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Index by Abstract

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

Bodoni, A.1; Coeli-Lacchini, F.2; Sobral, L.1; Moreira, A.2; Elias, L.4; Silva, W.2; Leopoldino, A.3; Castro, M.1; Antonini, S.1

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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, elevated 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 sequential 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 cytomtery 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.

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

Martinez-Aguayo, A.1; Campino, C.2; Carvajal, C.2; García, H.1; Aglony, M.1; Bancolari, R.1; Tapia, A.2; García, L.1; Loureiro, C.1; Kalerquis, A.4; Mendoza, C.1; Vecchiola, A.2; Valdivia, C.2; Fuentes, C.2; Lagos, C.2; Pinochet, C.1; Grob, F.1; Allende, F.4; Solari, S.4; Fardella, C.2

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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.
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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**O05**

**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, respectively, in accordance to most cohorts. Seven rare mutations (p.G424S, p.R408C, IVS2-2A>G, p.Ser170fs, p.W19X and p.V358I) were identified. 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%).

**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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**O06**

**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

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

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<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>
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<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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**O-1.2 Oral Session 1.2**

**O-1.2 Oral Session 1.2**

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**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


1CEDIE-CONICET-FEI-División de Endocrinología, Hospital de Niños ‘Ricardo Gutiérrez’, Buenos Aires, Argentina; 2Servicio de Nefrología, Hospital de Niños ‘Ricardo Gutiérrez’, Buenos Aires, Argentina

**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 \textit{SLC34A1} (gene encoding the NPT2a) mutation c.1485G>A, p.Arg495His and non-consanguineous parents with \textit{SLC34A1} heterozygous mutation. Index case was diagnosed by whole exome sequencing \textit{(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 potassium citrate supplements. Nephrocalcinosis did not worsen. The girl has short stature (–3.0 SDS) while the boy had normal stature. Both have normal neurodevelopment. Parents have normal biochemical studies and neither nephrocalcinosis nor renal phosphate leak.

**Conclusions:** The NPT2a defect found in this family leads to a severe transient hypercalcemia and to a hypophosphatemic disorder without 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 \textit{Npt2a} mouse. Early detection and proper treatment of this disorder of phosphate and calcium metabolism probably prevented further kidney damage.
**Association of SLC16A11, TCF7L2 and ABCA1 Polymorphism with B-Cell Function, Insulin Resistance and Early Onset of Type 2 Diabetes. Question of Time or Modifiable Risk Factor by Obesity?**

Miranda Lora, A.1; Molina Díaz, M.1; Cruz López, M.2; Flores Huerta, S.1; Gutiérrez Cuevas, J.2; Klünder Klünder, M.1

1Hospital Infantil de México Federico Gómez, D.F., México; 2Unidad de Investigación Médica en Bioquímica Hospital de Especialidades CMNSXXI

**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, 2h glucose, fasting insulin, 2h insulin, glycated hemoglobin A1c, C-peptide, quantitative glycemic traits (fasting glucose, 2h glucose, fasting insulin, 2h insulin, glycated hemoglobin A1c, C-peptide, and quantitative glycemic traits (fasting glucose, 2h glucose, fasting insulin, 2h insulin, glycated hemoglobin A1c, C-peptide) linear regression was used, adjusting by age, sex and cBMI, only rs7903146 and rs12255372 main-
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 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.

Abstracts

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

Table 1. (for abstract O11)

<table>
<thead>
<tr>
<th></th>
<th>SBP</th>
<th>DBP</th>
<th>SPL</th>
<th>DPL</th>
</tr>
</thead>
<tbody>
<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>
</tr>
</tbody>
</table>

SBP: systolic blood pressure

Table 2. (for abstract O11)

<table>
<thead>
<tr>
<th></th>
<th>Dipper revers</th>
<th>Non-dipper</th>
<th>Dipper</th>
<th>Hyper-dipper</th>
</tr>
</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>
</tbody>
</table>

O12
Elevated AMH and Insulin Cord Levels in Daughters Born to Mothers with Type 2 Diabetes
Villarola, 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; Departamento Ginecología y Obstetricia Universidad de Chile Campus Centro, Santiago, Chile

Introduction: Effect of 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 mDG 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.1; Wan, J.2; Valdes, C.1; Avila, A.3; Codner, E.1; Cohen, P.2

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

**O14 Timing of Pubertal Events in Boys with Type 1 Diabetes Mellitus (T1D)**

Gaete, X.1; Vivanco, M.2; Romero, P.3; Lopez, P.1; Rocha, A.1; Codner, E.3

1IDMI, Santiago, Chile; 2Hospital Roberto del Río, Santiago, Chile; 3Hospital Exequiel Gonzalez Cortés, Santiago, Chile

**Introduction:** T1DM 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.
Table 1. (for abstract O14)

<table>
<thead>
<tr>
<th></th>
<th>TD1 (years)</th>
<th>Controls (years)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<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>16.5±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>
</tr>
</tbody>
</table>

Methods: Children aged 8–18 yr with T1D (n: 96, age 13.8 ± 0.26) and healthy Chilean school children (C) (n: 391, age 12.8 ± 2.2 years) were studied. A Pediatric Endocrinology evaluated pubertal development. Genital and pubic hair development were evaluated according to Tanner stage. Axillary and facial hair presence was assessed. Probit and logistic regression were used for statistical analysis.

Results: T1D and C had a similar age of initial pubertal events, including genital and pubic Tanner stage 2 (table 1). Appearance of axillary and facial hair occurred at the same age in both groups. However, genital Tanner 5 occurred earlier in T1D compared to C. Appearance of intermediate axillary hair occurred earlier in T1D than in C. Duration of diabetes, metabolic control (HbA1c 8.1/8.10) or insulin dose were not associated with earlier age of final events of puberty in T1D.

Conclusions: 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. These data suggest that pubertal delay is not a frequent problem for T1D. Future studies should evaluate the relationship of pubertal delay with possible shorter time of growth period and higher testosterone levels in boys with T1D.
phins were not elevated, with FSH predominance (LH <0.10 U/l, FSH 0.73 U/l). Karyotype was 46,XX. These results were suggestive of the presence of ovarian tissue. Diagnostic laparoscopy was performed, and the histopathological study confirmed the presence of bilateral ovoestes.

Absence of SRY in peripheral leukocytes was documented by QF PCR analysis (Devyser Kit). A genome-wide copy number analysis, performed by single-nucleotide polymorphism using CytoSNP-850K microarray (Illumina), confirmed the absence of SRY and of Y chromosome sequences. Furthermore, a de novo duplication of 502,127 bp at 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.

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**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; Lerário, A.1; Nishi, M.1; Funari, M.1; Dénès, F.2; Costa, E.1; Mendonca, B.1; Domenice, S.1

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

**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 (ERTS).

**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.R151W) was identified in another sporadic ETRS patient. These two allelic variants were not founded in 194 controls studied and in 1000GENOME, ExAC and ESP6500 population databases. Both variants were considered damaging by in silico analysis.

**Discussion:** DHX37 gene (1q24.31) 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 1q24.31-33 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)**

Merino, P.1; Pastene, C.2; Salinas, A.1; Lopez, P.1; Jesam, C.1; Villarroel, C.1; Cispedes, P.1; Cassorla, F.3; Cadner, E.1

1University of Chile, Santiago, Chile; 2Hospital Gustavo Fricke, Viña del Mar, Chile; 3Hospital San Borja Arriaran, Santiago, Chile

**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 (mUI/ml)</td>
<td>5.75±1.54</td>
<td>5.85±2.63</td>
</tr>
<tr>
<td>LH (mUI/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 ± 1.1 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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**O19**

**New Diagnostic Criteria of Polycystic Ovarian Morphology (PCOM) in Healthy Adolescents: Impact of New Criteria on Prevalence of PCOM and Antimüllerlian Hormone (AMH)/INHIBIN-B (INHB) Levels**

Merino, P. 1; Villarroel, C. 1; Jesam, C. 1; Lopez, P. 1; Cadner, E. 1

1University of Chile, Santiago, Chile; 2Hospital San Borja Arriaran, Santiago, Chile

**Introduction:** Diagnostic criteria of PCOM have changed during the last 20 years. Rotterdam criteria (RC) defined PCOM when at least one ovary had an ovarian volume (OV) >10 ml or >12 follicles. Recently, a task force (2014) and a worldwide consensus (2015) modified the definition of PCOM in adolescents, and suggested that the diagnosis should rely in OV, using a cutoff level of 10 ml (OV10) or 12 ml (OV12) (2014 and 2015 criteria, respectively). The aim of the study was to determine the prevalence of PCOM in adolescence with new criteria, and to determine the impact of the changing criteria on AMH and INHB levels.

**Methods:** We studied 103 non-obese non-hyperandrogenic adolescents with regular menstrual cycles. AMH and INHB levels were measured during follicular phase. Transabdominal gynecological ultrasound was performed. PCOM was defined by the three published criteria.

**Results:** POCOM according to RC, OV10 and OV12 was present in 33%, 20.4% and 9.7% of the adolescents, respectively. Serum AMH levels and waist-hip ratio (WHR) were elevated in adolescents with PCOM diagnosed with the 3 different criteria (see table). INHB, however, was higher only in OV12 compared to OV less than 12 ml. OV correlated with WHR (r = –0.29, p = 0.002), AMH (r = 0.38, p = 0.0001), INHB (r = 0.32, p = 0.002) and ovarian follicle number (r = 0.30, p = 0.002). In addition AMH and INHB correlated with small follicles (2–5 mm) (AMH: r = 0.30, p = 0.003 and INHB: r = 0.23 p = 0.03), but not with larger follicles (6–9 mm).

**Conclusions:** Using the new diagnostic criteria of PCOM results in a lower prevalence of this ultrasonographic pattern in healthy adolescents. AMH is associated with PCOM regardless the criteria used. However INHB was associated only with the OV of 12 ml criteria (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.

**O20**

**Analysis of DAX1 and SF1 Genes and Their Interaction with Genes Involved in Stem Cell Maintenance in Adrenocortical Tumors**

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**Background:** Activation of the Wnt/beta-catenin pathway is frequent in adrenocortical tumors (ACTs). This pathway and DAX1, a negative regulator of SF1 expression, control adrenal stem/progenitor cells, which can be involved in ACTs formation.
Objective: To explore the interaction between the Wnt/beta-catenin pathway and the expression of a stem cell maintenance markers NANOG, STAT3 and OCT4, DAX1 and SF1 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, in 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.

P-1 Poster Session 1

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 BMI ≤ 96th) 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 ug/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 dehydrogenase (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 pycnolecia, no arterial stenosis; normal renal function. Normal urine, except for a high calcium/creatinine index. Aldosterone: <1 (reference value (RV): 5–80) and plasma 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
creatinine gr (RV: 7–26); midnight plasmatic cortisol: 3.8 ug/dl (RV <0.1); morning cortisol was not supressed post 23 hrs dex-hametasone administration; nocturnal salival cortisol was 0.132 and 0.146 ug/dL (RV: <0.1 ug/dL) in two different samples. ACTH: 33 pg/ml (RV: 10–60); F/E relation: 175.5 (RV: 1.7–5.6). Urinary catecholamines, urinary metanephrines; androstenedione; 17OH progesterone, prolactine and thyroid hormones resulted normal. Head and abdominal MRI were normal. 11BHS2D2 genetic study was performed and showed the mutation R213C on exon 3, confirming AME.

**Discussion:** Molecular study confirmed AME, which was compatible with her medical history although the laboratory strongly suggested hypercortisolism. AME is defined by normal levels of cortisol, therefore the biochemical hypercortisolism difficulted the diagnosis in this patient.

**Conclusion:** Although AME is a really unusual disease it must be considered in the differential diagnosis of severe hypertension in childhood when the clinical medical record is compatible.

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**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 (ECLI).

**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 ECLI (Cobase411-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.
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-sectional 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 serum levels in any of the determined periods. Statistical difference was found between groups of Andro levels in the two years period nearest ultrasonography.

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.

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 ureter 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


Hospital das Clínicas da Faculdade de Medicina da USP, São Paulo, Brazil

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 five 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 p.Thr577Ile [1]). LH and FSH levels were prepubertal in three patients on the diagnosis occasion. Three patients (I, II, IV) were treated with cyproterone acetate only. In addition, two patients (II and IV) had secondary estradiol replacement (5 mg/m²). These patients had usually normal gonadotropin profile and fertility in the adult life.

Materials and Methods: Anastrozole (2 mg/day) was associated in one of these cases (I). One patient received medroxyprogesterone (70 mg/m²); and anastrazole (2 mg/day) was associated in one of these cases (I). Patient I with severe testotoxicosis due to p.Leu457Arg had short stature and persistently suppressed gonadotropin levels during his long-term follow-up (24 years). He was 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 estradiol replacement (5 mg/m²). These patients had usually normal gonadotropin profile and fertility in the adult life.

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 oligozoosperma in adulthood. This case illustrates the potential role of high levels of intratesticular testosterone in the spermatogenesis.

GnRH Infusion in Females with Hypogonadotropic Hypogonadism

Freire, A.; Arcari, A.; Grinspan, R.; Bailerini, M.; Sanguinetti, N.; Bergadá, I.; Escobar, M.; Ropelato, M.; Gryngarten, M.

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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 gonadotropin 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: Group 1 (G1)– acquired or congenital pituitary pathology (n = 7) or Group 2– hypo/anosmia (n = 6) or G3-lack of spontaneous pubertal progression after a brief estrogen 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 assignment, 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
(AutoDELFIA® 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.

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

<table>
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<th>17 OHPe (ng/ml)</th>
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**P11**

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

**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 at INEN. We 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. Normoandrogénicos 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 < 0.001). 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-

XXV Annual Meeting, SLEP
Puerto Varas, Chile
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 during the First Month of Life. 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 RI 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 chitormegaly. 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 chitormegaly. 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 in males 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.

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. 21.2% had secondary amenorrhea, 55.6% has oligomenorrhea, 54.5% had hirsutism, 63.6% acne and 27.3% acanthosis. 20% had fasting hiperinsulinism and 41.7% dyslipidemia.

Conclusions: The prevalence of PCOS in adolescents with polycystic ovaries was 53.2%. 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 hiperinsulinism and 41.7% dyslipidemia.

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 hypertrophic 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, prolactine, estradiol, 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 than in females (5:1), but more relevant in females. The diagnosis is clinical based, the skin lesion must be present, no other numbered criteria have been established, but with more criteria present the possibility of the diagnosis is higher. Regarding the treatment the use of anti-androgen medication has demonstrated adequate clinical response, Spironolactone alters adrenal and gonadal steroidogenesis, in a dose of 50 mg/day is the ideal treatment to favor 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.
**P17**

**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.

**P18**

**Van Wyk – Grumbach Syndrome: Report of a Case**

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**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 areolar pigmentation, pubic and axillary hair was absent. External genitalia were stroganized 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 UI/ml (<4.11) and 76.4 UI/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 stroganized 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.

**P19**

**17-Hydroxyprogesterone Levels in Blood Spot According to Age and Birth Weight in Neonates Born Healthily at Term**

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**Introduction:** Congenital adrenal hyperplasia (CAH) is a recessive autosomal condition caused by 21-hydroxylase deficiency in 90–95% of cases. OMIM: #201910. Newborn screening for CAH is performed by quantifying 17-OH–progesterone in heel dry spot blood. The cut-off point is 99 percentile from values by Radioimmunoassay RIA or enzyme immunoassay (ELISA). Values may vary according to weight, gestational age, sex and stress.

**Material and Methods:** In order to analyze variations related to weight, gestational age, sex and natural birth, we include only healthy neonates born at term at Universitario de Santander Hospital between July 2014 and March 2015 divided in six groups by sex and weight (2500–2999 g, 3000–3499 g, and 3500–3999 g). Samples for screening were obtained between 3 and 5 days; protecive transversal descriptive study with repeated 17OHP if upper
cutoff 20 ng/ml. Hormone quantification was performed using heel dry spot blood in FT-2-460 filter paper.

**Results and Conclusions:** From 72 neonates, (55.6%) were male. Birth weight 3.275 gr (CI95% 3.179–3, 370); 17-OHP levels were between 2.6–29.5 ng/ml (median 10.3, RIQ 7.0–14.9). There are no changes in 17-OHP values according to sex, weight, age and birth weight. There is no variation in 17-OHP levels taken from heel dry spot blood related to weight, gestational age and sex in neonates born at term.

**P20**

**Bone Status Assessment in Healthy Children and Adolescents**


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**Introduction:** Much of a subject’s bone mass is acquired during childhood and adolescence until reaching peak bone mass, the major determinant of the risk of osteoporosis. Quantitative Bone Ultrasound (QUS) is a non-invasive technique, which could be used 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; RIQ 7.0–14.9). There are no changes in 17-OHP values according to sex, weight, age and birth weight. There is no variation in 17-OHP levels taken from heel dry spot blood related to weight, gestational age and sex in neonates born at term.

**Results:** Among the 45 participants (12.2 ± 4.1 years old), only 42% had adequate calcium intake [median = 885 (222–2425) 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 universalis.

**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 dentigenesis, 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. Whereas 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 patient’s improvement; currently without drug side effects. Whereas orthopaedic management corrected genu valgus with improved gait, alopecia universalis persists; she is undergoing medical management with paediatric endocrinology, orthopaedic, dermatological and genetic counselling.

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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.
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/creatinine 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 mean 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 osteoclast activity, and this effect is as higher as more cycles of PD are administered.

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**P26**

**Hypophosphatemic Rickets Associated with Epidermal Nevus Syndrome-Clinical and Laboratory Evolution**

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**Introduction:** The epidermal nevus syndrome (ENS) is characterized by epidermal naevis associated with abnormalities involving the nervous, skeletal systems among others. Rarely hypophosphatemic rickets have been associated to epidermal naevis. The mechanism involved in the appearance of hypophosphatemic rickets in SNE is not totally understood. Different studies suggest that phosphaturia, caused by the circulating FGF23, may be related.

**Objective:** To report the clinical and laboratory follow-up for a four-year period of a patient with a history of diffuse cutaneous neavi on the trunk and limbs from birth and developed rickets with hyperphosphaturia.

**Case Report:** JU, aged 13.6 y, white, female, hospitalized at the age of 5 with diagnosis of pylonephritis. Diagnosed Wilms’ tumor and subjected to unilateral nephrectomy. She has diffuse cutaneous naevis, scoliosis and cerebellar lipoma since birth.

**Family History:** There are no cases of bone metabolism disorders in her family. She was conceived by in vitro insemination, and her twin sister is normal. Adressed to our department due to pain and radiographic abnormalities. Laboratory tests confirmed hypophosphatemic rickets with decreasing TR TF (82.3%), Ca (9.4 mg/dl), FA (2492 U/L), P (2.3 mg/dl), and normal FGF23 (128 RU/ml). Introduced vitamin D (calcitriol 0.5 mcg/day) and phosphate (1.25 g/day) with improvement of both clinical and radiographic symp-
Abstracts

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 1o) 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%.

Due to the extreme change in ionic minerals homeostasis after removing the source of excess PTH, bone previously subjected to a chronic process of desmineralization, sharply change a state of remineralization of the bone matrix with the consequent fall of the serum calcium, phosphorus generating the hungry bone syndrome.

Objectives: Describe a patient with parathyroid adenoma, who also presented a hungry bone syndrome.

Material and Methods: Patient with hypercalcemia and high values of PTH. In addition to hyperparathyroidism presents deformity in the ribcage, sternoclavicular bumps and a bone deformity in the osteocentral region, which corresponds to a mass on the left second rib. slipped capital femoral epiphysis, pain and difficulty to walk. A scan with MIBI TCc–99 showed adenoma in the upper pole and less than 1% of cases corresponds to carcinoma. Ectopic glands can be seen in the 4–16%.

Evolution: After the adenoma resection the patient presents...

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.

P28
Use of Zoledronic Acid in the Treatment of Osteogenesis Imperfect
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Introduction: Patient diagnosed with osteogenesis imperfect who consults for the first time at 12 years of age for evaluation and treatment. It did not antiresorptive therapy in the years prior to the consultation.

Material and Methods: Patient of 12 years and six months reaching consultation with a thoracolumbar corset, blue sclera normal teething, scoliosis, pubertal development: prepubertal. Weight: 46 kg, Height: 145.7 cm. As family history presents mother and maternal uncle and maternal grandfather with the same disease. In the Rx backbone the presence of fish vertebrae, anterior wedging and kyphosis is observed; and lumbar vertebrae of fish. Study: deoxypyridinoline to highlight 24 hours of 19 nmol/umol. Bone age of 11 years and 6 months. Bone mineral densitometry (Hologic) L1-L4: 0.284 Z-score: −4.7.

Results: You will be shown the following treatment schedule: adequate calcium, vitamin D3 1,200 U/day and zoledronic acid sigiendo scheme for the pediatric population: Initial dose: 0.0125 mg/kg, diluted in 50 ml 0.9% NaCl happen in 30 minutes. At 6 weeks: 2nd dose: 0.025 mg/kg. At 12 weeks (from the 1st dose): 3rd dose: 0.025 mg/kg.

Conclusions: 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 (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.

P29
Comparative Effect of Letrozol and Anastrozol on Bone Age Progression
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Introduction: Aromatase inhibitors (AI) have emerged as a new investigative type of treatment for boys with growth disorders, once they prevent bone age (BA) advancement. Few reports address the comparison of third generation AI letrozol (LTZ) and anastrozol (ANZ) on their capability to prevent BA advancement. The aims of this study was to compare BA progression during LTZ and ANZ therapy employed alone or in combination with GH.

Material and Methods: We retrospectively evaluated 99 boys (LTZ: n = 46; mean age = 13.3 ± 1.1 y; initial height (SDS): −0.8 ±...
Hormonal therapy and some elements related developments. Patients diagnosed with PP treated at a consultation of Endocrinology had lower among girls with CPP.

The prevalence of organic disease is notably higher than BA variation (ΔBA = BA final – BA initial) in both LTZ (ΔCA: median (IQV) = 2.0 (1.4–2.8) y; ΔBA: median (IQV) = 1.6 (0.9–2.1) y; p < 0.001; Mann-Whitney test) and ANZ (ΔCA: median (IQV) = 2.1 (1.6–2.4) y; ΔBA: median (IQV) = 1.5 (0.5–2.1) y; p < 0.001; Mann-Whitney test). The difference between chronic and bone age variations (ΔCA-ΔBA) was similar when comparing LTZ vs. ANZ (LTZ: 0.7 ± 0.8 y; ANZ: 0.6 ± 0.9 y; t test, p = 0.385).

During short term therapy of two years, both LTZ and ANZ are able to reduce bone age advancement, with similar efficacy.

### P30
**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 of 58.8% of patients and 61.8% acceleration of skeletal maturation. Congenital adrenal hyperplasia was a cause of 14.7% of patients and hypothyroidism in a similar percentage was identified, no patients with tumour aetiology is found and the rest were unable to establish causality. The treatment was started at an average of 6.39 years and 2.6 years on average, 50% of patients received an LHRH analogue, 14.7% cyproterone acetate and the like levothyroxine. The concentrations of prolactin are related to the tumor size.

**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 hypogonadotrophic 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 include 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.
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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 (Kruskall-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 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.Glut237del in two non-related patients, and Gly44Arg in one patient. The program polyphen-2 suggests that these new GCK varieties 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**

Arrizaga, M.; Lagos, M.; Gonzalez, M.

1 Hospital Dr. Gustavo Fricke, Viña del Mar, Chile; 2 Pontificia Universidad Católica de Chile, Santiago, Chile

**Introduction:** MODY (Maturity-onset diabetes of the young) is a heterogeneous group of diseases characterized by nonketotic diabetes mellitus, autosomal dominant inheritance and early onset. It begins 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 gene sequence variant 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 deleterious role and its autosomal dominant inheritance.

**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 ng/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/kg/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.

**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), c-peptide 0.8 (2.6–24.9 mcU/mL), insulin 34.7 μU/ml, c-peptide 0.8 (1.1–5.0 ng/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.

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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 OGGT 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.
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 31/36VHL2) and group 2, aged ≥21 y (n = 31:8/31VHL1, 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 point mutations and small deletions. MLPA and UPQFM-PCR was performed using PCR and automatic sequencing for the study of gross deletions.

**Results:** The VHL genetic analysis of 33 families showed: 24 missense mutations, 6 nonsense mutations, 1 small deletion, 1 gross deletion and 1 small insertion.

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).

**Conclusion:** 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**

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


Instituto Nacional de Pediatría, Distrito Federal, Mexico

**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 germinal mutations in genes susceptible to the tumor, SDG (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 retropertoneal 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-

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Puerto Varas, Chile
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. Antimullerian 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. goamenorrhea and 27.7% had amenorrhea during the last year

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.

Molecular Study of Rasopathies in Patients with Isolated Cryptorchidism

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Introduction: Cryptorchidism is a frequent finding in patients with molecular confirmed RAStopathies. 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 monosymptomatic 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 RAStopathy. Genomic DNA was extracted for molecular analysis of PTPN11, 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 RAStopathy (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.Q456Q) and one HRAS intronic 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 PTPN11_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 RAStopathies. Analysis of the synonymous substitution SOS1_c.1953A>G and

Abstracts

O-4.1 Oral Session 4.1

O31

Molecular Study of Rasopathies in Patients with Isolated Cryptorchidism

Conclusion: 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.
Whole Exome Sequencing Identifies Genetic Causes of Disproportional Short Stature

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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 disproportional short stature by exome sequencing.

Subjects and Methods: We selected six patients with disproportional 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 FBN1 gene (c.5183C>T/p.A1728V). Mutations in FBN1 are associated with Gelophysic and Acromicric dysplasia, but this patient lacks some of the cardinal features of these conditions. Case 3 has a height SDS of −2.5 with bilateral osteo-enurosis of the femoral epiphysis. We identified a heterozygous mutation in COL2A1 gene (c.1368.G>A). Mutations in COL2A1 cause several skeletal disorders with highly variable phenotype.

Conclusion: We identified 3 heterozygous mutations in 3 different genes that explain the disproportional short stature phenotype observed in our patients. Because of the mild and unspecific phenotype, only a genomic approach allowed the identification of the etiology of short stature in these patients.
Identification of a Novel Mutation in STAT3 Gene by Exome Sequencing in a Patient with Neonatal Diabetes and Early Onset-Autoimmune Disease

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Introduction: 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 control.

Conclusions: Our results agree with the recent findings about the association between activating mutations in STAT3 gene and an early-onset autoimmuniebne disease combined with NDM, reinforcing the fact STAT3 mutation is good candidate to be responsible for the clinical features of our patient. Our results support WES is 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

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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-arial communication and seizures. She had a female karyotype, without any suggestion of chromosome alteration. We performed the Chromosomal Microarray Analysis (CMA) on the proband and her parents. The array was used was Afymiexrix’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, 4p16.3, a 1.35 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.

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Novel Mutation in ABCC8 Gene Causing Persistent Congenital Hyperinsulinism

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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 hypoglycemias 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 polimerosa 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 hypoglycemepidodes 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.
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 to 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 predicted binding sites for POU1F1/SP1 and NF1, respectively. Functional study was performed aiming to check the effect of these variants on the phenotype.

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 POUI1F1 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.
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, desmactative 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), low IGF-I (20 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). P2, a 3 year old male (height –5.36 SD), had a history of primary IGF-I deficiency (20 ng/ml), normal IGFBP-3 (2.2 μg/ml) and elevated prolactin (30.6 ng/ml). He also presented low IGF-I (57 ng/ml) and normal IGFBP-3 (2.2 μg/ml). WES analysis identified two different heterozygous STAT3 variants: a private de novo c.1847_1849delAAG (p.Glu61del) in P1, and a missense c.1276T>C (p.Cys426Arg) in P2. The patients’ phenotypes suggest that the identified STAT3 variants could be activating mutations. In vitro functional characterization is required to confirm this assumption.

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.

Individual Quality of Life in Parents of Youth with Type 1-Diabetes: Exploration of Life Domains in a Context of Rural Area

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Introduction: Parental involvement are very important in the management of type1-diabetes (T1D) during the childhood. It may cause parental distress and contribute to diminish parent quality of life (QoL). The aim of this study is to investigate the individual, as opposed to predetermined, quality of life in parents of children with T1D, in the specific and unexplored context of rural Chilean area.

Materials and Methods: We conducted an exploratory study with a methodological mixed design, during 2014–2015, composed by two phases: (1) The first phase consisted on the exploration of the most important domains of parents QoL through 12 semi-structured interviews. (2) The second phase investigated the QoL of 21 parents through an evaluation adapted from the Schedule for the Evaluation of Individual Quality of Life – Direct Weighting interview, which allows respondents to nominate and evaluate their own quality of life domains.

Results: 11 life domains were identified through the first phase. During the second phase, the most frequently nominated life domains were ‘family’, ‘finances’, ‘child health’, ‘psychological well-being’ and ‘access to physician trained in diabetes care’ respectively, ranked in terms of importance, domains were ‘family’, ‘child health’, ‘social network’, ‘psychological well-being’, and ‘access to physician trained in diabetes care’; ranked in order of satisfaction, domains were ‘family’, ‘social network’, ‘psychological well-being’, ‘beliefs’ and ‘finances’. Total QoL scores ranged from 43.1–97.7 M = 72.0, SD = 14.3.

Conclusions: Parents nominated many life domains not identified by WHO or classic Parent QoL questionnaire and related to the child diabetes care and health system. These findings are underscoring that parent QoL is multidimensional, with domains which can depend of the geographic place, like public health system characteristics. These findings should be replicated with larger sample to be able to associate these findings to demographic and diabetes characteristics.
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 ketoadsosis 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% showed acanthosis nigricans, HbA1c: 9.56 (±1.87), C-peptide: 0.57 (±0.74). Whereas patients with T2DM have an average age of 12.59 (±2.32), 50% were male, 93.3% showed acanthosis nigricans, 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% showed acanthosis nigricans, HbA1c: 9.56 (±1.87), C-peptide: 0.57 (±0.74). Whereas patients with T2DM have an average age of 12.59 (±2.32), 50% were male, 93.3% showed acanthosis nigricans, 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% showed acanthosis nigricans, HbA1c: 9.56 (±1.87), C-peptide: 0.57 (±0.74). Whereas patients with T2DM have an average age of 12.59 (±2.32), 50% were male, 93.3% showed acanthosis nigricans, HbA1c: 10.39 (±2.76), C-peptide: 0.57 (±0.74).

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.

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 autoimmune 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.

Novel Mutation of Gene ABCC8 Causing Hyperinsulinism in an Infant

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Introduction: Hyperinsulinism is a heterogeneous condition which cause 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 Hydroxyacyl 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 ABC8.

**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, diazoxide 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 be associated with lesions and its detection may avoid pancreatectomy and improve the quality of life. We are standing patients parents.

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**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 patients’ 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 poorly controlled diabetes, asymptomatic infection or causing lumbar and 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 UTT in diabetic patients are similar to those evident in the general population.

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**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:** Patients with good glycemic control were similar to those evident in the general population.

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**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 glycaemic control is more precarious, is characterized by the development of the autonomy, which concerns the decision-making and the realization of behav-
ior 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 glycaemic 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 self-care built from the autonomy of decision and not only the autonomy of realization. This self-care includes behavior of diabetes management not only to satisfy the requirements of medical care but also in a salutogène perspective to take care of its psychosocial life. Our results also 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.

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**P38**  
**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 youngadults. 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 clinic, but the laboratory and images helps, and it is directly related to a poor metabolic control.

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**P39**  
**Growth and Development of Children with Type 1 Diabetes Mellitus**  
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**Introduction:** One of the rare long-term complications of type 1 diabetes mellitus (T1DM) is change in growth and development, maintaining controversy if linked to poor metabolic control. Our objective was to evaluate the effect of T1DM on growth and development of a group of diabetic children followed in a pediatric Institute.

**Materials and Methods:** A retrospective study of thirty patients with T1DM treated in a pediatric Institute, excluding the carriers of other chronic diseases that could affect growth. Affiliation, date of diagnosis, type of treatment, anthropometry and glycosylated hemoglobin (HbA1c) at diagnosis, and five years of follow-up were recorded. Anthro software (version 3.2.2) and anthro plus using standards-based WHO were used for evaluation. Setting Z score for weight for height (WHZ), weight for age (WAZ), height for age (HAZ) and body mass index for age (BAZ).

**Results:** Among the 30 patients followed, 36.6% were men and 63.3% women. At diagnosis, 23.3% were younger than 5 years. 90% by Tanner pubertal stage 1. In 76.6% insulin analogs were used and 90% had HbA1c >7.5%. 13.3% showed HAZ <–2SD (Mean –0.89 + 1.27 SD) and BAZ > + 2 SD 3.3% (Mean 0.32 + 1.71 SD).

A year of diagnosis; 6.6% had a HAZ <–2SD (Mean –0.95 + 0.93 SD) corresponding to 100% the group of 5–9 years. As for the BAZ, 23.3% was greater than + 1 DE (Mean 0.77+ 0.70 SD). HbA1c in the 60% was >7.5%.

At five years of diagnosis; 37.5% (Mean –1.79 + 1.35 SD) showed HAZ <–2SD 55.5% in the age group diagnosed for 5–9 years. 12.5% had a BAZ <–2SD and 6.3% > + 1 DE (Mean –0.43 + 1.01 SD). HbA1c in the 70% was >7.5%.

**Conclusions:** No significant deteriorative effect of T1DM on auxological parameters were observed at year of diagnosis. However after five years of disease both, height for age and BMI for age were affected probably associated with the degree of metabolic control.

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**Abstracts**
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 diagnose 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 discordant 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 useful 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 normosomic 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/TAC3R in nIHH, KAL1 in SK and FGFR1/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
18.2% of families with PAIS (4/22) and 6.25% of the families with gonadal region was normal. Mutations in AR were not identified in main (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 AR gene, followed by direct sequencing. The mutations were searched in the literature, genomic sites and the novel regions of the AR gene, 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).

**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.

**Abstracts**

**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 13 in 16 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).

**Conclusion:** The mutations related to different phenotypes allows for greater insight into genetic defects in our patients. The strategy of seeking mutations in the promoter region, when there is clinical suspicion of AIS without mutations in exonic region of the AR may allow the identification of genetic defective in some patients.

**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 patients 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).

**Results:** 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.

**Conclusions:** The prevalence of PCOM 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 8.5±0.8; 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.
P45

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 novel p. Cys301Tyr alteration, located in exon 5 at the ligand-binding domain of the gene. Her asymptomatic mother presented the variation as the previously described p. Gly146Ala polymorphism.

Patient 4: 46XY boy with micropenis and bilateral anorchia presenting in heterozygosis the previously described p. His24Leu mutation.

Patient 5: 46XY boy presenting with scrotal hypospadias, unilateral cryptorchidism and bifid scrotum. He carried in heterozygosis the previously described p. His24Leu mutation.

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

P46

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>
<thead>
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<th></th>
<th>HO (n = 18)</th>
<th>C (n = 36)</th>
<th>p</th>
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</thead>
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<tr>
<td>Age at menarche (y)</td>
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<tr>
<td>Gynecological age (y)</td>
<td>3.8±2.4</td>
<td>2.6±1.5</td>
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<tr>
<td>Height (z-score)</td>
<td>−0.3±0.9</td>
<td>−0.2±0.9</td>
<td>0.99</td>
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<tr>
<td>BMI (z-score)</td>
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<td>0.7±0.6</td>
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<td>Waist-Hip ratio</td>
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<td>0.5±0.0</td>
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<tr>
<td>Ferriman score</td>
<td>14.1±4.7</td>
<td>16.1±1.9</td>
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<tr>
<td>OV (ml)</td>
<td>11.9±3.8</td>
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<tr>
<td>OV (mg)</td>
<td>9.7±2.4</td>
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<tr>
<td>NFM (n)</td>
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<tr>
<td>NEmean (n)</td>
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<td>IGF-1 (ng/ml)</td>
<td>248±52.2</td>
<td>259±48.1</td>
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XXV Annual Meeting, SLEP
Puerto Varas, Chile
P47
Evaluation of 47XY Syndrome in Disorder of Sex Development (DSD) Multidisciplinary Clinic: Lessons Learned
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Introduction: The Y chromosome polisomy or 47XY 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: hypoplasic genitalia in male. The association of craniosynostosis, craniofacial defects, bone malformations and changes in adrenal steroidogenesis refers to the rare form of congenital adrenal hypoplasia caused by POR deficiency, with different clinical presentations.

Conclusion: The 47XY should be suspected in children who present with unilateral cryptorchidism, microphallic, and increase stature. The natural history of testicular cells in 47XY 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.

P48
Antley Bixler Syndrome: Case Report in a Newborn with Ambiguous Genitalia
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Background: Antley Bixler Syndrome (ABS) is characterized by several skeletal changes and synostosis. When associated with impaired adrenal function, is related to P450 oxidoreductase (POR) deficiency, a coenzyme of many adrenal routes. Clinical spectrum varies from mild to severe forms, with multiple skeletal malformations, including craniosynostosis, brachycephaly, severe midface hypoplasia, radiohumeral synostosis and multiple joint contractures. Manifestations of POR deficiency can include ambiguous genitalia in both males and females.

Case Presentation: First child from non related paterns, pre-term newborn (gestational age 33 weeks) presented ambiguous genitalia and confirmed karyotype 46 XY with undervirilization. At clinical exam, genitalia with bilateral inguinal hernia, palpable gonads, phalus of 1.8 X 0.7 cm, urethral meatus topic and hypotrophic scrotum. Other features included brachycephaly, hands with arachnodactyly and clubfeet. The mother had significant virilization during pregnancy. Echocardiography with ASD secundum septal (5 mm) with left to right shunt. Hormonal profile showed normal basal cortisol, ACTH and electrolytes levels; ACTH-stimulated cortisol 18.9 mcg/dL, 17OH progesterone 553 ng/dL, progesterone 2806 ng/dL and low androgen levels (testosterone 53 ng/dL, androstenedione 57 ng/dL); developed early respiratory distress and required emergency tracheostomy. The use of glucocorticoid was recommended only in stressful situations.

Conclusion: We presented a case of ABS phenotype with ambiguous genitalia in male. The association of craniosynostosis, craniofacial defects, bone malformations and changes in adrenal steroidogenesis refers to the rare form of congenital adrenal hypoplasia caused by POR deficiency, with different clinical presentations.

P49
PHHI:FYE

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Introduction: Persistent hyperinsulinemic hypoglycemia of infancy (PHHI) is a heterogeneous group of problems from the point of view clinical, genetic, morphological and functional. It is the leading cause of persistent hypoglycemia in infants and is an important factor of neurological damage for survivors.

Methodology: The aim of this study was to describe the clinical features, evolution and complications of patients diagnosed with PHHI. The medical records of patients diagnosed in the last five years (2010–2015) were reviewed, collecting information related to age, sex, perinatal history, onset of symptoms, laboratory tests, images, anatomopathological study and genetic, therapeutic, evolution and consequences.
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 homozymous 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. 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 puberty 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 in-
dex (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-consanguineous 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 glucagon 8 ug/kg/hour. Hyperinsulinism was suspected. Galium 68 PET/CT showed a diffuse compromise of pancreas. Sequence analysis for the ABCC8 and KCNJ11 gene showed no mutation. Diazoxide was started (with hydrochlorothiazide). There was no response despite the increase of dose (5 to 20 mg/kg/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 response to maximal dose of Diazoxide and had a major 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.
Abstracts

**O-5.1 Oral Session 5.1**

**O41**

**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 benign and malignant nodules before surgery in order to identify malignancy predictors.

**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 a final diagnosis (benign vs. malignant) by surgery (n = 24) or by reevaluation at 3.3 years of age. The median age at presentation was 13.6 years. 75% were females, 69% prepubertal. Papillary thyroid carcinoma (PTC) was found in 8 patients (25%). Risk factors, present in 3/32 ([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.

**Results:** Upon admission mean age was 13.6 years, 75% were females, 69% prepubertal. Papillary thyroid carcinoma (PTC) was found in 8 patients (25%). Risk factors, present in 3/32 ([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 (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.

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**O42**

**Transient Congenital Hypothyroidism Due to Biallelic Defects in DUOX2 Gene**

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**Introduction:** Dual oxidases (DUOX1 and 2) are components of the thyroid hydrogen peroxide (H2O2) generating system needed for the thyroid hormone organification.

Mutations in the DUOX2 gene (DUOX2) have been described in transient and permanent congenital hypothyroidism (CH) presenting with goiter and positive perchlorate discharge test.

**Subjects and Methods:** We report two siblings born from unrelated healthy parents. The eldest was detected through neonatal screening with slightly elevated TSH. At 1 month she was treated with LT4 with TSH: 32 mU/L, T4 13 μg/dl, FT4: 1.46 ng/dl and TG: 266 ng/dl (Normal reference (NR): 30–100) and goiter in the Tc99 scan. Treatment was withdrawn at 2.9 years of age when she showed normal TSH, T4 and FT4 levels and TG: 41.7 ng/dl (NR 6–30). Perchlorate discharge was 17% (normal <15%). Treatment was restarted and stopped again at 7 years. A month later thyroid profile was normal, perchlorate test negative and TG: 51.2 ng/dl. She is now 12 years old, grows normally, undergoes normal puberty and keeps euthyroid. Her brother, also positive for CH screening, started treatment at age 15 days (TSH: 33 mU/l, T4: 7.9 μg/dl, FT4: 0.9 ng/dl and TG: 666 ng/dl). Reevaluation at 3.3 years showed normal thyroid profile and negative perchlorate test. With 7 years of age he is euthyroid and grows normally.

With suspicion of organification disorder, all 17 exons of the TPO gene (TPO) and the 33 exons of the DUOX2 were studied by SSCP. Afterwards DNA sequence analysis was performed with Sanger technic in all fragments with abnormal migration.

**Results:** SSCP revealed no abnormalities in the TPO. Regarding DUOX 2, in both patients, a novel deletion in exon 9 (c.1057_1058delTT, p.F353 fsX388) of the paternal allele and an exon 2 (c.1057_1058delTT, p.F353 fsX388) of the maternal allele were found. Their healthy brother harbored only the exon 1 mutation.

**Conclusion:** Molecular TPO and DUOX evaluation should be carried out when permanent transient organification disorders are suspected. As our findings confirm, the magnitude of the defect is not related to the number of inactivated alleles. Biallelic defects of DUOX2 in transient CH infers compensatory mechanisms in the peroxide supply.
**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 Nr1d1), steroidogenesis-related genes (Star and Mc2r) and plasma corticosterone (B).

**Material and Methods:** Male Wistar rats were kept under a 12 h light/dark cycle (lights on at 0700 h, zeitgeber time-ZT0). Plasma and adrenal tissue samples obtained every 4 h over a 24 h period on postnatal days (P) P1, P3, P6, P12, P14, P16, P21 and P24 were used for plasma B measurement (RIA) and mRNA expression by qPCR and the results were analyzed using the Cosinor method that tested the presence of biological rhythms throughout the 24-hr 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, Cry2, Rora, and Nr1d1, 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.

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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 inhibit B were compared between groups; we also compared testosterone (T) and basal and post-stimulation FSH and 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 (p 0.41), the lag between chronological and bone age (p 0.264), and parental history of pubertal delay (p 0.104), the lag between chronological and bone age (p 0.0008) and parental history of pubertal delay (p 0.41).

**Conclusions:** Lower levels of Sertoli cell markers (AMH and inhibit 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 consanguineous 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 year, 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 hippocampal-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 heterogeneous 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 levels (LDL-C; 142.4 ± 27.0 vs. 50.8 ± 14.6 mg/dl, p = 0.04) were similar in both groups. Triglycerides and TSH, FT4 and BP and glycemia. 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) comparing 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.

O48

Thyroid Dysfunction Is Associated with Biochemical Markers of Non Alcoholic Fatty Liver Disease (NAFLD) in Pediatric Population

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Background: Due to the obesity epidemic in pediatric population, nonalcoholic fatty liver disease (NAFLD) is an increasingly common condition associated with metabolic syndrome. Thyroid dysfunction has also been associated with metabolic syndrome, cardiovascular disease and mortality. Elevated serum TSH, even within the normal range, is positively correlated with elevated biochemical markers of NAFLD in adults. In pediatric population there is scarce evidence of this association.

Objective: To determine the association between thyroid function and biochemical markers of NAFLD in Chilean pediatric population.

Methods: 82 children, 57% female, 13.5 years-old (range 6.1–18.9 years) were studied. Anthropometry, systolic blood pressure (BP) and diastolic BP were measured. Serum TSH, FT4, AST, ALT, GGT, glucose and lipid profile were determined and their results were expressed as mean ± SD. Variables were transformed to log10 prior Pearson correlation. To perform statistical analysis we used STATA SE 12.0 for windows. We define biochemical criteria of NAFLD as GGT or ALT >40 U/L and Subclinical Hypothyroidism as TSH >5 mUI/ml and normal FT4 for age.

Results: 28.8% were obese, mean TSH and FT4 were 3.16 ± 2.06 SDS uU/ml and 1.26 ± 0.19 SDS. 5 patients (6%) meet biochemical criteria of NAFLD (GGT >40 U/L), 2 of them had TSH >5 mUI/ml with normal FT4 (40%). We observed a positive association between TSH and ALT (R: 0.35; p < 0.01) and GGT (R: 0.24; p < 0.05), but not with AST. There was a positive association between triglycerides and TSH (R: 0.42; p < 0.001) and a negative correlation between HDL and TSH (R: -0.33; p < 0.001), this relationship persists after adjusting for body mass index. There was no association between FT4 and liver enzymes. There was no association between TSH, FT4 and BP and glycemia.

Conclusion: NAFLD markers were associated with higher TSH levels. This relationship persists after adjusting for body mass index, suggesting that thyroid dysfunction could have a direct effect on liver parenchyma, independent of nutritional stage. Higher TSH levels are associated with less favorable lipid levels in children.

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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. Only 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.

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 CRP and CRP with HDL cholesterol 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 following the methodology used by Kelly, data from 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.

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**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 GH 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.
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.

**P58**

Analysis of Growth Hormone Treatment Response in Prepuberal Children with Growth Hormone Deficiency

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**Introduction:** Growth hormone (GH) treatment response may be variable in children with GH deficiency (GHD). The objective was to analyze growth response in GHD patients treated with conventional GH dose.

**Material and Methods:** Forty-six GHD children (M:25, F:21), with isolated and 23 with multiple GHD, were selected according to the following criteria: a) prepuberal (telarche Tanner stage 1 or testicular volume ≤3 ml) during follow-up period, b) adequate treatment compliance. Mean GH dose used was 0.18 ± 0.02 mg/week. Median age at start, height SDS at start, 1, 2, 3, 4 and 5 years of treatment were calculated. Yearly gain in height was analyzed in 19 patients assessed in each visit during 5 years. Patients were divided according to peak serum GH (PSGH) in two groups: G1) severe (PSGH ≥3 ng/ml), and G2) less severe (PSGH <3 ng/ml). Gain in height was compared between two groups. In 18 children (M:10, F:8) final height (FH) was obtained and compared with target height (TH). Statistical analysis: Student test was used to compare FH with TH and to assess gain in height.

**Results:**

Median age at start was 4.3 (0.06–13.3) years. Mean height SDS was: 2.97 ± 1.17 SDS at start (n = 46), –2.54 ± 1.11 SDS at 1 year (N = 46), –2.22 ± 1.23 SDS at 2 years (n = 38), –2.05 ± 1.07 SDS at 3 years (n = 32), –1.85 ± 1.08 SDS at 4 years (n = 25) and –1.79 ± 1.08 SDS at 5 years (n = 20). Gain in height was: 0.5 ± 0.9 SD at 5th year (p = NS).

**Conclusions:**

1. Gain in height was significant during the first four years of treatment despite GHD severity.
2. Using conventional GH dose, although mean FH was normal, it was lower in some patients. Moreover, in boys FH was below TH.
**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 familiar 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**

**Villegas, N.; Figueroa, V.; Malavolta, Y.; Hernandez, C.; Brunetto, O.**

Hospital de Niños Pedro de Elizalde, Buenos Aires, Argentina

**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, anathomical, 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. Epidemiologic data: Median age at presentation (in months) was 14 (range 0.73–72, with a patient presenting at 11.9 years old). 53% were referred from the pedriatric/neonatal units, while the others were derived from neurologists (26%), ophthalmologists (10.5%) and genetist (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. Ophtalmological 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.

The agenesia/hypoplasia septum pellucidum was the most frequent anatomical finding, giving the possibility of prenatal diagnosis.

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**

**Hayes Dorado, J.; Barañá Ríos, C.; Lopez Rossell, M.**

Caja Petrolera de Salud, Santa Cruz de la Sierra, Bolivia

**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

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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 crests, and 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.

Table 1. (for abstract P63)

<table>
<thead>
<tr>
<th>Patients</th>
<th>17</th>
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<tbody>
<tr>
<td>sex</td>
<td>Men 55%</td>
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<tr>
<td></td>
<td>Women 45%</td>
</tr>
<tr>
<td>Age averages</td>
<td>5–16 years</td>
</tr>
<tr>
<td>time consult</td>
<td>More 1 years</td>
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<tr>
<td>Adenomas &lt;(10 mm)</td>
<td>Microadenomas 75%</td>
</tr>
<tr>
<td></td>
<td>Macroadenomas 25%</td>
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<tr>
<td>Classifcation (production)</td>
<td>Prolactinoma 4</td>
</tr>
<tr>
<td></td>
<td>GH 5</td>
</tr>
<tr>
<td></td>
<td>Cushing (ACTH) 2</td>
</tr>
<tr>
<td></td>
<td>Adenoma not function 3</td>
</tr>
<tr>
<td></td>
<td>Apoplegia 3</td>
</tr>
<tr>
<td>Panhypopituitarism</td>
<td>66%</td>
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<tr>
<td></td>
<td>23.5%</td>
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<tr>
<td></td>
<td>30% macro 80%</td>
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<td></td>
<td>micro 20%</td>
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<td>12%</td>
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<td></td>
<td>17.6% Inmunohistoquimic</td>
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<td></td>
<td>ACTH +</td>
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<td></td>
<td>17.6%</td>
</tr>
</tbody>
</table>

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 6/14, 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.

P63
Pituitary Adenomas in Pediatricas Characterization in One Multicentric Serie in Colombia

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1Fundacion Clinica Infantil Club Noel, UNILIBRE, Corderinsa, Cali, Colombia; 2Unit of Growth and Bone Metabolism, Instituto de Ortopedia Infantil, Bogota, Colombia; 3Hospital Pablo Tobon, Medellin, Colombia; 4Fundacion Clinica Infantil Club Noel Fellow Pediatric UNILIBRE, Bogota, Colombia; 5Hospital San Jose, Bogotá, Colombia

Introduction: Pituitary adenomas are extraordinarily rare in early childhood; their frequency increases during adolescence but...
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 and inmunohystoquimic. 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 SMMCI 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.

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**P64**

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


**Universidad de Antioquia, Medellin, Colombia**

**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). Choanal 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 later a central hypothyroidism and an abnormal response to glucagon 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 (SMMCI).

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 35th percentile.

**Review:** The SMMCI 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 holoprosenceph-aly spectrum. The etiology is unknown, but it has been associated to missense mutations in SonicHedgeHog SHH gene (7q36).

**Conclusion:** The prevalence of MS in children with a history of prematurity, less than 36 weeks of gestation and AGA vs premature and low birth weight, is 26.1% vs 8.6% respectively, with statistical significance with p < 0.05. The three components of MS were evaluated in this study: triglycerides >110 mg/dl: 34.1%, HDL cholesterol <40 mg/dl: 32.0%, systolic or diastolic blood pressure >90 percentile.

**Results:** 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.

**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.

**Abstracts**

Horm Res Paediatr 2015;84(suppl 2):1–77 57
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 Hb1Ac (≥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 Gastrectomy in Obese Adolescents: Effects on Bone Metabolism

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Instituto da Criança – Hospital das Clínicas – Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

Background: Laparoscopic sleeve gastrectomy (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


Instituto da Criança/Hospital das Clínicas, Universidade de São Paulo, São Paulo, Brasil

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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Hospital Pediatrico Docente Centro Habana, La Habana, Cuba

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 cardiometabolic 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), hypertriglyceridemia (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 dislipidemia 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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University of Chile, Institute of Nutrition and Food Technology, Santiago de Chile, Chile

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
Chiarpenello, J.
Hospital Provincial del Centenario de Rosario, Rosario, Argentina

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 (glycemia 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 insulinemias 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...
(50.53%). 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 ultrasound 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 ultrasound (27.25% vs 25.28%). Hepatic steatosis correlated with lipid profile hipercolesterolemia 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.

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**P72**

**Development of Nodular Goiter in Adolescents with Congenital Hypothyroidism with Eutopic Thyroid Gland Screened by the New Screening Program of the State of Minas Gerais (PTN-MG)**


Universidade Federal de Minas Gerais, Belo Horizonte, Brasil

**Introduction:** It is described in literature that in patients with Congenital Hypothyroidism (CH) with eutopic Thyroid gland it is common to find thyroid nodules, either malignant or benign. The aim of this study is to evaluate, using a sample, the profile of adolescents with CH with eutopic thyroid gland presenting goiter, screened by the PTN-MG.

**Materials and Methods:** This is a cohort study based on the data from the PTN-MG of 9 adolescents screened for CH who had developed goiter. Free T4 and TSH measurement was made by chemiluminescence, with the reference value from 0.75 to 1.8 ng/dL and from 0.30 to 5.0 μIU/ml, respectively. The ultrasound evaluated the gland volume and the presence of nodules. The scintigraphy with radioactive iodine (131I) was used to identify function of the thyroid tissue. The perchlorate test was done in patients after administration 131I and its uptake was calculated 2 hours later. The test was positive when the reduction in uptake was greater than 20%.

**Results:** Nine patients aged between 8 and 16, of whom 7 were female were selected. The minimum, maximum 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.

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**P73**

**Demographic and Clinical Characteristics of Graves’ Disease at a Pediatric Hospital During the Period 2004–2014**


Instituto Nacional de Pediatría, Ciudad de Mexico, DF, Mexico

**Background:** Graves’ disease is an autoimmune disorder, is rare in childhood, with an incidence of 0.1–3 per 100,000. There are no studies that describe clinical characteristics of this disease in Mexico.

**Objective:** To describe the clinical course of patients with Graves’ disease a children hospital during the period 2004–2014.

**Patients and Methods:** Retrospective cohort of patients with Graves’ disease during 2004–2014.

**Results:** We collected clinical and demographic data on 87 patients; there were 64 (73.6%) women. The mean age was 11 years 1 month. The most common symptom was weight loss in 65.5% (57%). The most frequent physical examination finding: goiter 98.9% (86) and exophthalmos 79.4% (69). Tall stature 32 (36.8%) and short stature 1.1% (1). Malnutrition in 28 (32.2%) patients, overweight in 10 (11.5%) and obesity in 7 (8%) patients. In 28/30 (93.3%) patients thyroid-stimulating immunoglobulin were positive. The first line of treatment was Thiamazole in 64 patients (73.6%) and Iodine 23 (26.4%). The mean duration of methimazole treatment was 2 years 4 months. Thirty-four (47.9%) patients are currently under treatment. Remission was achieved in 33 (37.9%) patients, 26 (78%) women and in 7 (22%) men. Relapse was seen in 20 (23%) and the average age of relapse was 13 years 6 months. It was more common in women 13 (65%), prepubertal 11 (55%) and the most common cause was no response to methimazole 14 (70%). The most common indication for use of iodine was associated with unfavorable socioeconomic conditions in 28 (56%) patients; the most common dose was 15 mCi in 45 (90%) patients. The average of follow-up was 3 year and 6 months. One patient with early menarche was found, and 6 (13.3%) had irregular cycles. Of the patients who have already completed growth, 18 (40.9%) have normal stature, 20 (45.5%) have high stature and 6 (13.6%) short stature.

**Conclusions:** Mexican population evaluated in this study, has clinical characteristics similar to that reported in different studies in Caucasian population. The findings raise the need for prospective studies related to duration of treatment, assessing antithyroid drug treatment for long time, given its low frequency of remission and high rate of relapse.
**P74**

**Helicobacter Pylori Infection in Children and Adolescents with Autoimmune Thyroid Disease**

*Hayes Dorado, J.; Eid Lit, M.; Montero Justiniano, W.*

Caja Petrolera de Salud, Santa Cruz de la Sierra, Bolivia

**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**

*Calderon Vargas, M.*

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The most frequent cause of thyrotoxicosis in children and adolescents is Graves’ disease, an autoimmune disorder characterized by diffuse goiter, hyperthyroidism and ophthalmopathy. The cornerstone of treatment is 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 Graves’ 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**

*Mejia Zapata, L.; Suarez, V.; Millan, J.*

1Fundacion Clinica Infantil Club Noel Unilibre Corserinsa, Cali, Colombia; 2Fundación Clinica Infantil Club Noel UNILIBRE, Cali, Colombia; 3MedicoGeneral Universidaddel Valle, Cali, Colombia

**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. It is recommended when antithyroid drugs fail or cause allergic reaction.

**Table 1.** (for abstract P76)

<table>
<thead>
<tr>
<th>Number patients</th>
<th>15</th>
<th>Average age 10.5 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Female</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>20%</td>
</tr>
<tr>
<td>Clinic characteristics</td>
<td>Exophthalmos</td>
<td>74%</td>
</tr>
<tr>
<td></td>
<td>Tachycardia</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Goiter</td>
<td>100%</td>
</tr>
<tr>
<td>Hormon levels</td>
<td>TSH</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td>T4L</td>
<td>4.9</td>
</tr>
<tr>
<td></td>
<td>T4T</td>
<td>14</td>
</tr>
<tr>
<td>Diagnostic</td>
<td>Graves</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td>Thyroiditis</td>
<td>20%</td>
</tr>
<tr>
<td>Treatment</td>
<td>Pharmacological</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>25–30 mCi I131*</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>Average of time for use I131*</td>
<td>19.4 Months</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Average dose of levotiroxina post I13*</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>110 mcg</td>
</tr>
</tbody>
</table>
**Materials and Methods:** We describe 15 patients with hyperthyroidism (Graves or thyroiditis) which consulted at Fundación Clínica 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 I131. Patients included Down syndrome (two) and associated cardiomyopathy and 3 for unresponsiveness to antithyroid drugs. Response was excellent.

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**P77**

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


Universidade Federal de Minas Gerais, Belo Horizonte, Brasil

**Introduction:** Maternal antithyroid drugs and thyrotropin receptor blocking antibodies (TRAb) are the most common cause of transient hypothyroidism in newborns. Undefeated 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.

**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 of the thyroid, without alterations in the gland’s texture. Laboratory exams in the day after the birth revealed blood levels of total T4=5.6 mcg/dL and TSH = 44.2 mcUI/mL consistent with congenital hypothyroidism. L-T4 supplementation (37.5 mcg/day) was initiated, with new exams performed 14 days after birth, revealing decrease in the thyroid hormones blood levels (FT4 = 1.7 ng/ml). The TSH = 0.49 mcU/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-T4 supplementation was decreased to 25 mcg/day, being suspended at 2 months old, with blood levels of FT4 and TSH remaining in the reference range throughout monitoring. The last exam at 8 months old showed levels of FT4, TSH and TRAB of 1.06 ng/dl, 0.55 mcU/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 diagnosis 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.

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**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**

*Silveira, F.; Claudino, L.; Leite, H.; Dias, V.; Luz, M.; Silva, R.; Chagas, A.*

NUPAD/UFGM, BELO HORIZONTE, Brasil

**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 (dysmorphogenesis) 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 Triângulo and North Triângulo.
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 etiological CH found in 704 children was dysgenesis with a frequency of 44.3%, followed by dysmorphogenesis in 16.8% and Transient hypothyroidism (1%). In dysgenesis group, Hypoplastic thyroid with 22.4% and the Ectopic thyroid with 11.1% stood out. In the dysmorphogenesis group, the Thyroperoxidase 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 dysmorphogenesis. 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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**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 ug/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 hypoTBGemia. 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 hypothyremia (13 non-thyroidal illness; 1 healthy). One additional multi-malformed patient died at 3 days of life. Five boys had hypoTBGemia (mean T4 2.6 μg/dl; TBG <3.5 μg/dl). Three had permanent CH-C (mean T4 3.9 μg/dl) due to a hypothalamo-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 mayor 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-dependent pubertal 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 leucocytes of the peripheral blood and a 100 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, testsis-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 (Ensembl, 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.

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**OS4**

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

Cabello Morales, E.; Miranda Cabrera, B.; González Lagos, I.; Lozano Rojas, G.; Ramírez Alvear, E.; Mendoza Luna, Y.

Hospital Cayetano Heredia, Lima, Perú

**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 ≥425 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 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
Franco, R.; Ybarra, M.; Cominato, L.; Velhote, M.; Damiani, D.
Instituto da Criança – Hospital das Clínicas – Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

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 anemia 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.

O56
McCune-Albright Syndrome in Eight Patients, Clinical Correlation and Spectrum of the Disease
Mejia Zapata, L.; Lammmoglia, J.; Boric, A.; Johnson, M.
1Fundacion Clinica Infantil Club Noel UNILIBRE, Corserinsa, Cali, Colombia; 2Unit of Growth and Bone Metabolism, Instituto de Ortopedia Infantil, Bogota, Colombia; 3Biology Molecular Institut of Investigation Materno Infantil IDIME, Chile

Introduction: Albright-McCune Sternberg syndrome (SAMS) is a rare disorder which originates in a germinal mutation of gene GNAS1, which codifies the alpha subunit of protein G (Gsa). It is characterized by a typical phenotype which includes polyostotic fibro dysplasia, precocious puberty independent from gonadotropins, cafe-au-lait spots and a series of endocrine abnormalities. The most common mutations include a cysteine or histidine for arginine substitution in codon 201 of exon 8 (R201C or R201H) or a glutamine for arginine or leucine substitution in codon 227 of exon 8 (Q227L or Q227L). Woman to male relation is 10 to 1.

Objective: To describe 8 patients with with MaCCune-Albright syndrome and a GNS1 mutation and your evolution.

Description: See table 1.

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>Mutation arg 201</th>
<th>Pelvic usg</th>
<th>Fibro dysplasia</th>
<th>Other 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>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
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<td>+</td>
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<td>+</td>
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<td>–</td>
</tr>
<tr>
<td>12</td>
<td>Female</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>Pending</td>
<td>Cyst</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>
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<tr>
<td>1</td>
<td>Female</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Cyst recurrent</td>
<td>+</td>
<td>Hyperthyroidism, gigantism</td>
</tr>
<tr>
<td>7</td>
<td>Female</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>Pending</td>
<td>Cyst</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>Female</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>Pending</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.

**O57**

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

Scaglia, P.1; Bergadá, I.; Braslavsky, D.; Keselman, A.1; Espinola Castro, A.2; Doméné, S.1; Jasper, H.1; Doméné, H.1

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**Background:** In ALS-deficient patients, some IGFALS 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 mutagenic 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 IGFALS gene and uniparental lineage markers in families harboring the c.103dupG and c.[1225C>T;1424C>T] variants.

**Methods:** We sequenced the IGFALS 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 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 (CA12/gtgggtgcc/(CA)21). On the other hand, the c.[1225C>T;1424C>T] carriers of the two remaining families shared a common microhaplotype (CA15/acgaaacct/(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.

**O58**

**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.
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 showed TCH forms in 31 (23.5%) cases. LTd (2.1%), and eutopic thyroid gland 132 (19.5%). Patients with 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 permanent CH (PCH) and transient forms (TCH).

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 (3.4%) 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%) had PCH. Etiologies of PCH forms were: athyreosis 161 (23.9%), ectopic 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.
**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 hypoechogetic, 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**

Prieto, L.; Mendez, V.; Enacan, R.; Bergadá, I.; Chiesa, A.; Grueiro-Papendieck, L.

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 began 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 premature <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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**Table 1.** (for abstract O62)

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<th>Disease</th>
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<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>44.639</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>

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**O63**

**TRH Test Utility for Primary Hypothyroidism Diagnosis in Pediatric Patients**

Tourrier, A.; Sosa, S.; Vogliore, D.; Pattin, J.; Marianelli, A.; Martins, E.; Gonzalez, V.; Morin, A.; Balbi, V.

1Hospital de Niños SSM Ludovica de La Plata, La Plata, Argentina; 2Facultad de Ciencias Exactas UNLP, La Plata, Argentina

**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
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 TRH test) were compared. TSHb of TRH test 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 TRH test. 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.
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