of diet and type of secondary education.

Results: Prevalence of leptin resistance was 14.8% (95% CI: 11.8–17.7). Leptin resistant adolescents had a significantly lower high school GPA compared to leptin sensitive participants (GPA mean difference = 34.95% CI: 12.7–55.4). After controlling for eating patterns at age 16, the odds of good academic performance among leptin resistant adolescents were 35% (95% CI: 0.17–0.69) that of their leptin sensitive peers. The association remained significant after adding sex and educational confounders (OR: 0.41; 95% CI: 0.19–0.82).

Conclusions: In this sample of Chilean youths of middle-to low SES, leptin status was associated with academic performance in high school. Further research is needed on the cognitive effects of leptin in younger populations.
Children with Noonan and Noonan-Like Syndromes Had a Lipid Profile Resembling Metabolic Syndrome and Type 2 Diabetes

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Introduction: Noonan syndrome (NS) and Noonan-like syndromes (NLS) are autosomal dominant disorders caused by heterozygous mutations in genes of the RAS/MAPK pathway. Important hormones involved in metabolic control act through this pathway and NS-related mutations can affect their actions. The aim of this study was to describe metabolic profile in children with NS/NLS.

Subjects and Methods: We selected 58 children with previously identified pathogenic mutation in NS/NLS genes and 96 age-matched controls to undergo anthropometric measurements and basal metabolic profile. Height and BMI were expressed as SDS for age and sex. The differences between controls and genotypes were analyzed by t-test and ANOVA.

Results: Patients with NS/NLS were shorter than the control group, whereas BMI-SDS were similar. Both groups showed normal glycemia and insulin levels. Patients with NS presented total cholesterol (142.4 ± 27.0 vs. 156.4 ± 24.7 mg/dl, p = 0.001) and high-density lipoprotein cholesterol levels (HDL-C; 41.4 ± 12.6 vs. 58.0 ± 12.4 mg/dl, p < 0.001) lower than controls. Low-density lipoprotein cholesterol (LDL-C) levels were similar in both groups. Triglyceride levels were higher in patients with NS/NLS than the control ones. 66.2 ± 23.0 mg/dl, p = 0.004). Patients with NS/NLS were more likely to have a low HDL-C (odds ratio 18.6; 95% CI 7.5–46, p < 0.001) and higher triglyceride levels (odds ratio 3.8, 95% CI 1.4–10.7, p = 0.011) compared with control children (corrected by sex, age, BMI).

Conclusion: Despite BMI was within normal range, patients with NS/NLS presented a low HDL-C and higher triglyceride levels, a lipid profile that resembles features of metabolic syndrome and type 2 diabetes. Since SHP2 and SOS1 seem to have a role in insulin signaling through PI3K/AKT pathway, it is worth noting that other mutated molecules involved in NS could influence serum lipid levels suggesting a role of RAS/MAPK pathway mutations in insulin signaling.

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**O49**

**Early Infancy Body Composition (BC) in Very Low Birth Weight (VLBW, <1500 GRS) Preterm Is Dependent on BW SDS and Is Differently Associated to Adipokines**

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**Introduction:** Nutritional imbalance during critical windows in early life can influence long term metabolic profile and BC. VLBW infants accumulate nutrient deficit during hospital stay and demonstrate catch up in weight after this time, a period equivalent to that in term infants associated with later metabolic risk and altered BC. In this population, differences in BC by birth weight SDS and early CUG have not been consistently found at this age. We tested this hypothesis and analyzed whether differences in BC were associated to adipokines collected prospectively.

**Patients and Methods:** VLBW preterm infants prospectively recruited had BC at corrected age (CA) 2 (n = 39, 19 AGA, 15 male) and 3 years (n = 31.19 AGA, 11 male). These infants belong to the National Program of Follow Up for VLBW infants. Adiponectin and visfatin were measured from 3 months to 3 years of CA. BC was expressed in SDS and data was adjusted by height SDS by regression analysis.

**Results:** Mean gestational age, birth weight/length of these children were 29 ± 2.0 weeks, -2.03 ± 1.02 and -1.27 ± 1.40 SDS respectively. Weight and length at age 2 and 3 yr were lower in SGA children. They had lower total lean mass at 2 years and lower subcapital mineral content, total, trunk and limb fat mass and total lean mass at 3 years. Adiponectin and visfatin decreased during infancy up to 3 years without differences by BW SDS. Only in AGA, adiponectin at 12 months was inversely associated to subcapital mineral bone content, fat percentage and trunk fat mass at 24 months and with fat percentage at 36 months, and adiponectin at 24 months with total fat mass at 24 months. In AGA, inverse correlation was obtained for visfatin at 12 months with fat percentage at 24 months and with total fat mass at 24 months.

**Conclusion:** In this cohort BC differs early in childhood, and associations with adipokines are BW SDS dependent suggesting a different fat tissue functioning.

**O50**

**Validity Assessment and Determination of Cutoff Values for Different Anthropometric Indicators to Diagnose MetS in Adolescents**

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**Background:** Several aspects of body composition, in particular the amount and distribution of body fat and the amount and composition of lean mass, are important health outcomes in children and adolescents. Because their measurement is considered in clinical practice, it is necessary to assess their validity to identify patients with higher cardiovascular and metabolic risk.

**Aim:** (1) To validate the use of a number of anthropometric indicators in assessing the cardiovascular and metabolic risk in adolescents. (2) To determine the optimal cutoffs for diagnosis of Metabolic Syndrome (MetS) in this population.

**Methods:** In 678 (348 males) 16.8 ± 0.2 years old adolescents from a follow-up study, body mass index (BMI), waist and hip circumference (WC and HC), total fat mass (%) (TFM), total fat free mass (%) (TFFM), leg lean mass (%) and arm lean mass (%) (DEXA), blood pressure, lipid profile and glucose were measured. Fat mass index (FMI) and Fat-Free Mass Index (FFMI) were estimated according to Wells and Fewtrell. MetS was diagnosed using the IDF criteria. The optimal cutoff value to diagnose MetS was determined using receiver operating characteristic (ROC) analysis.

**Results:** In male adolescents, a WC value of 94 cm showed the best sensitivity (100%) and specificity (94.6%) for diagnosing MetS (AUC: 0.97), followed by a FMI value of 9.7 (AUC: 0.96), TFM value of 28.9% (AUC: 0.95) and a TLM value of 66.1% (AUC: 0.94). In females, a BMI value of 10.8 had the best sensitivity (85.2%) and specificity (78.0%) for diagnosing MetS (AUC: 0.85), followed by a BMI value of 26.3 (AUC: 0.84), a WC value of 85 cm (AUC: 0.84) and a TFM value of 40.9% (AUC: 0.82).

**Conclusions:** In the overall population, WC, FMI and TFM were the best anthropometric indicators for MetS diagnosis. In males the best indicator for MetS diagnosis was WC, whereas in females it was FMI. Funding: NHLBI/NIH (grant nº R01HL088530).
Objective: Assess the impact of low birth weight (LBW) on heart rate variability (HRV), endothelial function (EF), arterial stiffness (AS) and C-reactive protein (CRP) on vascular function in children and to determine its relationship with early markers of cardiometabolic risk.

Methods: Children aged 4 to 6 years with LBW (n = 51) or not (control: n = 31) were studied. Waist circumference, height, weight, blood pressure (BP), glucose, insulin, HOMA index, Quicky, lipid profile and CRP were determined. EF was measured by pulse wave plethysmography evaluating flow-mediated vasodilation. AS was determined by morphology of digital pulse wave. Variability of heart rate (HR) beat to beat (VFC: standard deviation of the interval between beats); spontaneous variability of heart rate (percentage of consecutive beats that differ more than 50%; pNN50) and the product of the maximum HR and SBP (MHRxSBP) were measured.

Results: Although waist circumference, height, weight, systolic BP (SBP) and diastolic BP (DBP) were within the 90th percentile in LBW and control; LBW had higher SBP (p < 0.05) and HR (p < 0.01). Furthermore, insulin, HOMA and Quicky were within normal limits; but in LBW insulin and HOMA were increased and Quicky was decreased. LBW presented increased CRP (control: 0.7 ± 0.2 mg/l vs. LBW: 2.0 ± 0.5; p < 0.029). The EF was decreased in LBW (control: 69 ± 11 vs. LBW: 38 ± 6%; p < 0.01) without changes in AS. Only LBW presented a positive correlation between SBP and DBP and negative correlation between EF and AS. VFC and pNN50 was similar in both groups. MHRxSBP was higher in LBW (control: 9,463 ± 629 vs. LBW: 10,923 ± 409 beat (mm Hg)/min; p < 0.01). Only in LBW a positive correlation between pNN50 with MHRxSBP and a negative correlation between EF with pNN50 and with CRP was found.

Conclusions: Although LBW have anthropometric and biochemical parameters and BP within normal limits, they have SBP increased. The decreased EF supports the hypothesis that these alterations involve endothelium-dependent vasodilator tone more than AS. Endothelial dysfunction would be early associate with a proinflammatory state (increased CRP). Alterations of autonomic control (increase of MHRxSBP and its relationship with pNN50) would be added.
fully monitored by an experienced team and may raise safety issues, especially in a child with co-morbidities. Previous studies aiming to identify risk factors for GHD do not include specific known phenotypes and/or clinical findings that could anticipate GHD.

Objective: To identify risk factors that might predict with high accuracy the presence GHD in children eligible for GHPT.

Patients and Methods: Case-control retrospective study, with clinical chart review of all patients meeting the criteria for GHPT between 2005 and 2014.

Results: Seventy-three out of 364 patients who underwent GHPT had GHD. The presence of history of sellar and/or suprasellar region surgery, one or more anterior pituitary deficiency associated with diabetes insipidus, hypogenitalism in males, neonatal hypoglycaemia or cholestasis, craniofacial midline defects or pituitary dysgenesis by imaging studies showed a positive predictive value of 100% (IC 95% 0.83 to 1.00) to diagnose GHD. Using this proposed group of risk factors in our study population, 21 patients could have been identified as GHD without GHPT (28.8% of GHD patients). There was a strong association between GHD and the existence of at least one of the postulated risk factors (Fisher’s exact test P < 0.0001). The odds ratio for having a risk factor was 238.8-fold higher (95% CI 14.2 to 4005) in the GHD group.

Conclusions: We identified a group of risk factors that predicted GHD with high accuracy. Therefore, in patients with these risk factors, performing GHPT would not be necessary to confirm the diagnosis of GHD.

P55

Growth Rate Ranges for Colombian Children

Llano, J.; Llano, M.

Objective: Growth rate is one of the most important health indicators in children. However, the charts commonly used (Tanner 1967, 1976) are adjusted to north-American population and recently a study by Kelly et al showed differences for the same population. Following the methodology used by Kelly, data from our cohort of healthy children were taken in order to compare results with the three types of puberty and evaluate growth rate concordance between north American and Colombian children.

Design: Descriptive study of healthy children aged 5–19 years in a cohort of school population followed on average 5 years (3–7), with a total of 3888 data for boys and girls 5194, evaluating data in a cohort of school population followed on average 5 years (3–7), evaluating data in a cohort of school population followed on average 5 years (3–7).

Results: Reference ranges (percentiles 3–97) were generated for the entire cohort and the subgroups (average, early and late puberty), comparing dynamic of growth for the entire cohort. We found slower growth velocity compared to Tanner-Davies data. For our cohort, mean growth rate was 6.3 cm/year for men and 5.8 cm/year for girls, which is also lower than published recently by Kelly et al.

Conclusions: The growth in our children show differences compared with north American population, probably explaining differences in final height compared with international growth charts. This differences is presented mainly during puberty, when time of puberty were shorter and leasser growth spurt.

P56

Isolated Growth Hormone Deficiency Owing to a Growth Hormone (GH1) Gene Deletion

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Introduction: Isolated Growth Hormone Deficiency type 1A (IGHD-1A) (OMIM #262400) is an autosomal recessive disorder, with extreme short stature, prominent forehead, small immature facies; absent or very low GH production due to point mutations in the GH1 gene or large deletions within the GH1 gene cluster.

Patients and Methods: We report two patients, brothers from consanguineous parents (father and mother heights: 157.2 cm). Patient 1, 10.5 year old prepubertal boy, born at term (weight 3600 g, length 49 cm) height 88.2 cm (Ht SDS –8.1), BMI-SDS –0.87, head circumference 49 cm, BA 4 years. Patient 2, 14.9 year old prepubertal boy, born at term (weight 3500 g, length 48 cm), height 111 cm (Ht SDS –6), BMI-SDS 1, head circumference 49.4 cm, BA 12 years. Their clinical phenotype includes prominent foreheads, depressed nasal bridge, small immature facies, hypoplastic maxillae and chin and high pitched voice. Both patients were treated with rhGH. They responded during the first months of treatment; however, there was no response thereafter despite good adherence to therapy. The patients underwent complete endocrine and radiological evaluations and genetic testing. The diagnosis of severe IGHD was confirmed and molecular studies were performed with the analysis of the 5 coding exons and their intronic flanking regions by Sanger sequencing. Deletions within the GH1 gene cluster were sought by restriction analyses of PCR products.

Results: The patients have severe GH deficiency (peak GH <0.05 ng/ml), IGF-I levels were 4 and 8.2 ng/ml. Cortisol, PRL, TSH, FT4, serum electrolytes and glycemia were normal. MRI showed hypoplastic anterior pituitary with a normal posterior pituitary and stalk. The molecular studies revealed a homozygous 7-kb deletion encompassing the whole GH1 gene. Their parents were found to be heterozygous for the GH1 deletion.

Conclusion: IGHD with severe growth failure, a positive family history and no response to rhGH therapy should motivate molecular studies that are essential for appropriate genetic counseling.
Short-Term Safety of GH Treatment in Latin American Patients Enrolled in KIGS

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Background: Idiopathic Growth Hormone Deficiency (IGHD), Idiopathic Short Stature (ISS), Turner Syndrome (TS) and Small for Gestational Age (SGA) are the most common indications for growth hormone therapy in childhood. The therapeutic effects and safety profile of GH in these pediatric conditions have been reviewed extensively but sparse data are available for patients treated in Latin America.

Aim: This is a retrospective analysis of the safety profile reported from Latin American children registered in Pfizer International Growth Database (KIGS).

Patients and Methods: Patients registered in KIGS from Argentina, Brazil, Colombia, Mexico, Peru and Venezuela with at least one year of follow up were included in this short-term safety analysis. We assessed the incidence of adverse and serious adverse events (AEs and SAEs) as reported by the investigators.

Children enrolled with IGHD (n = 763, F = 282 (37%), mean age = 10.3 yrs, height SDS = –2.8), ISS (n = 517; F = 257 (50%), mean age = 11.0 yrs, height SDS = –1.9), TS (n = 300; mean age = 10.3 yrs, height SDS = –2.8), and ISS (n = 517; F = 257 (50%), mean age = 10.3 yrs, height SDS = –2.8). Number (%) of girls and boys who were prepubertal at start of treatment were N = 669 (73%) and N = 608 (75%), respectively.

Results: Median treatment duration was 404 days and total treatment duration was 3123 patient-years. Median (10th-90th centiles) GH dose at start of treatment was 39 (24–53) μg/kg/day. Incidence of AEs was 14.8% and of SAEs was 1.7%. The most commonly reported AEs were upper respiratory infections, otitis, injection site reactions, scoliosis, arthralgia and headaches. Endocrine disorders reported as AEs included hyperthyroidism, adrenal insufficiency, thyroiditis and autoimmune thyroiditis (one of each). Hyperglycemia and insulin resistance were reported in 10 cases. Among SAEs of note there was one case each: T1DM, femur (n = 2) and skull (n = 1) fractures, seizures, ventricular hypertrophy, osteonecrosis and ischemic stroke. The last three SAEs occurred in patients with TS.

Conclusion: This study shows that the most common AEs and SAEs were similar to those previously reported from the Global KIGS data analyses. No new unexpected safety signals were reported during this short follow-up. However, there is a need to follow the patients for longer time periods.
P59
Characteristics of a Cohort of Tall Stature Patients
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Introduction: During last years, there is an increasing interest in overgrowth, because new syndromes and new causative genes have been identified. Nevertheless, few patients are referred because they are tall.

Objective: To describe clinical manifestations, differential diagnosis and management in patients with tall stature (TS) who were seen in our institution between 2007–2014.

Materials and Methods: A retrospective medical chart review was done for patients with TS. Data was processed with the SPSS program. TS was defined as Height >2 SD at the first visit.

Results: 147 patients (69 males, 78 females) were referred because of TS. Mean age at first visit was 6, 4 years old. The main diagnosis was obesity (39.24%), genetic causes (26.5%) and familial tall stature (20%), being endocrinological causes, as Precocious Puberty, Somatotropinoma and Hyperthyroidism, less frequent etiology of TS. GH-IGF1 axis was normal in all patients, except in the case of Somatotropinoma. Bone Age was advanced in the majority. None of the patients received any treatment, but reassurance was needed. Obese patients were followed by nutritionists.

Conclusion: TS is usually a benign condition, that requires no treatment. Patients with dysmorphic features, developmental delay, acromegalic features, should be studied in order to detect relevant diseases. In our cohort of patients we did not see the female predominance described in most of the literature. The high frequency of genetic syndromes in our TS patients could be explained because our institution is a Pediatric Tertiary Care Hospital.

P60
Septo Optic Dysplasia: Epidemiological, Anatomical, Ophtalmological and Endocrinological Findings
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Introduction: Septo Optic Dysplasia (SOD) is a rare condition, that present variable clinical presentation, usually with a triad of: 1. optic nerve hypoplasia/aplasia, 2. different degree of pituitary dysfunction, 3. hypoplasia/agenesia of septum pellucidum with or without other midline brain defects.

Objective: To describe the epidemiological, anathomal, ophtalmological and endocrinological findings in 19 patients seen at the Endocrinology Unit during the period 2005–2015

Material and Methods: A retrospective medical chart review was done for patients with SOD. The diagnostic criteria included 2 or more of the triad components.

Results: 19 patients were included. Epidemiological data: Median age at presentation (in months) was 14 (range 0.73–72, with a patient presenting at 11.9 years old). 53% were refered from the pediatric/neonatal units, while the others were derived from neurologists (26%), ophthalmologists (10.5%) and geneticist (10.5%). Median maternal age at conception was 22.6 years (14–38), with 37% being ≤19 years old (vs. 16–20% of adolescence pregnancy rate in our population). Anatomical data: 44.4% had agenesia/hypoplasia septum pellucidum; 27.7% had pituitary hypoplasia; 16.6% had agenesia/hypoplasia Corpus Callosum; 11.1% had ectopic neurohypophysis and 11.1% had schizencephaly. Ophthalmological data: 16/19 had optic nerve hypoplasia, 1/19 had anophthalmia. Endocrinological data: 39% had multiple pituitary deficiency, 33% had isolated pituitary hormone deficiency, (11.1% TSH; 5.5% GH; 5.5% ACTH and 11.1% ADH) and 28% had normal pituitary function.

Conclusion: Septo Optic Dysplasia remains a rare, heterogeneous and phenotypically variable disorder with a progressive course.

As literature refers we agree that young maternal age might be a risk factor for developing SOD.

Regarding endocrinological findings, multiple pituitary deficiency was the most frequent, but it showed a progressive course, so it is important to be aware of the possibility of other deficiencies over time.

P61
Evaluation of Anterior Pituitary Function in Prepubertal Patients Who Had Meningitis
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Introduction: Meningitis is a rare cause of hypopituitarism; in adults they have studied the effects of this infectious process on the hypothalamus and pituitary; the growth hormone deficiency in 28.6% and adrenocorticotropic hormone deficiency in 21% of patients with a history of meningitis have been described; it has been reported that 31% of adults who were infected the central nervous system developed at least one anterior pituitary hormone deficiency; in some cases mild hyperprolactinemia and gonadotropin deficiency diagnosed. Regarding the pediatric population, there are few publications concerning pituitary effects of meningitis.

Objective of Study: To evaluate the anterior pituitary function in prepubertal patients who had meningitis.

Material and Methods: Study of prepubertal patients with a history of meningitis. Variables studied: Age, sex, height and body mass index (BMI) of patients; age at diagnosis of meningitis, cerebrospinal fluid culture (CSF); Plasma levels of thyrotropin (TSH), free thyroxine (FT4), corticotropin (ACTH), cortisol, prolactin (PRL), insulin-like factor 1 (IGF-1) growth. Exclusion criteria: Diagnosis of endocrine disease before the episode of meningitis, malnutrition, obesity, traumatic brain injury, malformation of the central nervous system, anticonvulsant treatment, inhaled corticosteroid therapy and patients with irregular checkups.

Results: Universe investigated, 19 patients; excluded, 5; studied, 14. Age: 8 ± 3.9 years. Sex: 11 males (57.9%). Age at diagnosis of meningitis: 6 ± 3.5 years. Time from meningitis: 1–3 years, 8 patients (57.1%). Size: 0.04 ± 1.1 S.D. BMI: 0.7 ± 0.9 S.D. CSF culture: Streptococcus pneumoniae (6 cases), Haemophilus influenzae type b (5 patients), Staphylococcus aureus (3 cases). Plasma hor-
mone levels: TSH, 2.1 mIU/ml (0.9–3.9), reference: 0.4–4.0 mIU/ml; FT4, 1.1 ng/dL (0.8–1.6), reference: 0.8–1.9 ng/dL; ACTH, 31.1 pg/ml (11.4–43.2), reference: <60 pg/ml; cortisol, 15.8 μg/dl (9.3–22.5), reference: 7–31 μg/dl, PR, 7.7 ng/ml (6.3–13.8), reference: 2.5–14.5 ng/ml; IGF-1, -0.8 ± 1.3 SD.

**Conclusions:** The anterior pituitary function was normal in prepubertal patients who had meningitis.

It is recommended that multicenter studies to assess the levels of pituitary hormones in prepubertal patients who had meningitis.

**P62**

**Clinical Features of Hypothalamic-Pituitary Tumors in Childhood and Adolescence. Pediatric Endocrinology Hospital Pereira Rossell. Universidad de la República. Udelar. Montevideo, Uruguay**

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**Introduction:** Primary tumors of the central nervous system are the second most common malignancy in children and teens. 10–20% belong to the hypothalamic-pituitary (HP) region. Pituitary tumors are rare in childhood and adolescence, with a reported prevalence, one per 1 million. They present by neurological symptoms, producing mass effects on surrounding tissues and the brain: headaches, and/or visual impairment, hormonal overproduction or deficiency, or incidental finding on magnetic resonance imaging (MRI). Those with endocrine manifestation are: a) at childhood: craniopharyngiomas, astrocytomas, gliomas and tumors derived from germ crest, b) in adolescence, pituitary adenomas, of which the prolactinoma is the most prevalent.

**Patients and Methods:** This was an observational, retrospective, descriptive study in Pediatric Endocrinology, period, 2006–2013. We included children and teens from 0 to 18 years with HP tumors diagnosis with alterations of the endocrine system. We analyzed age, sex, clinical presentation, oncotype, size, tumor extension and engagement of pituitary hormones.

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<td>Panhypopituitarism</td>
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**Results:** We found 15 patients with HP tumors, age 14.1 ± 4.1 years, 11 (73.3%) were female. The clinical presentation was 6 (40%) gonadal disorders: amenorrhea/oligomenorrhea, 5 (33.3%) galactorrhea, 3 (20%) central precocious puberty, 3 (20%) overweight and 2 (13.3%) short stature. The entire sample prolactinoma oncotype was the most frequent (60%) and then ACTH-producing adenoma (20%). They presented 11 (73.3%) in adolescence and 4 (26.7) in childhood. Prolactinoma (72.7%) was more frequent in puberty. The mean diameter by MRI was 9 mm in 13/15: 8 microadenomas and five macroadenomas. Regarding insufficiency of pituitary hormones in 14, 43% showed hypogonadotropic hypogonadism, and one hypopituitarism patient.

**Discussion:** HP tumors are rare at this stage in our study female predominated unlike what was reported. As we saw, the incidence of pituitary tumors increases at puberty being the predominant oncotype prolactinoma, which is consistent with the literature. Consequently, gonadal manifestations and microadenoma were predominant. Fifty % showed deficiency of other pituitary hormones with predominance of hypogonadotropic hypogonadism.

**Conclusions:** HP tumors predominated in pubertal female and 70% were microprolactinomas.
they remain relatively rare tumors: approximately 3% of all diagnosed intracranial tumors in childhood are pituitary adenomas. Adenomas produce a variety of hormonal conditions such as hyperprolactinemia, Cushing disease and acromegaly or gigantism. The diagnosis actually is histology and molecular studies genetics perprolactinemia, Cushing disease and acromegaly or gigantism.

Abstracts

P64

Newborn with Microphallus and Nasal Obstruction: A Case of Solitary Median Maxillary Central Incisor Syndrome


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Case Report: We present a newborn with an unremarkable prenatal history who after delivery presents nasal obstruction, dysmorphic features (ocular hypertelorism, arched palate, phallic length less than 2 cm and bilateral cryptorchidism). Choaanal atresia was excluded; the sinus CT scan shows pyriform aperture stenosis related to medial displacement of the nasal process of maxilla.

During the workup he showed cortisol deficiency and low values of gonadotrophins, developing latter a central hypothyroidism and an abnormal response to glaucan stimulation test for growth hormone. No hypoglycemia. The brain MRI reports a small sella turcica, an ectopic neurohypophysis, no adenohypophyseal tissue was observed.

At 5 months of age he received testosterone (3 doses) showing an increment in length and width of the penis, the testes remain undescended, requiring surgical management. At eleven months, his mother reports the eruption of a single central incisor, which related to the previously hormonal deficiencies in the neonatal period and the CT findings, configures the Solitary Median Maxillary Central Incisor Syndrome (SMMC). Currently, he is being treated with a multihormonal treatment (glucocorticoid, levothyroxine, testosterone, growth hormone replacement), he is 4 years old, has a normal neurological development, and his weight and height are in the 3th percentile.

Review: The SMMC is a rare dental anomaly with an incidence of 1:50,000 live births; its occurrence is related to congenital hypopituitarism. It can occur alone or as part to holoprosencephaly spectrum. The etiology is unknown, but it has been associated to missense mutations in SonicHedgeHog SHH gene (7q36).

Patients can be asymptomatic or present nonspecific symptoms like hypoglycemia, apnea, jaundice, cholestasis, convulsions and shock. In some cases can present anatomic anomalies like microphallus, criptorquidism and craniofacial anomalies.

Conclusions: The SMMC syndrome is related to pituitary anomalies, as in this case, the early diagnosis of pyriform aperture stenosis could be the first clue to diagnose this syndrome and rule out the endocrinological anomalies. Congenital hypopituitarism must be suspected, evaluated and treated in these patients in order to decrease morbidity.

P65

Prevalence of Metabolic Syndrome and Insulin Resistance in Premature Infants Small for Gestational Age

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Introduction: Small for gestational age (SGA) is a risk factor for metabolic syndrome (MS) and insulin resistance (IR) in childhood. This can be explained by fetal metabolic adaptations to the low nutrient supply. Nonetheless few studies have been done in prematures.

Objective: To compare the prevalence of MS and IR in school age children with a history of prematurity, less than 36 weeks of gestation and SGA vs appropriate weight for gestational age (AGA).

Material and Methods: A historical cohort study was performed in school children 6–12 years without motor or mental disabilities, birth defects, or systemic diseases such as renal tubular acidosis. Group 1: Premature babies with a birth weight between the 10–90 percentile and Group 2: Prematures with weight less than the 10th percentile. Anthropometric, biochemical and blood pressure evaluations were performed. MS was diagnosed with the modified NCEP ATP II criteria by Cook for children and IR by HOMA IR ≥3.4. Descriptive statistics, mean difference, chi square and odds ratio were done, with statistical significance with p < 0.05.

Results: 205 children were included, 135 from group 1 and 70 from group 2. The prevalence of MS was 13.3% in group 1 vs 7.1% in group 2. There were 23 cases of MS, of which 69.5% occurred in pubertal children with an OR 4.53, 95% CI (1.77–11.6) p < 0.001. IR prevalence was 13.3% in group 1 vs 10.0% in group 2. Of the 25 cases of IR, 64.0% occurred in pubertal children, with an OR of 3.40 95% CI (1.42–8.16) p < 0.004. The three components of MS in order of frequency were: triglycerides >110 mg/dl: 34.1%, HDL cholesterol <40 mg/dl: 32.0%, systolic or diastolic blood pressure >90 percentile: 22.2%.

Conclusion: The prevalence of MS and IR is the same in both groups of premature infants with and without low birth weight, predominating in the puberty stage. Other factors such as the growth rate should be assessed.
P66
Obese Prader-Willi versus Obese Controls: Metabolic Profile in Brazilian Patients
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Background: Prader Willi syndrome is a rare condition (1:15000) that starts with intense hypotonia in the first years of life to reach a condition of voracious appetite which leads to life threatening obesity. The obese Prader Willi syndrome patient (OPWS) has peculiar characteristics which could confer different metabolic profiles compared with obesity of other causes.

The aim of this study is to describe and compare the metabolic profile in obese patients and OPWS patients followed in a Pediatric Endocrinology outpatient unit.

Methods: We evaluated in a cross-sectional study 45 obese patients and 22 OPWS between 8 and 20 years old and compared them according to cholesterol levels, triglycerides, glycated hemoglobin (HbA1c) and fasting glucose.

Results: The mean age of the 67 patients was 14.1 (±3.2) years old, 45 were male and the mean BMI Z SCORE was +3.1 SD (±0.6 SD). Both groups did not differ in sex, age and BMI Z SCORE. The metabolic profile in OPWS versus obese patients showed: high LDL-c level (LDL-c ≥130 mg/dl) in 18.2% X 11.1%, low HDL-c level (<40 mg/dl) in 36.4% X 46.7%, hypertriglyceridemia (≥150 mg/dl) in 13.6% X 24.4%, respectively; Probably due to the low number of patients, there was no significant difference between both groups. However, there was a significant difference (p < 0.001) in abnormal HbA1c (≥5.8%) between OPWS (73.3%) and obese patients (7.1%). Only 1 patient in each group had high fasting BLOOD glucose (>100 mg/dl).

Conclusion: The comparison between obesity in Prader Willi syndrome and in other patients shows that HbA1c tends to be higher in OPWS. The differences in lipid levels show a tendency of more elevated levels in OPWS but the number of patients is small to reach statistical significance.

P67
Laparoscopic Sleeve Gastroectomy in Obese Adolescents: Effects on Bone Metabolism
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Background: Laparoscopic sleeve gastroectomy (LSG) is one of the most effective treatments in patients with severe obesity (SO). Despite routine supplementation of vitamins and minerals, it can implicate in some nutritional deficiencies, which could affect bone metabolism. The aim of this study was to assess the effects of LSG on bone metabolism in obese adolescents.

Methods: We performed a retrospective observational study of 22 adolescents with SO who underwent LSG. All patients were evaluated regarding body size measurements and serum bone metabolism markers. Bone densitometry was performed after the intervention in 11 of them.

Results: The mean weight and BMI before surgery were 127.8 kg and 46.1 kg/m² and 24 months after were 99.6 kg and 36.1 kg/m² (p < 0.05). The mean bone metabolism markers before and after the surgery were, respectively: ionized calcium 1.22 mmol/l and 1.19 mmol/l; parathyroid hormone (PTH) 40.8 pg/ml and 36.6 pg/ml; Vitamin D 22 ng/ml and 26.1 ng/ml (p > 0.05 for all). The mean bone mineral density (BMD) assessed in a mean time of 23.6 months after the surgery was 1.16 Kg/m² at the lumbar anteroposterior spine and 1.31 Kg/m² at the total body (normal values expected for age and gender).

Conclusions: Our results showed that LSG was not associated with bone metabolism changes in obese adolescents.

P68
Prader-Willi Syndrome – A General Picture of 51 Cases
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Introduction: Prader Willi Syndrome (PWS) is the most common genetic cause of obesity. The aim of this study is to describe the morphological characteristics of patients with SPW who have been followed in a Pediatric Endocrinology Outpatient Clinic.

Method: We performed a retrospective study on 51 patients evaluating the age of diagnosis, genetic mutation, use of growth hormone (rhGH), age of beginning of follow-up, and Z-score of weight, height and body mass index (BMI). Data on their first and latest visit to our clinic were compared.

Results: Fifty one patients were analyzed, and the mean diagnosis age was 3.43 (±3.28) years old. The mean age of their first appointment was 4.95 (±4.26) years old and the average time of follow up was 6.45 (±5.24) years. The mean Z-BMI at the beginning and at the latest visit was 2.26 (±2.61 SD) and 2.97 (±1.58 SD), respectively. At the latest visit, their mean age was 11.3 (±6.31) years old and the mean height was Z = –1.41 (±1.52 SD). Eighteen patients have never used rhGH, 15 had it irregularly and 18 regularly for more than 2 years. Genetic diagnosis: 17 of the patients have chromosome deletion, 14 have maternal uniparental disomy. Nineteen patients did only the methylation test.

Conclusion: Despite the early diagnosis of PWS, it is noteworthy the delay between the diagnosis and the start of follow-up, postponing the measures to minimize the weight gain. An adequate coping since the time of diagnosis could introduce the basic concept of the disease in order to avoid obesity and raise adherence to accomplish diet restriction and effective rhGH treatment. SPW is a rare disease that needs specialized attention and a multidisciplinary team struggling to minimize the deleterious effects of obesity, which is the cause of bad quality of life and early death in these patients.
P69

Insulin Resistance and Cardiometabolic Risk Factors in Obese Children and Adolescents

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Introduction: Insulin resistance (IR) is a main factor involved in the development of type 2 diabetes and atherosclerosis. Its complex diagnose during childhood contribute to the recognition of individuals in high cardiometabolic risk. The present study was designed to expose the characteristics of insulin resistance in obese children and adolescents and its relationship with cardiovascular risk factors such as hypertension, dyslipidemia and impaired fasting glucose (IFG).

Methodology: 187 obese children and adolescents with a mean age of 10.5 ± 3.0 years participated in the study. Family history of diabetes, gestational diabetes and impaired birth weight antecedents, weight, height, waist and hip circumference, nigricans acanthosis, pubertal stage, blood pressure, blood glucose, insulin, cholesterol, triglycerides and high-density lipoprotein-cholesterol (HDL-c) were determined. IR was assessed through the insulin resistance index (HOMA-IR).

Results: The prevalence of IR was 63.6%, highest in female than in male obese (p = 0.011). It was associated to puberty (p = 0.015) and the presence of nigricans acanthosis (p = 0.001). Obese children and adolescents with IR showed highest means of waist circumference (p = 0.012), diastolic/systolic pressure (p = 0.019/p = 0.017), and fasting glucose, insulin (p = 0.000) and triglyceride (p = 0.014) plasmatic levels. Impaired fasting glucose (p = 0.001), hyperglycemia (p = 0.041) and low HDL-c (p = 0.032) were more frequent in obese with IR. There was no association between family history of type 2 diabetes, gestational diabetes in mothers or impaired birth weight, and the presence of IR.

Conclusions: IR was related to pubertal development, nigricans acanthosis and the presence of prediabetes and atherogenic dislipydemia in obese children and adolescents.

P70

Metabolic and Cardiovascular Risk in Children with Severe Obesity: Association with Dietary and Physical Activity Habits

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Introduction: The severity in obesity among children and adolescent is associated with an increased cardio-metabolic risk, including type 2 diabetes, ischemic heart disease and hypertension. The prevalence and severity of childhood obesity have quadrupled its prevalence, close relation with drastic changes in the quality of the diet and physical activity (PA).

Objectives: (1) To determine the relationship between the severity of obesity and cardiovascular risk in pediatric population.

(2) To determine the association of dietary and physical activity habits with the magnitude of excess weight after adjusting for confounders.

Methods: Cross sectional study in 516 children and adolescents (210 male), 3 to 16 years, attending an obesity clinic program. Diet and PA (sedentary activities, exercise, active commuting and active play) were self-reported by means of validated questionnaires. BMI and waist circumference were measured. The severity of obesity was assessed by BMI z-score (CDC/USA); values ≥ 4 D.E. were considered severe obesity. Blood pressure (BP), lipid profile, glucose and insulin were measured. The cardio-metabolic risk and metabolic Syndrome (MetS) were diagnosed using Cook criteria. Parental BMI was recorded as well as information on birthweight, breastfeeding, and obesity duration.

Results: Severe obesity was observed in 53% of the sample. Fasting glucose and HOMA-IR were significantly higher in severely obese compared with non-severe obesity. Likewise, prevalence of abdominal obesity, high BP and MetS was significantly higher in patients with severe obesity. Dietary and physical activity habits were significantly less healthy in this group. The association of diet and PA habits with magnitude of obesity was positive and significant. Patients with unhealthy diet or reduced time allocation for exercise showed an increased risk of severe obesity. Extreme birthweight, parental obesity and exclusive breastfeeding duration and obesity duration were also associated with higher risk of severe obesity.

Conclusions: Patients with severe obesity had a cardiovascular and metabolic profile more deteriorated than non-severe obese patients. Magnitude of obesity was associated with quality of dietary habits and time allocation for exercise. Extreme birthweight, parental obesity and exclusive breastfeeding duration and obesity duration were also predictors of severe obesity.

P71

Evaluation of Metabolic Complications in Obese Children

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Introduction: Different metabolic parameters were studied in 93 obese children, in order to determine the same complications could result in this population. The children were between 2 and 14 6/12 1/12 years old.

Material and Methods: Clinical parameters (weight (kg), height (cm), body mass index (BMI)) were evaluated using the formula: weight/height^2 and HOMA (glucemia x Insulinemia/405) index, and laboratory (TSH, free T4, thyroid antibodies (peroxidase (ATPO) and thyroglobulin (ATA)) total cholesterol, triglycerides, HDL cholesterol, insulin, hepatic steatosis assessed by ultrasound.

Results: The average BMI was 26.11% (range 20.00% to 39.00%). Of total insulinemia evaluated (n = 89) were hyperinsulinemic (≥15) 52 children (58.42% average insulin: 30.82); presenting a high HOMA index (≥3) 54 children (60.67%). When comparing levels of TSH, they showed elevated TSH (between 4.2 and ≥10) (all had normal T4 levels free and only 7 positive Ac) 47 children...
Regarding the lipid profile cholesterol (≥160) was found in 38.7% (n = 36) (mean 184, range 160–244); hypertriglyceridemia (≥130) in 29.67% (n = 27) (mean 181, range 130–432). Liver ultrasonography was performed in 38 children being verified steatosis in 14 of them (36.84%); which had steatosis had a BMI two points higher than those with normal ultrasonography (27.25% vs 25.28%). Hepatic steatosis correlated with lipid profile hypercholesterolemia meeting in 42.85%, 35.71% hypertriglyceridemia and decreased HDL cholesterol (≤40) at 57.14%.

**Conclusions:** Childhood obesity determines important metabolic alterations that predispose to target organ damage in the future of these children. More than half presented hyperinsulinemia with high HOMA index that predisposes them to develop diabetes in the future; peripheral thyroid hormones were not altered, but TSH levels. Almost 40% had hypercholesterolemia (as hepatic steatosis) and about 30% had hypertriglyceridemia.

**Results:** Nine patients aged between 8 and 16, of whom 7 were female were selected. The maximum, minimum and median values of TSH of the sample in the first medical visit were 21.05 μIU/ml, 802 μIU/ml and 148.56 μIU/ml, respectively. Ultrasonography was done in all patients, showing the following results: 3 cases of multinodular goiter, 3 cases of solid nodules, 1 case of bilateral cyst, 1 case of micronodular goiter and 1 case of both bilateral cysts and a solid nodule. The minimum thyroid volume was 16 cm³ and the maximum was 72.3 cm³ (median 23.68 cm³). Scintigraphy was done in 8 patients. Of whom 6 had the gland with homogeneous distribution of the radiopharmaceutical and 2 had a heterogeneous distribution. Out of 9 patients who underwent the perchlorate test, 7 had positive results. Fine Needle Aspiration showed 2 cases of papillary carcinoma and 2 cases with benign pattern.

**Conclusion:** The results show the importance of regular evaluation mainly at puberty in order to exclude the presence of any malignancy.
P74

Helicobacter Pylori Infection in Children and Adolescents with Autoimmune Thyroid Disease
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Introduction: In the development of autoimmune thyroid diseases (ETA) – Hashimoto’s thyroiditis (HT) and Graves’ disease (GD) – participate certain environmental factors, including infectious agents have been mentioned, such as Helicobacter pylori (HP).

Objective of Study: To investigate the frequency of HP infection in patients with ETA.

Material and Methods: Study of patients under 15 years of age, diagnosed with ETA. Variables studied: Age, sex, pubertal development and body mass index (BMI) of patients; type of ETA, ETA age at diagnosis, presence of Helicobacter pylori stool antigen – HpSA – (enzyme immunoassay). Exclusion criteria: Antibiotic (previous three months); H2 blockers or proton-pump inhibitor (previous four weeks); duration of less than three months ETA; irregular checkups.

Results: Universe studied, 49 patients with ETA; excluded, 8; studied, 41 patients. Age: 11.8 ± 2.9 years; gender: 36 women (88%); pubertal development: Tanner I, 29 patients (71%); BMI between 10 and 85 percentiles: 35 patients (85.4%). ETA diagnosed: TH, 38 cases; EG, 3 patients. Time since diagnosis of ETA: High to 12 months, 22 cases (53.6%); 6 to 12 months, 14 patients (34.1%); HpSA: Positive test in 35 cases (85.4%): HpSA in 100% of EG (3 patients) and 78% of TH (32 of 38 cases).

Conclusions: A high frequency of HP infection in patients with ETA was evidenced, suggesting the association between the two conditions.

It is recommended multicenter randomized studies to analyze the association between HP infection and ETA observed in this study.

P75

Successful Use of Bisoprolol in Thyrotoxicosis for Grave’s Disease in a Teenager with Acute Asthma
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The most frequent cause of thyrotoxicosis in children and adolescents is Grave’s disease, an autoimmune disorder characterized by diffuse goiter, hyperthyroidism and ophthalmopathy. The cornerstone of treatment are based on the use of antithyroid drugs (derived from thionamides: propylthiouracil, methimazole; β blockers: propranolol, atenolol), radioactive iodine and surgery.

We report the case of a teenager 13 years newly diagnosed with Grave’s disease. Five days after initiated the therapy (methimazole and propranolol), he developed upper respiratory symptoms which complicates with a moderate exacerbation of asthma, associated with signs of thyrotoxicosis. Treatment was started with inhaled bronchodilator (β2 agonist), inhaled anticholinergic, magnesium sulfate and systemic corticosteroids. After this, he developed an exacerbation of cardiovascular symptoms: presenting arterial hypertension, tachycardia, and marked respiratory distress; for arterial hypertension and tachycardia, bisoprolol, an selective β1 blocker, was started with good cardiovascular symptom control.

This case illustrates that the bisoprolol, an selective β1-blocker, associated with a thionamide, can be useful and safe for the initial management of thyrotoxicosis in children and adolescents with a history of previous lung disease such as asthma.

P76

Characterization to Patients with Hyperthyroidism and Treatment with Radioactive Iodine
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Introduction: Main purpose of hyperthyroidism is to correct the metabolic abnormalities without causing untoward effects. First option is antithyroid drugs followed by surgery. However, radioactive iodine is safe and effective. Its is recommended when antithyroid drugs fail or cause allergic reaction.

Table 1. (for abstract P76)

<table>
<thead>
<tr>
<th>Number patients</th>
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<td>Average age</td>
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<tr>
<td>Sex</td>
<td>80% Female; 20% Male</td>
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<tr>
<td>Clinic characters</td>
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<tr>
<td>Exophthalmos</td>
<td>74%</td>
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<tr>
<td>Tachycardia</td>
<td>100%</td>
</tr>
<tr>
<td>Goiter</td>
<td>100%</td>
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<tr>
<td>Hormon levels</td>
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<tr>
<td>Diagnostic</td>
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<tr>
<td>Treatment</td>
<td>Pharmacological 100%</td>
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<tr>
<td>25–30 mCi I13*</td>
<td>33%</td>
</tr>
<tr>
<td>Average of time for use I13*</td>
<td>19.4 Months</td>
</tr>
<tr>
<td>Hypothiroidism</td>
<td>post I13* 100%; Average dose of levotiroxina 110 mcg</td>
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</tbody>
</table>
Materiales and Methods: We describe 15 patients with hyperthyroidism (Graves or thyroiditis) which consulted at Fundacion Clinica Infantil Club Noel between January 2009 and December 2014. See tables 1, 2.

Analysis and Conclusions: Thyroid disease is the most prevalent in female adolescents. Besides, antithyroid drugs, we treated 33% of our patients with I\textsubscript{13}. Patients included Down syndrome (two) an associated cardiomyopathy and 3 for unresponsiveness to antithyroid drugs. Response was excellent.

### Table 2. (for abstract P76)

<table>
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<tr>
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<tr>
<td>Female</td>
<td>80%</td>
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<td>80%</td>
</tr>
<tr>
<td>Tiroiditis</td>
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<tr>
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<td>Pharmacologic</td>
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<tr>
<td>25–30 mCi I\textsubscript{13}*</td>
<td>33%</td>
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<td>Mean follow-up I\textsubscript{13}*</td>
<td>19.4 Months</td>
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<tr>
<td>Hypothyroidism currently</td>
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</tr>
<tr>
<td>post I\textsubscript{13}</td>
<td>100%</td>
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<tr>
<td>Levotyroxine dose</td>
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<tr>
<td>post I\textsubscript{13}</td>
<td>110 mcg</td>
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</table>

Materials and Methods: Observational study, using data of the Neonatal Screening Program of the State of Minas Gerais (PTN-MG) and clinical and laboratorial data of a patient, who suffered from congenital transient hypothyroidism and suffocation due compression of airways born to a mother with Graves’ disease.

Results: Patient I.C.M.C, 3 years old, female. Mother had been diagnosed with Graves’ disease for more than 5 years with inadequate treatment. At birth, patient presented goiter with suffocation, needing emergency surgery. The ultrasound revealed increased volume the thyroid, without alterations in the gland’s texture. Laboratorial exams in the day after the birth revealed blood levels of total T\textsubscript{4}=5.6 mcg/dL and TSH = 44.2 mcUI/mL consistent with congenital hypothyroidism. L-T\textsubscript{4} supplementation (37.5 mcg/day) was initiated, with new exams performed 14 days after birth, revealing decrease in the thyroid hormones blood levels (FT\textsubscript{4} = 1.7 ng/ml). The TSH = 0.49 mcUI/ml; TRAb = 9.37 mUI/mL and thyroid peroxidase antibody = 159 mUI/mL. In the first consultation in the reference service at 1 month old, the L-T\textsubscript{4} supplementation was decreased to 25 mcg/day, being suspended at 2 months old, with blood levels of FT\textsubscript{4} and TSH remaining in the reference range throughout monitoring. The last exam at 8 months old showed levels of FT\textsubscript{4}, TSH and TRAB of 1.06 ng/dl, 0.55 mcUI/ ml and 0.92 UI/ml, respectively. During the patient monitoring, multiple ultrasounds were performed, revealed increased volume without alterations in the texture of the gland.

Conclusions: Children born to mothers with untreated or inadequately treated Graves’ disease need careful monitoring of thyroid function and thyroid imaging, so that they can receive the most appropriate diagnose and treatment, thus preventing the harmful consequences of a thyroid dysfunction, which can lead to losses in the brain development during pre- and early postnatal life.

P77

Evolution of Neonatal Goiter in Children Born to Mother with Graves’ Disease – Case Report


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Introduction: Maternal antithyroid drugs and thyrotropin receptor blocking antibodies (TRAb) are the most common cause of transient hypothyroidism in newborns. Untreated maternal Graves’ disease can lead to transient fetal hyperthyroidism or transient hypothyroidism in neonates, bringing a risk of serious complications such as asphyxia due to obstruction of airways, thyroid tissue disintegration and inability of maintenance of euthyroidism.

P78

Etiological Distribution in the States Macro-Regions of Congenital Hypothyroidism Diagnosed by the Newborn Screening Program of the State of Minas Gerais (PTN-MG) in 1997 to 2007

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Introduction: The prevalence of primary congenital hypothyroidism (CH) is of 1 in every 3,000 to 4,000 live births. The etiology of the disease can be classified into three groups: thyroid formation defect (dysgenesis); hormone synthesis defect (dys hormonogenesis) and transient hypothyroidism. The PTN-MG was implemented in the state of Minas Gerais in 1993. A health regionalization system has been established in Minas Gerais since 1960, called Regionalization Plan of Health and includes micro and macro-regions, that provide secondary and tertiary assistance. The 13 health macro-regions are: Central, South Central, Southeast, South, East, South-East, West, North, Northeast, Northwest, Jequitinhonha, South Triangulo and North Triangulo.
Method: Retrospective observational study, using the PTN-MG data in the period between 1997–2007. Free T4 and TSH measurement was made by chemiluminescence. The ultrasound evaluated the gland volume and the presence of nodules. The scintigraphy with radioactive iodine ($^{131}$I) was used to identify functional thyroid tissue. The perchlorate test was done in patients after administration $^{131}$I and its uptake was calculated 2 hours later.

Results: The types of etiologic CH found in 704 children was dysgenesis with a frequency of 44.3%, followed by dyshormonogenesis in 16.8% andTransient hypothyroidism (1%). In dysgenesis group, Hypoplastic thyroid with 22.4% and the Ectopic thyroid with 11.1% stood out. In the dyshormonogenesis group, the Thyroxidase defect predominated (9.2%). It was not possible to reach an etiological diagnosis in 37.9% of patients, because there were normal glands at the scintigraphy or at the ultrasound. It was noticed that the three main etiologies were prevalent in most macro-regions with the exception of macro-regions Central-South and Jequitinhonha regions where the athyreosis appeared with 22.2% and 21.4%, respectively.

Conclusions: Among the children screened for CH by PTN-MG the prevalent etiology was first dysgenesis and the next dys-hormonogenesis. It was observed that in a considerable percentage of cases it was not possible to obtain the etiological classification through both scintigraphy and ultrasound. New studies are necessary to evaluate the factors that may be involved in the distribution of the CH etiology in the state.

O-6.1 Oral Session 6.1

O51 Neonatal Screening Program for Central Congenital Hypothyroidism


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3 Hôpital Conception, Laboratoire de Pathologie Moléculaire, Marseille, France; 4 Hôpital Timone, Service de Pédiatrie Multidisciplinaire, Marseille, France; 5 Hôpital Conception, Service d’Endocrinologie, Diabète et Maladies Métaboliques, Marseille, France

Background: Congenital hypothyroidism (CH) is a heterogeneous entity that includes disorders of the hypothalamo-hypophyseal system. The latter are missed on TSH based screening programs leading to increased morbidity and mortality. Additional T4 determination allows an early detection of CH of central origin (CH-C).

Aim: To report the findings of a neonatal screening program based on determination of TSH and T4 for early detection of CH-C.

Population and Methods: From June 2014 to June 2015, 37045 Argentinean term newborns aged 2–7 days were included. Screening was carried out with TSH (IFMA Delfia; cutoff 10 mU/L) and T4 [FIA Delfia, cutoff 4.5 µg/dL (–2.3 SDS)] in filter paper blood samples. Infants suspicious of CH-C were referred to a pediatric endocrinologist. They underwent a thorough clinical assessment and determinations of serum TSH, T4, FT4, T3, thyroglobulin, antithyroid-antibodies, cortisol, GH, prolactin, LH, FSH and testosterone (boys). Serum TBG was measured in patients likely to have hypothyroidism. Brain imaging and studies of transcription factors involved in hypophyseal development were performed (France).

Results: Twenty-three (1:1610) infants had primary hypothyroidism (TSH 10.4–100 mU/L). Twenty four patients with only low T4 were recalled. Fourteen of these had transient hypothyrominemia (13 non-thyroidal illness; 1 healthy). One additional multiformalated patient died at 3 days of life. Five boys had hypothyroidism (mean T4 2.6 µg/dL; TBG 15.5 µg/dL). Three per cent had permanent CH-C (mean T4 3.9 µg/dL) due to a hypothyroid-hypophyseal disorder (1:12348) and had not been discharged due to morbid conditions (one hypernatremia; two hypoglycemia). All of them had combined pituitary hormone deficiency. MRI showed midline defects (n = 2); LHX4 and HESX1 mutations were excluded. POU1F1 heterozygous mutation (c.811C>T, p.Arg271Trp) was found in one patient. One additional patient normalized T4 but remained with isolated ACTH deficiency. Hormonal replacement was instituted at a mean age of 12.2 days.

Conclusions: T4 determination allowed us to identify CH-C as a prevalent condition and to detect T4 transport defects. It is important to highlight that this screening strategy requires an experienced specialist to confirm the diagnosis of CH-C as well as to rule out transient disorders with low T4. In CH-C infants, the detection of other life-threatening hormone deficits facilitated a timely treatment preventing major morbidity.

O52 Analysis of the MKRN3 Promoter Region in Patients with GnRH-Dependent Pubertal Disorder


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Background: Loss-of-function mutations in the coding region of the imprinted gene MKRN3 have recently been recognized as an important cause of familial central precocious puberty (CPP). The 5′untranslated region of MKRN3 is notable for potential transcription factors motifs.

Objective: To investigate potential pathogenic variants in the promoter region of MKRN3 in patients with GnRH-dependentPubertal disorders.

Patients and Methods: We studied 89 patients with GnRH-dependent pubertal disorders: 61 with idiopathic CPP and 28 with constitutional delay of growth and puberty (CDGP). Family history of precocious or delayed sexual development was presented in 25% and 29% patients, respectively. Inactivating mutations in
the coding region of MKRN3 were excluded in all patients. The control group consisted of 40 Brazilian individuals with normal pubertal development. Genomic DNA was extracted from leukocytes of the peripheral blood and a 1000 pb region (~750 to +350) of the MKRN3 promoter region, including the recognition sites for potential transcription factor motifs (PEA3, SRE, SRF, C/EBP, AP2, testis-R), was amplified and automatically sequenced.

Results: We identified a novel variant, c.-150_147delTCAG, in the promoter region of MKRN3 in a female patient with idiopathic CPP, who started pubertal development at 7.5 years. Her mother had menarche at 10 years and was wild-type for this variant. No other members were affected in this family. DNA from the father and 2 brothers were not available. Other rare variant, g.23565509T>A (rs182933790), in the promoter region of MKRN3 was detected in a girl with pubertal onset at 6.6 years. The minor allele frequency of this variant was <0.01% in the databases (Ensemble, 1000 Genomes), indicating that it is a very rare nucleotide change. However, this variant was also identified in a control individual and in one male patient with CDGP, suggesting lack of genotype-phenotype correlation.

Conclusion: A novel heterozygous deletion was identified in the promoter region of MKRN3 in a girl with idiopathic CPP. The impact of this variant in MKRN3 expression is still unknown and further studies will be necessary.

O53

A Novel OTX2 Mutation, P.H230L, Causes Hypopituitarism with Incomplete Penetrance: Exome Sequencing to Identify Modifier Genes

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1Hospital das Clínicas, Medical School, University of São Paulo, São Paulo, Brazil; 2University of Michigan, Ann Arbor, USA

Introduction: Mutations in the transcription factor OTX2 cause variable and incompletely penetrant effects on craniofacial development that can include the eyes, hypothalamus, and pituitary gland. Mouse studies demonstrate that genetic variation in multiple loci can suppress or enhance the features associated with Otx2 dysfunction, but the genes underlying these loci are unknown. Multiple pieces of evidence support the idea that hypopituitarism results primarily from the critical role of OTX2 in the development of neural ectoderm that gives rise to the hypothalamus, pituitary stalk, and neurohypophysis. In the literature only one mutation p.N225S in OTX2 was described in two unrelated patients associated with hypopituitarism and no eyes abnormalities.

Material and Methods: Sanger sequencing of OTX2 was performed in a proband with hypopituitarism (GH, TSH, LH/FSH and ACTH deficiency), polydyactyly, and no eyes abnormalities from a large Brazilian pedigree with 4 unaffected siblings. The exome sequencing was performed in the trio (patient, mother and father).

Results: A novel allelic variant in OTX2 (p.H230L) was found in heterozygous state. The histidine is conserved across all vertebrate species and in silico analyses predict that the leucine substitution is deleterious. The proband’s mother is a p.H230L carrier with short stature (~2.4 SD), and 2 unaffected siblings are carriers with normal stature (sister ~1.7SD, brother ~0.4 SD). All of these individuals have normal basal pituitary hormone levels suggesting incomplete penetrance. We carried out exome sequencing in the trio to identify variants in other genes that could contribute to the proband’s phenotype. No deleterious variants were detected in obvious candidate genes for hypopituitarism and allelic variants in DMXL2 and ASH1L, predicted as deleterious, were found in the father and the proband but they did not segregate, by Sanger sequencing, with the phenotype in the pedigree.

Conclusion: In the present study we were not able to identify modifier loci through the exome that influence the effects of OTX2 variation on normal pituitary and craniofacial development and exome sequencing of other large families with incompletely penetrant effects of OTX2 mutations could help to identify them.

O54

Risk Factors Associated with Obesity in Children Aged 3 to 5 Years Old

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Introduction: Obesity is a chronic disease caused by multiple factors that involves genetic and environmental factors. Daily consumption of high-calorie food and low physical activity are the most important factors for the dramatic increase in childhood obesity. In order to identify risk factors associated with obesity in early ages of life, where preventive measures could be taken, we evaluated the association between obesity in children aged 3–5 years with the lunchbox calorie content, the daily diet habits, daily physical activity and parent’s history of obesity.

Material and Methods: We included 114 children (57 M/57 F) aged 3–5 years old: 38 cases with overweight or obesity (according to WHO: BMI ≥2 SD), 76 controls (BMI ≤2 SD to –1 SD) matched for age and sex. The energy content of each lunchbox was calculated. We considered a ‘healthy lunchbox’ if the calorie content was 250 kcal. Weight, height, BMI, BMI z-score were evaluated. We interviewed parents through a structured and validated questionnaire of the daily consumption of sugar-sweetened beverages, snacks (including candies, cookies, chocolate, and cakes), fats and vegetables, the number of days of physical activity more than 30 minutes per week, the number of days watching TV and video games for more than 2 hours per week and parent’s history of obesity. Shapiro Wilks test, Student T, chi-square, and logistic regression were performed. p < 0.05 was considered significant.

Results: We found that 76.3% lunchboxes (87/114) contained more than 250 kcal. The analysis for each risk factor showed significant association with lunchboxes ≥245 kcal (OR = 2.92, 95% CI: 1.2–7.3, p = 0.022), physical activity per 30 minutes 0–1 day
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(OR = 2.49, 95% CI: 1.0–6.0, p = 0.042), maternal obesity (OR = 2.5, 95% CI: 1.2–7.2, p = 0.014) and the estimated risk adjusted for age and sex showed significant association with lunchboxes ≥425 kcal (OR = 3, 95% CI: 1.2–7.2, p = 0.014) and physical activity per 30 minutes 0–1 day (OR = 2.67, 95% CI: 1.1–6.3, p = 0.027).

Conclusions: Three quarters of the population studied had lunchboxes with energy content above the recommended standard. Obese children were exposed to higher-calorie lunchboxes and performed less physical activity.

O55
Laparoscopic Sleeve Gastrectomy in Adolescents: A Safe and Effective Treatment
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Background: Severe obesity (SO) among adolescents, defined as BMI ≥95th percentile, has dramatically increased worldwide. The immediate and long-term risks associated with SO in adolescents include cardiovascular diseases and metabolic disturbances. The results of laparoscopic sleeve gastrectomy (LSG) for the treatment of SO in adolescents are still uncertain. We aimed to assess the long-term safety and efficacy of LSG in adolescents with SO.

Method: We performed a longitudinal retrospective study which included 23 adolescents with SO who underwent LSG. Clinical and metabolic variables immediately before surgery and after 6, 12, 18 and 24 months were assessed.

Results: Seventeen females and six males between 13 and 18 years old were followed—up for a mean of 24 months. At the initial evaluation, mean BMI was 44 kg/m² and mean weight was 120 kg. The 6, 12 18 and 24-month mean BMI and weight were, respectively, 35.1, 34.9, 34.3 and 37.4 kg/m² (p < 0.0001), and 97.1, 96.6, 95.2 and 102.3 kg (p < 0.001). Type 2 diabetes, insulin resistance, dyslipidemia, hypertension and hepatic steatosis improved at 24 months of follow-up compared to prior surgery status (p < 0.05). Despite weight regain, metabolic improvements remained stable. One patient presented with unexplained iron deficiency anaemia during the follow-up. No other complications were observed.

Conclusion: LSG in adolescents with SO seems to be a safe and effective procedure associated to weight and BMI loss and resolution of comorbidities in the first two years.

Table 1. (for abstract O56)

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Café au-lait spots</th>
<th>Gamma graphy</th>
<th>PPP Mutation arg 201</th>
<th>Pelvic usg</th>
<th>Fibro-dysplasia</th>
<th>Other</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Female</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>Cyst</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>+</td>
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<td>–</td>
</tr>
<tr>
<td>12</td>
<td>Female</td>
<td>+</td>
<td>–</td>
<td>Pending</td>
<td>Cyst</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Cyst recurrent</td>
<td>+</td>
<td>Hyperthyroidism</td>
<td>thyroidectomy</td>
</tr>
<tr>
<td>1</td>
<td>Female</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Cyst recurrent</td>
<td>Hyperthyroidism, gigantism</td>
<td>Alendronate octeotride</td>
<td>methimazole</td>
</tr>
<tr>
<td>7</td>
<td>Female</td>
<td>+</td>
<td>+</td>
<td>Pending</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>Osteoprosis</td>
</tr>
<tr>
<td>7</td>
<td>Female</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

PPP = Precoz puberty peripheric; + = yes; – = no.
with aromatase inhibitors, GnRH analogues or biphosphonates have not been helpful in all cases in the literature, but the diversity of evolution and treatment is presented in our patients.

**057**

**Gene Founder Effect: The Underlying Mechanism of Recurrent IGFLS Mutations**

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**Background**: In ALS-deficient patients, some IGFLS variants have been reported in more than one family, raising the question whether they originated from a single common ancestor allele (founder effect) or alternatively, as independent mutational events (hot spot). Since c.103dupG (p.E35Gfs*17) is located in a stretch of 5 consecutive guanine residues, where both G-duplication and deletion have been described in several families, we speculate that this region could be a hot spot. In contrast, c.[1225C>T;1424C>T] (p.[L409F;A475V]) variants, both present in the same allele in two unrelated families, could result from a founder effect.

**Objective**: To test the hypothesis of hot spot vs. founder effect by studying polymorphic variants surrounding IGFLS gene and uniparental lineage markers in families harboring the c.103dupG and c.[1225C>T;1424C>T] variants.

**Methods**: We sequenced the IGFLS gene (2 exons and intron 1 plus 900 and 40 bp flanking exon 1 and 2, respectively) and characterized 2 flanking STRs in 30 individuals from 6 families, 4 of them carrying the c.103dupG (9 heterozygous individuals) and 2 families harboring the c.[1225C>T;1424C>T] variants (3 homozygous and 8 heterozygous individuals). Nine informative SNPs and the 2 STRs were used to define the specific haplotype associated to the 2 STRs were used to define the specific haplotype associated to the mutation (D16S3435/9 SNPs/D16S3024). In addition, paternal and matrilineal lineages were analyzed by means of 23 Y-STRs typing and mtDNA-D-Loop sequencing.

**Results**: The four families carrying the c.103dupG variant presented the same STRs and SNPs microhaplotype (CA)12/gtcgggtgcc/(CA)21. On the other hand, the c.[1225C>T;1424C>T] carriers of the two remaining families shared a common microhaplotype (CA)15/acgaaccgt/(CA)22 or (CA)23, differing only in one repeat in D16S3024 between the two families. Phylogenetic analysis revealed that all male lineages can be attributed to European or Eurasian haplogroups (50% E1b1b; 33% R1b and 17% Q) while mtDNA lineage belonged to Native American (56%), African (22%) and European (22%) haplogroups.

**Conclusion**: Based on the number of families studied, the finding of two particular microhaplotypes support the hypothesis of a founder effect for both variants, c.103dupG (p.E35Gfs*17) and c.[1225C>T;1424C>T] (p.[L409F;A475V]); each originating from two independent mutagenic events occurring in two different ancestor alleles.

**058**

**Molecular and Functional Characterization of the Novel Mutation C.2335-1G>C in the Human DUOX2 Gene Responsible of Iodide Organification Defects**

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**Introduction**: Iodide Organification defects (IOD) represent 10% of cases of congenital hypothyroidism (CH) being the main genes affected that of thyroperoxidase (TPO) and Dual Oxidasa2 (DUOX2).

**Subjects and Methods**: From a population of 20 patients with clinical and biochemical criteria suggestive of CH associated with IOD (high serum TG and high levels of serum TSH with simultaneous low levels of circulating thyroid hormones) TPO and DUOX2 genes were analyzed by means of PCR-SSCP and sequencing. Splicing mutations were analysed by bioinformatics using the NNSplice program and were functionally characterized by means of minigenes.

**Results**: A novel heterozygous compound to the mutations c.2335-1G>C (intron 17) and c.3264-3267delCAGC (exon 24) was identified. Exon 18 of DUOX2 gene was amplified together with the intron flanking regions from genomic ADN of our patient and cloning, both alleles (WT and mutant) in pSPL3 vector. HeLa cells were transfected with wild-type, mutant, and control pSPL3 and the resulting fragments were evaluated by RT-PCR and sequencing. The mutation c.2335-1G>C created a new or activated an existing unusual cryptic donor splice site in intron 17 located at position –14 of the authentic intron 17-exon 18 junction site. Additionally, ‘exon skipping’ and cryptic 5’activation in exon 18 were determined.

**Conclusions**: A novel heterozygous compound was characterized being responsible of IOD. Cryptic splicing sites have been identified in DUOX2 for the first time. The use of molecular biology techniques is a valuable tool for understanding the molecular pathophysiology of this type of thyroid defects.
Analysis of Children with Congenital Hypothyroidism Detected by Neonatal Screening Program

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Introduction: Screening neonatal programs show a wide variation in the incidence of congenital hypothyroidism (CH) along the years. The aims were: – To up-to-date CH incidence and describe etiology, associated malformations and Down Syndrome (DS) in CH children detected by neonatal screening program, – to search differences between permanent CH (PCH) and transient forms (TCH).

Material and Methods: We analyzed every newborn (NB) with positive screening results for CH referred to our confirmation center between 1995 and 2013. CH was confirmed with TSH ≥30 uU/ml and T4 <10 ug/dl. Two periods were analyzed: 1995–2004 (P1) and 2005–2013 (P2). Incidence was calculated in each period. We described associated malformations and DS. At three years of age, CH children were reevaluated to distinguish between PCH and TCH patients with eutopic thyroid gland. Statistical analysis: Student’s and Mann Whitney tests were used for continuous variables and Kruskal Wallis test for comparison between groups.

Results: Of 2,889,819 evaluated NB, 1,331 were confirmed (F:M, 2:1). They were treated with a mean LTd of 12.43 ± 2.12 ug/kg/day. Median age at diagnosis was 18 (14–26) days. CH incidence was 1:2.171 (P1 = 1:2.425, P2 = 1:1.969). Twenty-three CH children had DS. Associated malformations were 27 congenital cardiac defects, 10 DS, 8 genitourinary, 8 intestinal, 9 neurological and 4 skeletal anomalies. Of the total group, 675 children were reevaluated. Thirty-one (4.6%) had TCH and 644 (95.4%) were PCH. Etiologies of PCH forms were: athyreosis 161 (23.9%), eutopic disgenetic gland 368 (54.5%), eutopic disgenetic gland 14 (2.1%), and eutopic thyroid gland 132 (19.5%). Patients with eutopic thyroid gland showed TCH forms in 31 (23.5%) cases. LTd was the only variable that showed significant differences between PCH and TCH patients with eutopic thyroid gland (p < 0.0001).

Conclusions: 1- Last years’ CH incidence has increased in this program. 2- Associated malformations were found in 3.45% of these CH patients. 3- Transient CH forms showed a low frequency. 4- CH patients who required lower LTd at reevaluation were likely to have TCH forms.

Prevalence of Helicobacter Pylori Infection and Its Association with Thyroid Autoimmune Disease in Childhood and Adolescence

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Introduction: The interaction between genetic susceptibility and environmental triggers seems to be of fundamental importance in the development of autoimmune thyroid disease (ATD). The association between Helicobacter pylori (HP) infection and ATD is controversial. Some reports suggest higher prevalence of HP infection in adult patients with ATD. This association has been rarely reported in pediatric groups. The aim of this study was to evaluate the association between HP infection and ATD in childhood.

Material and Methods: Cross-sectional study of 142 patients, 1–19 years old, followed up at the Pediatric Endocrinology Service at a University Hospital: 27 with Hashimoto’s thyroiditis (HT), 9 with Graves’ disease (GD) and 106 with congenital hypothyroidism (CH). HP infection was diagnosed by using the 13C-urea breath test (13C-UBT). Thyroid function was assessed by TSH, FT4 and FT3 levels (ICMA). The evaluation of anti-thyroid antibodies – anti-thyroid peroxidase (anti-TPO), anti-thyroglobulin (anti-Tg) and anti-TSH-receptor (TRAb) – was done by ICMA and ECLIA methods. Data were evaluated using SPSS software. A p value <0.05 was considered statistically significant.

Results: The prevalence of HP infection in children with CH was higher than in ATD group (34.9% vs 19.4%), but without statistical significance (p = 0.08). Among patients with ATD, the H. pylori infection was neither associated with serum TSH levels (p = 0.20), FT4 (p = 0.09) and FT3 (p = 0.24), nor with levels of anti-TPO (p = 0.34), anti-Tg (p = 1.00) and TRAb (p = 0.65) antibodies. In patients with CH, no difference was found between H. pylori-positive and negative patients regarding TSH (p = 0.26) and FT4 scores (p = 0.20) and anti-TPO (p = 0.12) and anti-Tg (p = 1.00) antibodies. TRAb was not detected in all CH patients, being infected or not. There was a negative association between elevated FT3 and HP infection (p = 0.002), which remained after adjustment for age (p = 0.04).

Conclusions: HP infection was not associated with ATD in pediatric patients: they present neither a higher prevalence of infection, nor the ones infected with HP showed a higher frequency of anti-thyroid antibodies or altered thyroid function.
**O61**

**Thyroid Hydatid Cyst in Children: Case Report**  

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**Introduction:** Human Hydatidosis is a disease caused by echinococcus granulosus larvae. Its main location is in the liver and lungs, other organs involved such as the thyroid gland are rare, specially in children.

**Objective:** To describe a patient of 10 years old, seen at the Endocrine Unit with a tumour in the neck, with final diagnosis of Thyroid Hydatid Cyst.

**Discussion:** A 10 years old boy, from a suburban area, previously healthy, consulted for a mass in the anterior neck since 6 months ago. Clinically euthyroid, with a palpable round mass, firm in consistency, in left thyroid lobe. Thyroid scintigraphy showed a non-function nodule at the left lobe. Ultrasound described a cystic nodule of 41 x 40 x 33 mm, well defined and hypoechoic, so it was subjected to a fine needle aspiration, obtaining clear fluid, without cells. Lab workup showed eosinophilia. The tumor was surgically removed, and subsequently pathological examination confirmed the diagnosis of thyroid hydatid cyst. Following surgery he was treated with Albendazole orally and 1 year after, he remains asymptomatic.

**Conclusion:** Nodules in the anterior neck, could be caused by a variety of etiologies. Thyroid Hydatid Cysts are very rare. Argentina is an endemic country for Hydatidosis, more frequently in rural areas. It is important to keep suspicion of Hydatidosis in children with thyroid nodules, even though they live in urban or suburban areas, specially if they have eosinophilia and compatible ultrasound features.

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**O62**

**Fundacion de Endocrinologia Infantil (FEI): 30 Years of Experience in Newborn Screening**

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Fundacion de Endocrinologia Infantil (FEI), Caba, Argentina

**Introduction:** In August 1985, FEI started with a Neonatal Screening Program for Congenital Hypothyroidism (CH) and Phenylketonuria (PKU). Neonatal screening for Cystic Fibrosis (CF) Galactosemia (GAL) and Congenital Adrenal Hyperplasia (CAH) were begun in 1997, Biotinidase Deficiency (BD) in 2006 and Leucinosis (MSUD) in 2013.

**Objective:** To communicate the results of the FEI neonatal screening program during the period 8/1985-5/2015.

**Methods:** Screening was performed in dried blood spot samples obtained by newborn heel prick between 36 hours and 7 days of life. Biochemical markers for detection were: 1) CH: TSH with Delfia-IFMA assay from 1997 to 2003 (cutoff 15 mU/L) and 10 mU/L onwards (double sample strategy in prematures <33 weeks of gestational age (GA)). 2) PKU: Phenylalanine with fluorometric assay since 1990 (cutoff 2.5 mg/dl) 3) CF: Immunoreactive trypsin IRT (Delfia –IFMA) with cutoff adapted for GA and chronological age 6) BD: Biotinidase activity (colorimetric method). 7) MSUD: Branched chain amino acids (enzymatic colorimetric assay) for MSUD (cutoff 4 mg/dl).

The Program included the confirmation procedures in the detected newborn and started treatment in those affected continuing their follow up or referring them to the respective specialist.

**Results:** The table shows the detection results. Mean age of sampling was 3 days and treatment was indicated timely.

**Conclusion:** Detection was carried out properly with adequate parameters of analytical performance. Our screening program as conceived, was responsible for the confirmation and appropriate treatment of the screened newborn preventing the deleterious consequences inherent to these diseases. Moreover, our data provide information about the incidence and characteristic of these diseases in our country.

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**O63**

**TRH Test Utility for Primary Hypothyroidism**

**Diagnosis in Pediatric Patients**


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**Introduction:** There are many controversial issues about utility and cost–benefit of TRH stimulation test (TRHTest) for diagnosing subclinical primary hypothyroidism (SPH). The objectives were: 1. To evaluate diagnostic utility of TRHTest in SPH patients, 2. To analyze whether TRHTest could be avoided with a second

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**Table 1.** (for abstract O62)

<table>
<thead>
<tr>
<th>Disease</th>
<th>CH</th>
<th>PKU</th>
<th>CF</th>
<th>CAH</th>
<th>GAL</th>
<th>BD</th>
<th>MSUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of samples</td>
<td>1,483.976</td>
<td>1,494.142</td>
<td>576.994</td>
<td>467.378</td>
<td>475.559</td>
<td>391.056</td>
<td>19</td>
</tr>
<tr>
<td>Detected</td>
<td>744</td>
<td>124</td>
<td>93</td>
<td>40 (2/3 salt wasting)</td>
<td>19</td>
<td>3</td>
<td>–</td>
</tr>
<tr>
<td>Recall rate</td>
<td>0.59%</td>
<td>0.12%</td>
<td>0.51%</td>
<td>0.55%</td>
<td>0.012%</td>
<td>0.02%</td>
<td>0.27%</td>
</tr>
<tr>
<td>Diagnostic efficiency</td>
<td>0.13</td>
<td>0.02</td>
<td>0.05</td>
<td>0.011</td>
<td>0.34%</td>
<td>0.075</td>
<td>–</td>
</tr>
</tbody>
</table>
TSH determination, 3. To determine a TSH cut-off point according to Specificity (Sp) and Sensitivity (Sn).

**Material and Methods:** One hundred and twenty-five patients (M:54, F:71), with a median age of 9.0 (0.25–16.0) years, were evaluated retrospectively. TRH test was performed in patients who evidenced basal TSH >5 uU/ml and clinical symptoms or family medical history of thyroid disease. They were injected intravenously with 7 mcg TRH/kg (maximum 200 mcg). Basal TSH (TSHb) and post TRH values (at 25, 60 and 90 minutes) were determined through Chemiluminescence Immunoassay method. Serum TSH25' ≥25 uU/ml was considered as hyperresponsiveness to the TRH test. TSH level that defined the test request and a second determination (TSHb of TRHtest) were compared. TSHb of TRHtest was used to determine a TSH cut-off point according to Sn and Sp. Paired samples t Test (p < 0.001, as significant) and ROC curve analysis (Sn vs 1-Sp) were used for statistical analysis. In this case, the criterion applied was to obtain maximum Sn and Sp.

**Results:** Out of the 125 patients tested, 46 showed hyperresponsiveness (36.8%) and 79 showed normal response (63.2%). No significant differences were found between TSH level that defined the test request and TSHb of TRHtest. According to ROC curve analysis, with TSHb ≤4 uU/ml (52 patients) (Sn = 92.3% and Sp = 61.5%) only 4 (7.7%) showed hyperresponsiveness. With TSHb ≥7.5 uU/ml (24 children) (Sp = 87.5% and Sn = 44.7%), only 3 (12.5%) showed normal responsiveness. With TSHb levels between 4 and 7.5 uU/ml (49 patients), 28 (57.1%) showed normal responsiveness and 21 (42.9%) had hyperresponsiveness.

**Conclusion:** TRH test should not be performed when a second basal TSH is equal or lower than 4 uU/ml and equal or higher than 7.5 uU/ml. When TSH value is between 4 and 7.5 uU/ml, TRH test could be useful as an additional tool for diagnosis of subclinical primary hypothyroidism.
Dependent- and Independent-Endothelium Vasodilation in Children with Low Birth Weight and Its Relationship with Urinary Nitrites

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