HORMONE
RESEARCH IN
PÆDIATRICS

ABSTRACTS

XXII Annual Meeting of the Sociedad Latino-Americana de Endocrinología Pediátrica (SLEP)

Cartagena de Indias, Colombia, September 7–10, 2011

Guest Editor
Audrey Mary Matallana Rhoades, Cali, Colombia

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Program

September 7, Wednesday

14:00–17:45	Registration
15:30–16:30	Satellite Symposia
16:30–17:30	Satellite Symposia
18:00–18:30	Opening Ceremony
18:30–20:00	Ceremony in Honor of the 'Maestro de La Endocrinología Latinoamericana 2011, Award' Opening Lecture: Maestro de la Endocrinología Latinoamericana 2011 Award
20:00–23:00	Dinner/Cocktail

September 8, Thursday

08:00–09:00	Conference 1 'Up-Date On Puberty' Professor Olle Söder, MD, PhD Karolinska Institute and University Hospital, Sweden
09:15–10:15	Oral Presentation Session 1
10:15–10:45	Break
10:45–12:15	Oral Presentation Sessions 2 and 3
12:30–13:30	**SLEP/PES Symposia**
12:30–13:00	'Type 2 Diabetes in Youth. Why, Who and What We Should Do' Professor Francine Kaufman, MD Emeritus Professor of Pediatrics and Communications at USC The Center for Diabetes, Endocrinology & Metabolism Childrens Hospital Los Angeles, USA
13:00–13:30	'Metabolic Alterations in Obesity and Changes after Intervention Studies' Professor Roberto Lanes, MD Universidad Central de Venezuela, Caracas, Venezuela
13:30–15:00	Lunch/Symposia

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15:00–16:30	Posters Session 1
16:30–17:00	Break
17:00–18:00	Conference 2 'Neuroendocrinology of Anorexia Nervosa: In the Context of Bone Metabolism' Professor Madhusmita Misra, MD, MPH; USA
18:00–19:00	Conference 3 'New insights of SOX9 in 46,XX and 46,XY DSD' Professor Yves Morel, MD, PhD Service d'Endocrinologie Moléculaire et Maladies Rares, Lyon, France
19:00–20:30	SLEP Bussines Meeting

September 9, Friday

08:00–09:00	Conference 4 'Diabetes Technology and What It Can Offer Our Children' Professor Francine Kaufman, MD, USA
09:15–10:15	Oral Presentation Session 4
10:15–10:45	Break
10:45–11:45	**SLEP/ESPE SYMPOSIA**
10:45–11:15	'Systems Biology in Childhood Diabetes' Professor Francesco Chiarelli, MD, PhD Professor of Paediatrics and Paediatric Endocrinology University Department of Paediatrics, Chiety, Italy
11:15–11:45	'Adolescence in Girls with Type 1 Diabetes: From Puberty to Pregnancy Prevention' Professor Ethel Codner, MD Instituto de Investigaciones Materno Infantil (IDIMI) Universidad de Chile, Santiago de Chile
12:00–13:30	Oral Presentation Sessions 5 and 6
13:45–15:15	Lunch/Symposia
15:15	Free Afternoon

September 10, Saturday

08:00–09:00	Conference 5 'Management of Pregnancies at Risk of 21-Hydroxylase or 11-Hydroxylase Deficiency Using Fetal Sex Determination in Maternal Serum' (2002–2009) Professor Yves Morel, MD, PhD; Francia
09:15–10:15	Oral Presentation Session 7
10:15–10:45	Break
10:45–11:45	**CESAR BERGADA Lecture** 'Genetic Insights into Human Central Pubertal Disorders' Professor Ana Claudia Latronico, MD, PhD Universidad de Sao Paulo, Brasil
12:00–13:30	Posters Session 2
13:30–14:30	Lunch

14:30–15:30	Conference 6 'Pheochromocytoma in Children' Professor Camilo Jimenez, MD University of Texas, MD Anderson Cancer Center, Houston USA
15:45–16:45	Oral Presentation Sessions 8 and 9
16:45–17:15	Break
17:15–18:15	Conference 7 'Reproductive and Bone Health in the Female Athlete' Professor Madhusmita Misra, MD, MPH Mass General Hospital and Harvard Medical School, USA
18:15–18:45	Closing Ceremony and Awards
20:45–00:45	Gala Dinner

HORMONE RESEARCH IN PÆDIATRICS

Horm Res Paediatr 2011;76(suppl 4):1–31

Oral Presentations

1

Unbound/Bioavailable IGF-I Enhances Somatic Growth

H. Jasper[1], H. Domené[1], L. Karabatas[1], C. Guida[1], S. Yakar[2]

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Introduction and Objectives: Des1-3-IGF-I (DES) is an IGF-I analog with normal affinity for the IGF-I receptor but reduced affinity to IGFBPs. To determine whether IGF-I binding to IGFBPs is necessary for normal growth, we generated a knock-in mouse model of DES-IGF-I (KID). **Methods:** In KID the Igf1 gene was replaced by des-Igf1, and therefore expressed under the endogenous Igf1 promoter. Serum determinations: DES by RIA, IGF-I by RIA, IGBP-3 by ELISA, ALS by immunoblot, ternary complex formation (TCF) using either iodinated IGF-I or DES as tracers. **Results:** See table. Compared to controls KID increased body weight and length, relative weights of kidney, pancreas, uterus and ovaries ($p<0.05$). Serum DES was reduced ($p<0.0001$). KID TCF was reduced when WT-IGF-I was used as a tracer ($p<0.01$); bound IGF cpm/total cpm was reduced in KID ($p<0.001$) when DES IGF-I was used as tracer. **Conclusion:** Despite reductions in serum IGF and TCF, KID exhibited increased body weight and length, but not all organs responded equally. DES lower affinity for IGFBPs, reducing bound-IGFs in KID, suggests that an increase in bioactive DES (free plus that loosely bound to IGFBPs) at the target organ is responsible for KID´s increased body size and selective organ.

2

Analyses of the *GLI2* Gene in Patients with Congenital Isolated GH Deficiency (IGHD) or Associated to Other Pituitary Hormone Deficiencies (CPHD) Without Holoprosencephaly (HPE)

M. França, A. Jorge, L. Carvalho, A. Otto, F. Corrêa, E. Costalonga, B. Mendonca, I. Arnhold

HC - FM - USP - Unidade de Endocrinologia do Desenvolvimento, Laboratório de Hormônios e Genética Molecular, São Paulo, Brasil

Introduction: GLI2 is a transcription factor involved in early embryogenesis of the pituitary gland and ventral diencephalum. *GLI2* mutations were first described in patients with HPE. **Objective:** Study *GLI2* in 180 patients with IGHD or CPHD without HPE. **Methods:** The coding region of *GLI2* and the exon/intron boundaries were amplified by PCR in genomic DNA and sequenced. **Results:** In 3 families, 3 novel heterozygous nonsense or frameshift mutations were identified: p.L788fsX794, p.L694fsX722 and p.E380X, predicting truncated proteins with loss of the transcriptional activation domain. The phenotype of the subjects with these mutations included IGHD or CPHD, ectopic (or non-visualized) posterior pituitary lobe on MRI, polydactyly or midline facial defect, in addition to normal relatives, indicating an autosomal dominant inheritance pattern with incomplete penetrance. Heterozygous missense mutations were identified in 21 patients: p.A203T, p.P253S, p.A268V, p.R473H, p.A780V, p.F830L, p.R933H, p.G947D, p.V1117L, p.G1197D and p.M1241I/P1485A (all novel); and p.A268V, p.G1197D, p. M1444I/L1445F and M1352V/D1520N (previously published). According to *in silico* studies, p.P253S, p.A268V, p.P1485A and p.D1520N are probably deleterious; p.F830L, p.M1444I and p.L1445F are possibly deleterious and the other missense mutations are probably benign. All patients with missense mutations had CPHD and ectopic posterior pituitary lobe with the exception of 2 patients with p.G1197D and p.M1444I/L1445F who had IGHD and a eutopic posterior lobe. Polydactyly and midline facial defects were absent in the patients with missense *GLI2* mutations. **Conclusion:** *GLI2* mutations are relatively frequent (13%) in patients with congenital IGHD or CPHD without holoprosencephaly, suggesting an important role for GLI2 in

Table 1. (for Abstract 1)

Females age 16 weeks	Body weight (g)	Body length (cm)	Pancreas [p] (% of BW)	Kidney [k] (% of BW)	Uterus & ovaries [uo] (% of BW)	IGF (ng/ml)	TCF (% total binding)	Bound IGF cpm/ total cpm
Control N=9	22.7±1.3	9.3±0.3	0.8±0.1	1.3±0.03	0.6±0.06	IGF-I 157.3±7.1	28.8±3.9	57.2±3.8
KID N=12	27.1±2.1	9.8±0.2	1.2±0.1	1.6±0.03	1.2±0.09	DES 68.3±7.6	14.6±2.0	29.3±4.3
p	<0.05	<0.05	<0.05	<0.05	<0.05	<0.0001	<0.01	<0.001

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the etiology of congenital hypopituitarism, especially when associated to an ectopic posterior pituitary lobe.

3

In Vitro Characterization of F646S-STAT5b Mutant: A Bioinactive STAT5b Protein Associated with Severe Post Receptor Growth Hormone Insensitivity (GHI) and Immune Dysfunction

P. Scaglia[1], A. Martínez[1], E. Feigerlova[2], P. Fang[2], M. Ballerini[1], H. Jasper[1], J. Heinrich[1], R. Rosenfeld[2], V. Hwa[2], H. Domené[1]

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Introduction: Patients with STAT5b deficiency show growth hormone insensitivity and a variable degree of immune dysregulation. **Objective:** To characterize in vitro expression and functional transcriptional activity of the F646S-STAT5b mutant, found in a patient with severe GHI and immune dysfunction. **Methods:** FLAG-Tagged wild type (WT) and mutant F646S STAT5b, were transiently transfected into HEK293(hGHR) cell line. Functional studies included immunoprecipitation, Western immunoblot and immune detection of phosphorylated STAT5b proteins upon GH treatment. Luciferase (pGHRE-LUC)-transfected HEK293(hGHR) cells were analyzed for reporter activity. **Results:** In transiently expressed HEK293(hGHR) cell lines, expression of the F646S- STAT5b mutant was not as robust as WT. Upon GH treatment, F646S mutant can still be tyrosine phosphorylated, although to a lesser extent than WT. Immunologically equivalent concentrations of mutant F646-STAT5b protein showed no luciferase activity in contrast to a robust 100 fold induction of WT-STAT5b protein. **Conclusions:** In vitro characterization demonstrates that the F646S-STAT5b mutant retains some ability to become phosphorylated but is completely devoid of transcriptional activity. These findings suggest that this mutant results in a bioinactive STAT5b protein, responsible for complete GHI.

4

Non-Synonymous IGFALS Allelic Variants (ns-Av), Associated with Diminished Levels of IGF-I, IGFBP-3 and ALS, are Found in Nonfamilial (Nf) But Not in Familial (F) Idiopathic Short Stature (ISS) Children

A. Martínez[1], P.A. Scaglia[1], A. Keselman[1], M.G. Ropelato[1], M.G. Ballerini[1], S.V. Bengolea[2], V. Pipman[3], R. Rey[1], J.J. Heinrich[1], H. Jasper[1], H. Domene[1]

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Introduction: Low levels of IGF-I are found in about 30% of ISS children and some of them present heterozygous ns-AV-IGFALS allelic variants. **Aim:** Our aim was to identify potential carriers of ns-AV. **Methods:** Height (H-SDS), target adjusted height (TAH-SDS), were collected in 68 ISS prepubertal children, classified as F or NF and according to IGF-I levels (normal or low). Serum levels of IGF-I, IGFBP-3 and ALS were determined and the IGFALS gene was sequenced. **Results:** NF were significantly shorter than F children, but their levels of IGF-I, IGFBP-3 and ALS were not different. Those presenting low IGF-I had reduced levels of IGFBP-3 and ALS, but did not differ in H-SDS or TAH-SDS. ns-AV-IGFALS were present in 6/34 NF vs. 2/34 F (p NS), but if low IGF-I and IGFBP-3 were also considered, IGFALS ns-AV were present in 5/34 NF and 0/34 F (p=0.02). **Conclusion:** These findings suggest that the NF subgroup of ISS children with reduced levels of IGF-I and IGFBP-3, would be the most likely candidates for genotyping the IGFALS gene searching for ns-AV.

Table 1. (for Abstract 4)

	Familial ISS (1)	Non Familial ISS (2)	NF vs F (p)	Normal (N) IGF-I ISS	Low (L) IGF-I ISS (3)	N vs L IGF-I ISS (p)
N	34	34		44	24	
CA (y)	8.18±2.57	8.57±3.24	NS	8.66±3.12	7.85±2.45	NS
H-SDS	–2.65±0.45	–2.96±0.49	0.0080	–2.77±0.57	–2.86±0.31	NS
TAH-SDS	–0.97±0.47	–2.38±0.58	–	–1.61±0.87	–1.79±0.91	NS
IGF-I (SDS)	–1.20±1.33	–1.84±1.45	NS	–0.67±0.82	–3.07±0.85	–
IGFBP-3 (SDS)	–0.93±0.92	–1.05±1.45	NS	–0.67±0.99	–1.36±1.59	0.0313
ALS (SDS)	–1.23±1.17	–1.62±1.58	NS	–1.00±1.08	–2.2±1.59	0.0005
ns-AV	2/34	6/34	NS	3/44	5/24	NS

Results expressed as mean±SD. (1) TAH-SDS >–1.6. (2) TAH-SDS <–1.6. (3) IGF-I <–2.0 SDS.

5

Novel Heterozygous Mutation in the StAR (Steroidogenic Acute Regulatory Protein) Gene in a 46,XY Patient with Congenital Lipoid Adrenal Hyperplasia (CLAH)

M. Baquedano[1], *G. Guercio*[1], *D. Nápoli*[1], *M. Costanzo*[1], *E. Berensztein*[1], *R. Marino*[1], *M. Bailez*[2], *E. Vaiani*[1], *M. Rivarola*[1], *A. Belgorosky*[1]

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Introduction: StAR facilitates cholesterol entry into the mitochondria. Recessive mutations cause classic and nonclassic CLAH. **Aim:** To report the molecular consequences of a novel heterozygous StAR mutation. **Methods:** A 46,XY patient with ambiguous genitalia and primary adrenal insufficiency was studied. **Results:** We found a heterozygous de novo IVS1-2A>G change in StAR and the pGly146Ala heterozygous polymorphism in SF1. RT-PCR from patient's testicular mRNA showed a –exon2 transcript and the wild-type (WT) transcript. 37kDa precursor and 30kDa mature protein were detected in COS cell transfected with mutant and WT plasmids. Immunofluorescence showed almost no colocalization of mitochondria and mutant protein (delta22-59StAR). Delta22-59StAR activity was 65%±13 of WT. Cotransfection with WT and delta22-59StAR plasmids reduced WT activity by 62%±13.9. **Conclusion:** Novel splice-junction heterozygous StAR mutation (IVS-2A>G) results in the in-frame loss of aa22 to 59 in the N-terminal mitochondrial targeting signal. Deletions of 62 N-residues of StAR are known to preclude mitochondrial entry, without affecting its activity. However, although delta22-59StAR almost did not localize to the mitochondria, it showed a reduced activity. Aberrant folding may have compromise its activity. delta22-59StAR might interfere with WT StAR by competing cholesterol binding causing an autosomal dominant effect, explaining the clinical phenotype in heterozygosis.

6

Reduction of the Androgen Receptor (AR) mRNA in Urethral Mucosa Cells of Patients with Penile Grade-I Hypospadias

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Introduction and Objectives: Androgen levels and AR mutation analyses are usually normal in patients with penile grade-I hypospadias (Pradder V), remaining as idiopathic condition in most cases. **Methods:** To rule out the involvement of abnormal quantitative amount of ARmRNA in the genesis of this genital anomaly, we studied grade-I hypospadia patients (n=17; mean age (SD)=4.0 (3.0) years and control-patients with phimosis (n=41, age mean (SD)=4.7 (2.1) years. Methods: ARmRNA obtained from urethral mucosa cells were measured by qRT-PCR (Applied Biosystems, USA) and corrected by the normalizing gene BCR. **Results:** Penile size were similar in hypospadia and phimosis (median (p25–75)=4.9 (4.2–5.5)cm vs 5.2(4.8–5.8)cm, Mann-Whitney Test, p=0.137). ARmRNA were significantly reduced in patients with hypospadia vs. phimosis (median (p25–75)=0.5 (0.3–0.65) vs 0.3 (0.1–0.4) Mann-Whitney Test, p=0.002). In these patients, we also observed significant correlation between penile size and the number of CAG repeats (R=.5; p=0.039) and tendency toward correlation with ARmRNA (R=0.48; p=0.053). **Conclusion:** a reduced amount of androgen receptor mRNA is observed in grade-I hypospadia patients. In these patients, penile size is negatively correlated with the number of CAG repeats and positively correlated with urethral mucosa ARmRNA expression.

7

Polycystic Ovarian Morphology (PCOM) in Adolescents with Regular Menstrual Cycles is Associated with Elevated Anti-Müllerian Hormone (AMH)

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Introduction and Objectives: AMH serum levels are an index of the number of small ovarian follicles (2–5 mms), but whether this association is observed during adolescence is unknown.

Aim: To determine if AMH may be used as a surrogate marker of PCOM in healthy girls. **Methods:** We studied 74 non-obese non-hyperandrogenic adolescents with regular menstrual cycles. Transabdominal ultrasound and blood samples were obtained during follicular phase. PCOM was defined according to Rotterdam criteria. **Results:** PCOM was observed in 33.8% of the girls. Girls with PCOM had lower FSH and higher AMH than girls without PCOM (72.5±6.1 vs. 34.6±3.1 pmol/L; P<0.001 for AMH). AMH levels >60.15 pmol/L had 64.0% sensitivity and 89.8% specificity to diagnose PCOM (AUC=0.873). AMH levels correlated positively with 2–5 mm follicle number (r=0.302, p=0.009). Similar levels of inhibin B, androgens and LH were observed in girls with and without PCOM. **Conclusion:** PCOM in healthy adolescents was prevalent and not associated with hyperandrogenism. Elevated AMH and lower FSH observed in PCOM suggest that this ovarian pattern is secondary to a larger number of small follicles. An elevated AMH level is suggestive of the presence of PCOM during adolescence.

8

Developmental Changes in Androgen Receptor (AR), Estrogen Receptor (ER) (Alpha and Beta) and Aromatase (ARO) Immuno-expression in the Human Testis (HT). Comparison Between Mini-puberty (MINI) and Definitive Puberty (PUB)

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Introduction and Objectives: To study if mini-puberty (MINI)and puberty (PUB) human testis (HT) are differently regulated. **Methods:** AR, ER (α, β)and ARO immunoexpression was studied (n=32): 1) MINI vs PUB. 0-to7-month-old HT (MINI, n=16) was comred with 15-year-old (PUB, n=5) 2)correlation with age, 1- to 15-yea HT (n=16). Immunoexpression estimated as % of positive cells, X±SEM. **Results:** In Leydig cells (LC), AR and ERα in MINI were lower than in PUB (8.8±0.8 vs 52±5, and 3.7±0.8 vs 96±1.2, p<0.05)and ARO was higher (76±1.1 vs <1%, p<0.05). In Sertoli cells (SC), AR and ERβ in MINI were lower than in PUB (4±0.4 vs 92±2.9%, and 27±2.9 vs 69±1.7%, p<0.05). In Germ cells (GC), ARO and ERβ in MINI were lower than in PUB (45±1.6 vs 95±1.7%, and 30±1.9 vs 92±4%, p<0.05). Spematocytes and spermatids also expressed ARO. Correlation with age:SC, ERβ (p=0.0007, r=0.82) and AR (p=0.001, r=0.97) increased. In GC, ERβ (p=0.002, r=0.88) and ARO (p=0.000, r=0.94) increased. **Conclusion:** ARO and ERβ expression in GC in MINI and PUB suggests a role for local estrogens. Differences in ARO, ER and AR expression in LC in MINI and PUB, indicate local changes for sex hormones. Gradual changes confirm HT activity during prepuberty.

9

Molecular Diagnosis and Endocrine Evaluation in Aromatase Deficiency, Three Novel Mutations and a Possible Founder Effect

R. Marino[1], N. Perez[1], N. Saraco[1], C. Rocco[1], G. Guercio[1], M. Costanzo[1], D. Warman[1], M. Ciaccio[1], G. Pena[2], J. Garcia[3], M. Miras[4], L. De Lacerda[5], M. A. Rivarola[1], A. Belgorosky[1]

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Introduction and Objectives: Since 1991, 19 cases of aromatase deficiency, 11 females and 8 males, have been reported. The aims were to detect CYP19A1 mutations in aromatase deficient patients. To characterize clinical and endocrinological features. To construct haplotypes linked to a recurrent mutation. **Métods:** Seven female patients with ambiguous genitalia were studied. **Results:** Maternal virilization during pregnancy was absent in 4/7. Ovarian enlargement/cysts was detected in 5/7 and 3/7 presented spontaneous breast development. 4/7 nonrelated patients presented the c655G>A splice mutation, previously described in one aromatase deficient man from Argentina. Three novel mutations were found in 4 patients (p.Y81C, p.R192C, IVS9+5 G>A). To investigate a possible common ancestry linked to c655G>A in our population, the haplotypes of the 4 c655G>A patients were characterized with 22 polymorphic markers within the gene and compared with those published from caucasian american population. The 4 patients shared a common haplotype in the c655G>A allele. This mutation was found to be linked to the same haplotype with a significantly higher frequency than it was expected (p=0.019). **Conclusion:** These results suggest that c655G>A appeared just once in an ancestral haplotype and its high frequency in our population is a consequence of a founder effect.

10

A Novel Heterozygous Missense Variant on *FGFR2* Gene in Two 46,XY Sisters with Non-syndromic Partial Gonadal Dysgenesis

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Introduction and Objectives: Fgf9/Fgfr2 signaling seems to be essential to maintain SOX9 expression after sex determination, a critical effect for normal male gonadal development. Fgfr2 knockout mice present severe abnormalities in male gonadal development that cause male-to-female sex reversal. Deletions of 10q chromosome are classically associated with dysmorphic facial features, heart defects, neurodevelopmental deficits and urogenital anomalies

including 46,XY gonadal dysgenesis. FGFR2 is one of the genes located at 10q26 region, suggesting its potential role in the abnormal sex development phenotype of 10q deletion syndrome. Our aim is to analyze if FGFR2 inactivating mutations or deletions would be involved in the etiology of non syndromic 46,XY gonadal dysgenesis. **Methods:** We studied 39 46,XY patients with gonadal dysgenesis (GD), 13 with the complete and 26 with the partial form. The entire coding region of FGFR2 was PCR amplified and directly sequenced using a BigDye Terminator in ABI PRISM 3100 DNA sequencer. FGFR2 copy number variation was determined by multiplex ligation probe amplification (MLPA) using the commercial SALSA MLPA P231 Kit and were analyzed by GeneScan. **Results:** A novel heterozygous nonsynonymous FGFR2 variant c.1361 C>T (p.S453L) located at exon 11 was identified in two sisters with partial GD. Their mother is a carrier of this variant which was absent in 100 control males. This variant was tested in two prediction sites (PolyPhen and SIFT) and both confirmed that this protein is possibly damaged. No FGFR2 deletions were identified in MLPA analysis. **Conclusion:** A novel FGFR2 variant c.1361 C>T (p.S453L) was identified in two sisters with 46,XY DSD due to partial GD. If the prediction sites results were confirmed in further functional studies a real role of FGFR2 in human testis embryogenesis will be defined.

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C105fs114x Thyrotropin Beta-Subunit Gene Mutation Resulting in Congenital Central Hypothyroidism: A Genetic Study of a Brazilian Family

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Introduction and Objectives: Central congenital hypothyroidism (CCH) is a rare disease that can result from mutations on genes that regulate pituitary development. We report molecular analysis of a boy with C105fs114X TSH beta subunit gene mutation and his family. **Methods:** Revision of medical records. **Results:** A child presented CCH classical symptoms at 5 months old, not revealed by neonatal screening. Born from consanguineous parents, cesarean delivery, post-term, 4080g weigh and 53cm length. TSH:1.6µUI/mL (0.38–4.5); FT4: 0.1ng/dL (0.8–2.3); TPOAb<10UI/L; TgAb:<20UI/L; Glucose: 55mg/dL; Cortisol: 12.1µg/dL; Prolactin: 22.4ng/mL; H: 15.9ng/mL. Genotyping for beta TSH gene mutation was performed by PCR followed by restriction enzyme analysis with SnaBI, as the single base deletion (822delT) at codon 105 of the beta-TSH gene introduces a new SnaBI restriction site in exon 3, disclosing the C105fs114X mutation. The boy was homozygous; parents and sister heterozygous. **Conclusions:** The C105fs144X mutation, described by Medeiros-Neto et al.(1996) in two Brazilian families with CCH, was afterwards found in Europe, USA and Argentina in non-consanguineous families, differently from this case (parents are first degree cousins). It results in a truncated beta TSH subunit and seems to be the most prevalent mutation in the general population.

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Molecular Findings in Patients with Congenital Hypothyroidism Due to Mutations in the Thyroglobulin Gene

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Introduction and Objectives: Thyroglobulin (TG) is a 660 kDa-glycoprotein coded by a single copy gene 270 kb long that maps on chromosome 8q24.2–8q24.3. TG gene mutations are associated with congenital goiter and hypothyroidism with considerable phenotype variation. To identify mutations in the TG gene in patients with goiter, hypotiroidism and low serum TG levels. **Methods:** We studied nine patients from five nonconsanguineous families. The promoter and the coding regions of the TG gene, with the flanking intronic regions, were analysed by direct DNA sequencing. **Results:** Three novel TG mutations were identified: p.Y107X(exon4), p.C1262Y(exon17), and p.K1803fsX1833(exon28) and three previously reported mutations: p.R277X(exon7), p.A2215D(exon38) and p.R2317X(exon40). Two patients carried a compound heterozygous for p.K1803fsX1833/p.R2317X and p.Y107X/p.C1262Y mutations; five patients from two unrelated families showed a homozygous p.R277X substitution. The remaining, two patients with typical phenotype, had a single p.A2215D mutated allele. **Conclusion:** We report the occurrence of three new mutations of the TG gene. The prevalence of a limited number of mutations in each population will facilitate molecular genetic testing. The continued study of TG mutations may be helpful to understand the pathophysiology of hereditary diseases, carrier identification and genetic counseling.

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Clinical, Biochemical and Molecular Findings in Patients with Congenital Hypothyroidism Due to Mutations in the Thyroid Peroxidase (TPO) Gene

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Introduction and Objectives: Mutations in TPO gene are the most common cause for dyshormonogenesis. Its produce a variable

phentoype characterized by hypothyroidism and congenital goiter with autosomal recessive inheritance. **Objective:** To describe the clinical, biochemical and molecular findings in a cohort of patients with congenital hypothyroidism, goiter, and high thyroglobulin levels. **Methods:** We studied 11 patients from 7 unrelated families, 6 of them diagnosed by newborn screening. Ultrasound and Tc99-scintigraphy were performed and TSH, T4, Free T4, T3 and TG were measured (EQLIA). The promoter and the 17 exons of the TPO were amplified by PCR, along with its flanking intronic regions. The products were analyzed with SSCP and those with differential migration were sequenced. **Results:** Goiter characteristics, as well as T4, Free T4, T3 and TSH levels, were similar. Three new mutations were identified: p.R595K (exon11); p.V748M (exon13), and g.IVS16-2A>C (intron16). Mutations in TPO gene were found in homozygosis in 2/11 patients, in composed heterozygosis in 6/11, and in 3/11 patients a single mutated allele was detected in exons 8, 13 and in intron16. **Conclusion:** Our findings confirm genetic heterogeneity of the defects in TPO gene. Identifications of new mutations can be useful to better understand physiopathology of congenital hypothyroidism.

14

Determining Autoantibodies to Thyroid Peroxidase and Thyroglobulin in a Paediatric Population

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Introduction and Objectives: Autoantibodies to thyroid Peroxidase and Thyroglobulin are markers of thyroid autoimmunity and can be quantified by different assays. It is necessary to establish reference values for each method in paediatric populations for an effective use in the study of autoimmune diseases (AD). **Aims:** To determine the cut-off levels of TPOAb and TgAb for two methods in healthy children. To establish the diagnostic concordance and the prevalence in different AD. **Methods:** We determined TPOAb and TgAb in 616 samples using ECLIA-Roche and CLIA-Siemens. We analyzed 229 healthy children and 387 patients with associated autoimmune diseases. Cut-off levels, diagnostic concordance and prevalence were determined. **Results:** Cut-off levels (IU/ml) are presented in table. TPOAb and TgAb were more prevalent in Hyperthyroidism, Turner Syndrome and Diabetes Mellitus. We observed significative differences in the diagnostic concordance of TgAb measurement ($p=0.0003$). The highest TSH levels were observed with positive autoantibodies for each method. ($p<0.01$). **Conclusion:** Our results allowed us to establish cut-off levels for the methods used in pediatric patients and confirmed the high prevalence of these antibodies in autoimmune diseases.

Table 1.

	95 percentile	97 percentile	97.5 percentile
TPOAb CLIA	11.8	17.6	18.2
TPOAb ECLIA	26.1	31.7	43.1
TgAb CLIA	10.0	21.7	22.6
TgAb ECLIA	35.0	51.3	85.7

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Hot Nodule Harboring a Papillary Microcarcinoma of Thyroid in an Adolescent Girl from an Iodine Sufficient Area

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Introduction and Objectives: Hot nodules on thyroid scintigraphy are generally benign, only rarely associated with cancer in pediatrics. Higher incidence is reported in iodine deficiency area after introduction of iodine supplementation. We report of a girl with a thyroid hot nodule whith family history of thyroid cancer from a sufficient iodine area **Methods:** A firm mobile nodule on thyroid topography was palpated. Ultrasonography showed a cystic nodule of 19x14x13mm with heterogeneous irregular polypoid mass in right lobule. 99mTc thyroid scan showed an hyperfunctioning nodule with normal uptake in the rest of the gland. **Results:** Thyroid function tests showed T4: 9.24 ug/dl (6–14) free T4: 1.44 ng/dl (0.8–2.2) T3: 178 ng/dl (80–220) TSH 4.42 mUI/ml(0.27–4.2) Calcitonin and thyroid antibodies were negative. Fine needle aspiration biopsy (FNAB) was insufficient, this together with ultrasound findings and family history led to hemithyrodectomy. Histological nodular hyperplasia with lymphocytic thyroiditis with a papillary microcarcinoma of 0.25mm was detected. **Conclusions:** We report a new case of hot nodule associated with cancer in a iodine sufficient area. We recommend that FNAB in pediatric patients should be performed in hot nodules with suspicious US findings and/or positive family history for thyroid cancer.

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Severe Permanent Congenital Hypothyroidism (CH) with Apparent Athyreosis: Absence of TSH Receptor (TSHR) Gene Mutations

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Introduction and Objectives: Apparent athyreosis (AA) (negative 99Tc thyroid scan uptake with hypoplastic thyroid on ultrasound or detectable TG levels) represents 7% of permanent CH detected in our neonatal screening program and 30% of athyreotics. **Material and methods:** To search for mutations in TSHR gene, we selected

21 CH with AA detected by neonatal screening. 14/21 CH had negative thyroid scan, positive US and median TG 27 ng/ml (1.8–65). The remaining 7 had negative scan and US and TG levels of 49 ng/ml (6.8–81). All have negative anthythyroperoxidase and anti-thyroglobulin antibodies, The whole coding sequence of TSHR gene (exons 1–10) and intronic flanking regions were amplified by PCR from genomic DNA and automatically sequenced. **Results:** Sequenciation of TSHR gene revealed 4 different SNPs in heterozygous state in 9 patients: 1 P52T (rs2234919), 4 N187N (rs2075179), 2 D727E (rs1991517), 1 D727E/ N187N and 1 D727E/A459A (rs 113951800). No novel or previously described mutations associated with CH were found. **Conclusion:** TSHR gene mutations appear to be uncommon in AA in our population. Although a functional effect of TSHR polymorphisms could not be ruled out, previous studies of SNPs does not support this hypothesis

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The Effect of Transdermic Dihydrotestosterone Gel Treatment on Penile Size: Experience with Fifteen Patients

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Introduction and Objectives: Advantages of Dihydrotestosterone gel 2.5% (DHT) treatment to promote external genitalia virilization are: transdermal route of administration and absence of estrogen-related effects. Objective: Analyse the results of DHT treatment in patients with isolated micropenis or ambiguous genitalia with microphalus. **Materials and Methods:** Fifteen patients were evaluated: four with testosterone synthesis/action/metabolization defects; six with gonadal development defects and five with isolated micropenis. The stretched penile length was expressed as mean±SD. Treatment response was evaluated by the difference between the Z score before and after treatment. Brazilians penile anthropometry was used as reference. **Results:** Mean age: 6.43±3.95 yr. Mean daily dose: 3.55±1.42 g. Duration of treatment: 2.75±1.88 mo. Penile size before: 3.34±0.86 cm (Z .35±0.68). Penile size after: 4.76±0.74 cm (Z .86±0.88). Z score of treatment response: 1.49±0.29 ($p < 0.0001$). There was no difference in treatment response between the groups of patients. There is an inverse correlation between age and final penile size ($p = 0.024$). Tanner Stage of pubic hair development (12/15 patients): 6 unchanged; 5 progressed one stage and 1 two stages. **Conclusion:** DHT treatment was effective and safe on penile growth induction, particularly when initiated in earlier ages.

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Preserved Fertility in a Patient with a 46,XY Disorder of Sexual Development (DSD) Due to a New Heterozygous Mutation in NR5A1 Gene. 46,XY and 46,XX Gonadal Dysgenesis in the Affected Offsprings

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Introduction and Objectives: The nuclear receptor SF1 regulates the transcription of genes involved in reproduction, steroidogenesis and male sexual differentiation. Human mutations cause gonadal dysgenesis with/without adrenal failure in both 46,XY and 46,XX individuals. We previously reported extreme within-family variability in 46,XY affected patients. Low ovarian reserve with preserved fertility was reported in females harboring NR5A1 mutations. There is no report in 46,XY affected individuals raised as males. **Methods:** We studied a kindred with multiple affected members. Three 46,XX patients presented premature ovarian failure, a 3.8 year-old 46,XX girl presented high FSH levels. Four 46,XY individuals presented severe hypospadias at birth, one of them associated with micropenis and chryptorchidism. The others developed spontaneous puberty and one has fathered five children. **Results:** Mutational analysis revealed a novel heterozygous mutation c938G→A, predicted to cause a pArg313Hys amino acid change affecting a highly conserved aminoacid of the ligand-binding domain. This mutation was predicted to affect protein function with a highly deleterious tolerance index score using the sequence homology based SIFT tool, and by the structure-based approach PolyPhen. **Conclusions:** We described for the first time preserved fertility in a 46,XY DSD patient due to a novel heterozygous mutation in NR5A1 gene.

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Changes in Serum Inhibin B Levels After GnRH Agonist Stimulation in Girls with Precocious Pubertal Development

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Introduction: Precocious pubertal development includes a spectrum of maturity of ovarian axis between non progressive forms of idiopathic premature thelarche (IPT) and true central precocious puberty (CPP). There is scant information on basal Inhibin B (InhB), an early marker of follicular development, in these entities and no information is available after a GnRH analogue (GnRHa) test. **Objective:** To evaluate InhB levels under GnRHa test as an evidence of the ovarian axis maturity in these patients. **Material and Methods:** 33 girls aged 5.5–8.5 yr, breast development stage

3 (23 = CPP and 10 = IPT) underwent Triptorelin test (0.1 mg/m² sc), with blood sampling at 0-3-24h for LH and FSH (IFMA) and at 0–24h for Estradiol (E2)(ECLIA) and InhB (ELISA) measurements. **Results:** At baseline, CPP girls had higher LH, FSH and InhB levels ($p < 0.05$) and presented higher LH-3h and E2-24h responses ($p < 0.001$) than ITP girls. In both groups, InhB-24h levels increased significantly when compared to baseline ($p < 0.001$); this increment was higher in CPP ($p = 0.045$). InhB 24-h showed a positive correlation with E2-24-h ($r = 0.72$, $p < 0.001$). **Conclusion:** InhB reflects increased ovarian activity at baseline and under a sustained gonadotrophic stimulation in CPP; the magnitude of this increment is concomitant with the maturity of ovarian axis.

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Frasier Syndrome in Two Patients with 46,XY Gonadal Dysgenesis and Congenital Nephrotic Syndrome

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Introduction and Objectives: WT1 gene is involved in early gonadal development, kidney and testicular differentiation. Mutations in WT1 have been described in patients with Denys Drash and Frasier syndromes. Heterozygous mutations of the intron 9 alternative splicing site that avoid the synthesis of the WT1-KTS+ isoforms are present in Frasier patients, characterized by 46,XY sex reversal, testicular dysgenesis with high risk of gonadoblastoma, and late onset renal failure secondary mainly to focal and segmental glomerulosclerosis. **Methods:** We report two 46,XY sex reversal patients with congenital nephrotic syndrome. Both presented external female genitalia, non palpable gonads, high basal FSH levels, lack of response to hCG, dysgenetic intraabdominal gonads and müllerian structures. Bilateral gonadoblastoma was detected on patient one at the age of 3 years-old. Both patients developed congenital nephrotic syndrome with early onset of renal failure. Kindey histology was unusually associated with Frasier syndrome, patient one presented diffuse mesangial sclerosis and patient two membranoproliferative glomerulonephritis. **Results:** Both patients showed heterozygous mutations of the alternative splicing site at intron 9 of the WT1 gene (patient one IVS9+5G>A, patient two IVS9+1G>A). **Conclusion:** These patients broaden the phenotypic spectrum of Frasier Syndrome highlighting the importance of karyotype analysis as first-line investigation in phenotypic females with congenital nephrotic syndrome.

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Gene Expression and Protein Content of the Acid Labile Subunit in Fibroblasts from Children with Idiopathic Short Stature

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Introduction and Objectives: The acid labile subunit (ALS) contributes to prolong the half-life of IGF-I. We postulate that the tissue sensitivity to GH in children with idiopathic short stature (ISS) may be modulated by intracellular differences in ALS. Aim: To quantify the expression and protein content of ALS in fibroblast cultures obtained from skin biopsies of children with ISS and from control children with normal stature. **Methods:** We studied 8 prepubertal children between the ages of 5–10 years with short stature and evidence of reduced GH sensitivity, based in post-stimulated levels of GH > 20 ng/mL and a serum IGF-I level <1SDS for age. These patients were compared with children with normal stature ($n = 8$). RNA and proteins were extracted from fibroblasts and were quantified by RT-PCR and Western Blot, respectively. **Results:** We observed lower ALS expression (0.79 ± 0.02 vs 1.17 ± 0.07, $^*p < 0.05$), and borderline lower protein content (0.87 ± 0.04 vs 1.09 ± 0.08, $^*p = 0.06$) after GH stimulation in ISS children compared with controls. **Conclusions:** Some children with ISS show evidence of lower intracellular ALS gene expression and protein content, which may cause a reduction in GH sensitivity and impair their growth.

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Changes in the Profile of Melatonin Secretion in Pediatric Neuroendocrine and Metabolic Alterations

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Introduction and Objectives: There is an increasing interest in the role of melatonin in endocrine and metabolic alterations. We evaluated 3 pathophysiological models: GH Deficiency (GHD), Prader-Willi Syndrome (PWS) and obesity (Ob), and compared them to normal controls (C). **Methods:** We studied 36 children: 6 untreated GHD: 4.0–16.1 yr, BMI (median and range): 17.4(15.0–28.8); 6 PWS: 6.1–15.1 yr, BMI: 30.4(19.8–45.2), 12 obese: 4.7–14.7yr, BMI: 27.3(22.8–34.9) and 12 controls: 6.0–14.5yr, BMI: 19.1(12.2–22.0). Measurements of 6-sulphatoximelatonin (6-SM) were performed in diurnal and nocturnal urine samples (radioimmunoassay, Stockgrand Ltd, Guildford, UK). Delta (nocturnal-diurnal) and 6-SM/BMI ratio (ng/Kg/m2) were calculated. **Results:** (mean ± SEM): (TABLE1) Kruskall-Wallis: diurnal, nocturnal and Δ6-SM with and without BMI ratio were compared in all groups: $p < 0.02$. Mann Whitney: + $p = 0.02$

Table 1.

Groups	GHD	PWS	Ob	C
diurnal 6-SM (μg)	0.2 (±0.06)	3.6 * (±1.0)	1.3 (±0.5)	0.7 (±0.3)
nocturnal 6-SM (μg)	0.8 # (±0.4)	10.3 (±4.2)	9.0 + (±2.3)	4.0 (±1.1)
Δ6-SM (μg)	0.7 ### (±0.4)	6.7 (±3.8)	7.7 (±2.4)	3.3 (±0.9)
diurnal 6-SM/BMI	10.2 (±3.3)	116.0 ** (±31.0)	47.5 (±18.8)	37.1 (±17.1)
nocturnal 6-SM/BMI	43.9 ## (±25.6)	333.0 (±141.0)	341.0 (±99.4)	222.0 (±65.0)
Δ6-SM /BMI	0.03 #### (±0.02)	217.0 (±126.7)	293.0 (±102.0)	185.0 (±54.0)

vs. C, nocturnal 6-SM, * p=0.002 vs. C, diurnal 6-SM, ** p=0.01 vs. C, diurnal 6-SM/BMI, # p=0.02 vs. C, nocturnal 6-SM, ## p=0.03 vs. C, nocturnal 6-SM /BMI, ### p=0.04 vs. C, Δ6-SM, #### p=0.0003 vs. C, Δ6-SM/BMI. **Conclusion:** In GHD, 6-SM did not show nocturnal elevation; children with PWS showed higher diurnal levels and Ob children had higher nocturnal levels. The different 6-SM profiles found appear to demonstrate that in the pathophysiological models evaluated, circadian rhythm alterations might possibly involve various neuroregulatory mechanisms disorders.

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Relationship Between Growth Hormone Binding Protein (GHBP) and GH Secretory Response in Children with Auxological Parameters Compatible with GH Deficiency (GHD)

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Introduction and Objectives: Has been proposed that GHBP reflect GH-receptor tissue abundance. GHBP might be involved in GH response sensitivity, the role of GHBP is still unclear. **Methods:** We estudied basal GHBP and the maximum peak (Maxp) of 224 Pharmacological tests (PhT) in 112 patients (GrA: CA(y) 8.8±4.2, height<.0_SDS, GV<.3_SDS). GrA were divided into: adequate GH Maxp-PhT>6.1 and IGF1_SDS>.60 (GrA.1), and inadequate Maxp-PhT≤6.1 and IGF1_SDS≤.60, (GrA.2). Methods: GH/IGF1 IMMULITE-Chemiluminescence, GHBP_DSL-ELISA kit. **Results:** Review table. Negative correlation: GHBP and logGH-Maxp for GrA was found. **Conclusion:** GHBP levels might be negatively linked to GH secretion increasing GH half live. Higher GHBP levels might increase the serum GHBP-bound GH fraction and, by this mechanism, modify GH sensitivity in GHD.

Table 1.

	GrA.1	GrA.2	p value
n	61	13	
CE	8.8±4.2	9.2±5.0	NS
TOTAL GH	13.2±6.41	1.59±1.72	<0.01
FREE GH	9.19±6.08	1.05±1.16	<0.01
BOUND GH	3.97±1.49	0.54±0.58	<0.01
% TOTAL GH	(33.0±14.0%)	(43.0±17.0%)	<0.01
IGF1_SDS	–0.25±0.86	–3.80±1.77	<0.01
GHBP	808.0±420.0	1167.0±1067.0	<0.05

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IGF-IR/AKT and ERK Protein Content and Response to IGF-I in Small (SGA), Appropriate (AGA) and Large (LGA) for Gestational Age Human Term Placentas

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Introduction: We previously reported a higher mRNA expression and protein content of IGF-I and IGF-IR in SGA compared with LGA placentas. **Objective:** To study the protein content and the effect of IGF-I on the phosphorylation of IGF-IR, ERK and AKT in human full term SGA, AGA and LGA placentas. **Methods:** We collected placentas from 22 SGA (birth weight (BW)=.08±0.17SDS), 18 AGA (BW=.19±0.11SDS) and 22 LGA (BW=+2.78±0.24 SDS) newborns and we studied the protein content, and the effect of IGF-I on IGF-IR, ERK and AKT phosphorylation by Western Blot in the chorionic (CP) and basal (BP) plates of the placentas. **Results:** Results are shown as mean ± SEM. The differences were studied by ANOVA. We found a higher IGF-IR, AKT and ERK42/44 content in the CP and BP of SGA vs. LGA placentas. When stimulated with IGF-I, we observed a trend for an increase in the phosphorylation of IGF-IR and AKT in CP of SGA compared to LGA placentas. **Conclusions:** The higher protein content and response to IGF-I of IGF-IR and AKT in SGA compared to LGA placentas, suggest that the placental IGF-IR signal system may influence fetal growth.

Table 1.

		SGA	AGA	LGA
Total IGF-IR	CP	0.87±0.22*	0.46±0.09	0.27±0.04
(AU)	BP	0.64±0.11*	0.67±0.23	0.28±0.04
Total AKT	CP	0.86±0.23*	0.55±0.12	0.35±0.05
(AU)	BP	0.74±0.10*	0.72±0.22	0.37±0.06
Total ERK42/44	CP	0.96±0.20*	0.80±0.19	0.40±0.10
(AU)	BP	0.72±0.11	0.77±0.20	0.42±0.11
Phospho IGF-IR	CP	14.2±8.9	10.9±3.3	8.9±4.6
(AUC)	BP	6.5±1.4	15.9±4.6	16.7±6.9
Phospho AKT	CP	27.6±6.0	18.8±2.8	15.9±3.0
(AUC)	BP	24.1±6.9	14.3±4.5	15.7±3.8

*p<0.05 SGA vs LGA; AU: arbitary units; AUC: Area Under Curve.

Table 1. (Abstract 26)

SNP	cDNA (Protein) change	Ex/In	MAF(1) dbSNP-NCBI	Height SDS	GHBP SDS	IGF-I SDS	GH max. (ng/ml)	This study: Allele frequency		Polyphen*/Human Splicing Finder**
								Normal	Selected ISS	
rs6177	c.686G>A (p.R229H)	Ex7	0.007	–2.19	–1.98	–0.76	18.0	0.00	0.036	Benign*
rs6880730	c.875+132T>A	In8	0.072	–2.53	2.7	–0.50	24.1	0.025	0.036	Probably affecting enhancer site of splicing**
rs6182	c.1319G>T (p.C440F) (p.C440F)	Ex10	0.037	–2.62	–1.81	–1.34	29.4	Not determined determined	0.036	Probably damaging*

MAF(1) : Minor Allele Frequency in data base

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Differences in Circulating IGFS and Microstructural Brain and Multi-voxel Spectroscopy at Corrected Age (CA) 1 Yr in Very Low Birth Weight (VLBW) Infants Born Appropriate (AGA) or Small for Gestational Age (SGA)

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Introduction and Objectives: VLBW children have higher risk of neurologic disabilities. IGFs are essential to brain growth and maturation. **Methods:** Perform neurologic, psychometric (Bayley) and microstructural brain study at corrected age (CA) 1 yr in VLBW infants. MRI with diffusion tensor (DT: 27 areas) and spectroscopy (6 regions: relationships of NAA/creatine (neurons), creatine/choline (myelin). Differences by BW SDS and IGF-I/II, weight and length change between birth-CA0(0) and CA0-CA1(1) yr assessed. **Results:** 27 VLBW infants (10SGA,19F), BW 1.07±0.3 Kg, GA 29.5±2.7 weeks, Abnormal neurological exam 24/27 but no differences in psychometrics by BW SDS. 19 /27 DTI areas were better in 1 yr term infants vs VLBW. VLBW have different patterns of DT:AGA better maturation areas 5 ($p<0.05$), 17($p<0.01$) and spectroscopy in NAA/creatine left frontal ($p<0.05$). IGF-I(0)+ associated to areas 10, 26 and - to areas 4.11 and creatine/choline. IGF-I(1)+ with area 16 and -with NAA/creatine left frontal. IGFII(0) negatively to areas 14, 15. Change in weight and length(0)+ with areas 17, 18, 27 and with NAA/creatine left frontal. Change in weight(1) with area1 and NAA/creatine left basal ganglia, creatine/choline left parietoccipital. **Conclusion:** VLBW infants show a different brain maturation according to BW SDS which is also determined by circulating IGfs and anthropometry changes.

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Growth Hormone Receptor Gene (GHR) Heterozygous Variants in Idiopathic Short-Statured (ISS) Children Selected According to IGF-I and GH-binding Protein (GHBP) Levels

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Introduction: Previous studies showed heterozygous GHR gene variants in about 5–8% of children with ISS. **Aim:** To determine the prevalence of GHR gene variants in ISS children selected according to IGF-I and GHBP serum levels. **Methods:** From 61 prepubertal ISS children (height < SD, height velocity < 10centile, normal GH response after Arginine-Clonidine test), 14 (5 familial/8 non-familial, 1 unknown) were selected presenting, IGF-I (extractive-RIA) < .50 and GHBP (in house immunofluorometric assay) either < .0 SDS (n = 13) or >+2.0 SDS (n = 1). Coding exons and intronic flanking regions of GHR gene were PCR-amplified, purified and sequenced. These GHR gene variants were also screened in 25 normal subjects. **Results:** Previously reported common SNPs were found in all 14 ISS children: rs12521020 (Intron-1), rs10941579 (Intron-2), rs6179 (Exon-6), rs33972388 (Intron-7), rs2973015 (Intron-8), rs6180 (Exon-10). In addition, 3/5 familial ISS children presented uncommon SNPs in heterozygosis (Table). **Conclusion:** Adequate selection criteria (low IGF-I and either low or high GHBP levels) may improve the identification of carriers for GHR gene variants (3/14, 20%) in children with ISS. Interestingly, all these variants were found only in familial ISS children. However, the biological effect of these variants on GH sensitivity remains to be determined.

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Prevalence of Microvascular Complications in Children and Adolescents with Type 1 Diabetes Mellitus: Association with Metabolic Control, Age and Duration of the Disease

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Introduction and Objectives: To determine the frequency of microvascular complications (MC) in children and adolescents with type 1 diabetes (DM1), to associate with metabolic control, age and time of evolution. **Methods:** Records 253 patients with DM1 (2004–2006) were reviewed. Age, sex, pubertal status, duration of diabetes, metabolic control (mean HbA1c) and presence of MC (retinopathy, nephropathy, neuropathy) were collected. **Results:** Two hundred and fifty three patients were evaluated, 118 male (46.6%) 135 female (53.4%), 8.7% preschoolers, 31.7% schoolchildren and 59.6% adolescents. Good metabolic control was observed in 23.2%, poor control in 76.8%. The presence of complications was studied in 116 patients, 4 (3.5%) had retinopathy, 57 (49.1%) nephropathy and 26 (22.4%) neuropathy. Complications were significantly associated with disease duration ($p < 0.003$), age ($p < 0.009$), pubertal development ($p < 0.007$) and were more common in patients with poor control (N.S). Age was the most important explanatory variable of the presence of complications (R2: 0.200; Odd's ratio: 1.227, $p = 0.0001$) **Conclusion:** The MC in this group of patients had a similar prevalence than reported. They were associated with longer duration of disease and mainly with adolescence. Propose strategies to improve metabolic control

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Phenotype of Gene ABCC8/KCNJ11 Mutation in the Same Family with Diabetes

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Introduction: The Neonatal Diabetes may develop during the first days of life (6–9 months) in a transient or permanent fashion. Genetic abnormalities of KCNJ11/ABCC8 that code for subunits of potassium channels involved in insulin secretion have been identified **Aim:** To describe the clinical presentation of the genetic mutation of ABCC8/KCNJ11 in three siblings with Diabetes. **Methods:** Forty exons from two subunits of the gene was sequenced in the parents and the three children (two with neonatal diabetes) and describe clinical presentation. **Results:** Of the three siblings with diabetes onset associated with a viral infection, the first patient developed the disease at two months of age, the second at age 7 years and the third at 7 months of age. Insulin therapy continues in the 7 years old patient who is the only one who developed ketoacidosis. We found a mutation of L1147P on the three patient and the father was a carrier and mutation of G228D in the siblings and mother a carrier. **Conclusion:** The identification of mutations of the KATP channel are helpful in the diagnosis and management of patient with diabetes. The The clinical presentation and treatment of the diabetes in this family suggest the posibility of a double mutation of the gene affecting insulin

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Endothelial Dysfunction in Mexican Adolescents with Polycystic Ovary Syndrome and their Non PCOS Obese and Normal Weight Counterparts

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Introduction and Objectives: It has been suggested that patients with polycystic ovary syndrome (POS) have a remarkable cardiovascular risk given their metabolic and endocrine profile. Cellular adhesion molecules (sICAM, sE-selectin) and asymmetric dimethilarginine (ADMA) have been related to endothelial dysfunction. Carotid Ultrasonography and measurement of Carotid Intima-Media Thickness (CIMT) can detect early structural changes of atherosclerosis. The aim of this study was to compare biochemical markers and CIMT among PCOS, non PCOS obese (OB) and healthy controls (HC). **Material and Methods:** We studied 47 adolescents: PCOS ($n = 20$), OB ($n = 15$) and HC ($n = 12$). A complete medical history, anthropometry, metabolic and hormonal profile, pelvic USG, carotid USG, s-ICAM, sE-selectin and ADMA were obtained in all of them. **Results:** A difference in insulin levels and HOMA index was found between HC and PCOS and OB patients ($p < 0.05$). There was no difference in sICAM and sE-selectin expression among groups. ADMA was significantly lower in PCOS patients compared to OB ($p < 0.05$). Carotid diameter was significantly higher in OB compared to PCOS, but no differences were found in CIMT. **Conclusion:** ADMA levels were lower in PCOS than in OB patients. In our study endothelial dysfunction seemed to be more related to obesity than hyperandrogenism.

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The Effects of Glycemic Control in HDL Subclasses Distribution, Composition and Functionality in Type 1 Diabetic Adolescents

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Introduction and Objectives: An important part of the cardiovascular risk in type 1 diabetic (T1D) patients could be mediated by atherogenic lipid abnormalities. The aim of our study was to evaluate the effect of glycemic control in HDL subclasses distribution, composition and functionality in T1D adolescents. **Methods:** Cross sectional study that included 52 T1D diabetic patients and 43 non diabetic controls. T1D patients were divided into two groups according glycemic control. HDL-C sublcasses distribution, composition and its capacity to promote cellular cholesterol efflux and its anti-inflammatory action trough the levels of soluble adhesion molecules were measured. **Results:** Poor glycemic control (HbA1c≥9.6%) in type 1 diabetic adolescents was associated with a lower proportion of HDL2b subclass compared to non-diabetic subjects ($p=0.029$) and this association was independent of age, sex, Tanner stage, diabetes duration and insulin dose. Also poor glycemic control was associated to a enrichment in triglycerides ($p=0.045$) and a depletion in cholesteryl esters content of HDL particles ($p=0.028$) and an increased plasma levels of ICAM-1 concentrations ($p<0.001$). **Conclusion:** HDL subclasses abnormalities in distribution, composition and anti- immflamatory properties related to hyperglycemia, are mechanisms that could be associated to an increased risk of accelerated atherosclerosis in T1D patients since early age.

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Postprandial Lipemia in Adolescents with Excess Weight

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Introduction and Objectives: There is little data on postprandial lipemia in adolescents. Thus, this study assessed the triglyceride levels before and after an oral fat tolerance test in overweight adolescents. **Methods:** Adolescents with ($n=39$) and without excess weight ($n=25$) were included. Variables studied: BMI, waist circumference (WC), glucose, triglycerides (TG), total cholesterol (TC), HDL-C, LDL-C. After a 12-hour fasting the teenagers drank 100ml of a strawberry flavor drink (25g fat+25 g carbohydrate). The lipid fractions were measured at fasting and after 2 and 4 hours. **Results:** TG (mg/dl) in fasting (85.0 ± 39.5 vs. 105.0 ± 56.8, $p=0.10$) and after 2 hours (105.2 ± 57.4 vs. 125.4 ± 64, $p=0.20$) were similar between groups. However, after 4 hours TG were lower in eutrophic adolescents (97.1 ± 44.0 vs. 129.4 ± 69.7, $p=0.027$). In the overweight group, the postprandial TG correlated positively with TC ($r=0.32$, $p=0.04$) and negatively with HDL-C ($r=-0.45$, $p=0.004$). There was no significant association of fasting TG and postprandial with BMI and WC in both groups. **Conclusion:** The higher levels of postprandial triglycerides in overweight adolescents indicate higher risk of cardiovascular disease in this group.

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Metabolic Effects of Quetiapine in Adolescents with Obsessive Compulsive Disorder

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Introduction: Quetiapine is an antipsychotic which is indicated in adolescents with obsessive compulsive disorder (OCD). Studies have showed dyslipidemia and glucose metabolism alterations, such as adverse drug effects. **Aim:** To evaluate the metabolic effects of quetiapine in adolescents with OCD. **Methods:** A prospective study. Determination of plasma levels of glucose, insulin, triglycerides, cholesterol and its fractions at the beginning and after three months of treatment with quetiapine, patients from twelve to fifteen years of age diagnosed with OCD. **Results:** 29 patients were attended, 24 were studied. 62% were male. After three months of treatment with quetiapine hyperinsulinemia was observed in 58% of adolescents, 54% hypertriglyceridemia and low HDL cholesterol levels in 50% of patients. **Conclusion:** Hyperinsulinemia, hypertriglyceridemia and low HDL cholesterol levels are common findings in adolescents with OCD, treated with quetiapine. It is important to regularly monitor the cardiovascular risk in these patients. We recommend further studies in larger populations

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Insulin-like Growth Factor-1 (IGF-1) Regulates Pheochromocytoma Cellular Proliferation In Vitro and In Vivo

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Introduction: IGFs are involved in malignant transformation and tumoral growth of the adrenal gland. **Aim:** To evaluate the impact of IGF-1 on Pheochromocytoma's development. **Methods:** MPC4/30 cells proliferation, apoptosis, colony formation and migration with or without rhIGF-1. MPC cells were injected to control and liver-IGF-1-deficient (LID)mice treated with rhIGF-1or vehicle. **Results:** MPC proliferation and BrdU incorporation increased significantly upon rhIGF-1 while the percentage of apoptotic cells was significantly lower; migration and soft agar colonies size and number were also stimulated by rhIGF-1 (Table 1). Six weeks after MPC injection all control but only 40% of LIDmice developed tumors. LID harboring MPC and treated with rhIGF-1 developed tumors as controls. The latency period for tumor growth increased in LID as compared to both

Table 1. Insulin-like Growth Factor-1 (IGF-1) Regulates Pheochromocytoma cellular proliferation in vitro and in vivo

rhlGF-1 Stimulation	(–)	(+)	Test
Cell Proliferation (cells)	$15\pm4\times10^4$	$30\pm3\times10^4$	$p<0.05$ t test
BrdU incorporation (% cells)	26±6%	35±6%	$p<0.01$ M. Whitney
Caspase-3 (% positive cells)	36±3%	11±1%	$p<0.01$ M. Whitney
Tunel (% positive nuclei)	21±3%	7±1%	$p<0.01$ M. Whitney
Migration (cells/field)	12±1	18±1	$p<0.01$ M. Whitney
Colonies/quadrant	11±3	26±3	$p<0.01$ t test
Colony size (urn)	217±13µm	288±69µm	$p<0.01$ t test

control and LID+rhIGF-1 [MedianSurvivalRatio: 2.2, 95%CI1.6–2.8;1.8,95%CI1.4-.3respectively, $p<0.0001$]. LID had 10 times lower probability for developing tumors than controls (HR:0.10, 95% CI0.02–0.27); rhIGF-1 treatment increased this risk 8 times (HR:7.9, 95% CI1.6–67.1). **Conclusion:** Cellular proliferation of pheochromocytoma is regulated by IGF-1 in vitro and in vivo. IGF-1 enhanced proliferation, migration and cell's ability to grow unattached.

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Impact of Glucocorticoid Receptor Gene Polymorphisms on Lipid Profile of Children and Adolescents with Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency

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Introduction: CAH patients receiving glucocorticoid (GC) therapy could develop obesity and adverse metabolic profile. However, there is limited data regarding the frequency of these comorbidities in CAH and previous studies did not evaluate the involvement of genetic predisposition. Glucocorticoid receptor (GR) gene polymorphisms could result in alterations in the GC sensitivity and are associated with dyslipidemia in the normal population. **Objectives:** To analyze if GR variants are associated with obesity and lipid profile in CAH patients. **Methods:** 41 classical patients (26 F), mean age of 11.4±3.9 yrs, receiving cortisone acetate (CA) 16–18 mg/m²/d in order to obtain normal androgen levels according to age/sex. Obesity was defined by BMI > p95th. GR alleles were screened by sequencing. Association of obesity, lipid profile and GR polymorphisms were evaluated by Chi-square, linear regression and t-test. **Results:** All variants were in Hardy-Weinberg equilibrium and the BclI and p.A3669G alleles were found in 28% and 11% of patients, respectively, with similar frequencies between salting wasting (SW) and simple virilizing forms (SV). Obesity was observed in 34% of patients. Linear regression showed that BMI was significantly correlated with blood pressure and HOMA-IR, but not with CA doses and/or GR polymorphisms. Mean CA doses did not differ between SW and SV forms. SW patients had a worse lipid profile (total cholesterol, LDL-c and triglycerides, $P<0.05$) than SV patients, independently of BMI. We did not identify a significant effect of the BclI allele on the obesity prevalence and/or metabolic profile. On the other hand, the p.A3669G allele was associated with higher CT ($P=0.03$) and LDL-c ($P=0.006$, power of test 99.8%) levels in comparison with wild type carriers independently of BMI, clinical form, sex and age. **Conclusions:** We observed that genetic predisposition, instead GC doses, plays a role in the development of adverse lipid profile in CAH.

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Differences in the Expression of 5alpha-reductase Type 2 on Genital Skin Contribute to the Variability of External Genitalia Virilization in CAH Females

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Introduction and Objectives: CAH is a frequent disorder characterized by ACTH-dependent hyperandrogenism resulting in prenatal external genitalia virilization in females. Despite good genotype-phenotype correlation, the degree of external genitalia virilization (Prader-P) presents significant variability among females with similar CYP21A2 genotypes. It is thought that an interindividual difference in the peripheral androgen action is a determinant factor for this variability; however, it has not been demonstrated so far. Objective: To evaluate if different AR, SRD5A1, SRD5A2, AKR1C3 gene expressions in genital skin influence the external genitalia virilization in CAH females carrying similar CYP21A2 genotypes. **Methods:** 12 females carrying CYP21A2 mutations abolishing the enzymatic activity, six patients with P3 and six with P4 score. RNA was extracted from genital skin during genitoplasty. AR, SRD5A1, SRD5A2 and AKR1C3 mRNA expressions were determined by real-time quantitative PCR (Taqman system). A pool of genital skin from healthy male child was used as reference sample. Relative quantification was determined by the 2-ΔΔCT method. A twofold change in mRNA levels was considered as significant. **Results:** SRD5A2 overexpression was observed in 4/6 patients with P4 (5.5, 16.2, 6.1, 21.2 fold). Two/6 patients with P3 had mild SRD5A2 overexpression (2.0, 2.9 fold). There was a significant difference of SRD5A2 expression between P3 and P4 groups ($P=0.037$). AR, SRD5A1 and AKR1C3 expressions were similar between P3 and P4 groups; but 1/2 patients with P4 and with normal SRD5A2 expression had AKR1C3 overexpression. **Conclusion:** Interindividual differences in the expression of sex steroid enzymes in genital skin explain the phenotype variability of external genitalia virilization in CAH females bearing similar CYP21A2 genotypes.

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Mutationsin Genes Related to GNRH Deficiency (GND): Spectrumof Phenotypes in Patients with Anosmic (aHH) or Normosmic Hypogonadotropic Hypogonadism (nHH)

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Introduction: GND can be congenital/adquired, and often associated with smell abnormalities wich suggests a more severe phenotype. **Aim:** To compare the reproductive phenotype in anosmic men (aMH) and women (aWH) with patients with nHH (nMH and nWH) and to correlated with genetic defects. **Methods:** 27males and 41women with HH were recruited. A complete health evaluation, smell test and DNA screening were performed. **Results:** A 55.6% of males and 17.1% of women have aHH. In aMH 56% had micropenis, 69% cryptorchidism and 81% absence of puberty, vs. 50%, 62% and 25% in nMH, respectively. A 25% of aWH had spontaneous menarche vs. 54% of nWH. Eleven males (47.8%) have mutations: 5 monogenic disease (FGFR1, KISS1R, KAL1) and 6 digenic mutations (TAC3R, KAL1, PROK2, FGFR1, KISS1R). In 6women (19.4%) mutations were identified: one digenic (GNRHR/PROKR2) and 5 monogenic (FGFR1, TAC3R). A 43% of aMH and 40% of aWH had identified mutations vs. 63% of MH and 17% WH without anosmia. **Conclusion:** Reproductive phenotype in patients with aHH is more severe than nHH. Attention to phenotype/anosmia may induce an early suspicion. Normosmia does not exclude the presence of genetic defects in the gonadal axis, specially in males.

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Association of Cdx-2 Polymorphism of Vitamin D Receptor Gene with Higher Turnover in TS Patients

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Introduction and Objectives: A previous work from our laboratory showed an association of BsmI and FokI polymorphisms of vitamin D receptor (VDR) gene with bone mineral density (BMD) in Turner syndrome (TS) patients. The aim of the present study was to analyze the relationship between Cdx-2 polymorphism of VDR gene with BMD, bone formation and resorption markers and other biochemical bone parameters in TS patients. **Methods:** DNA was extracted from blood samples of 60 TS patients (15± years old) and 59 healthy controls (17±8 years old) and amplified by real time PCR. Alleles were identified by Taqman probes. Lumbar and femoral BMD was determined. Calcium, phosphorus, PTH, osteocalcin and ß-crosslaps were measured in serum. **Results:** Genotype distribution was similar in both groups. No association between Cdx-2 genotypes and BMD was observed. GG genotype was associated with higher levels of both osteocalcin (92.75±6.99 ng/mL vs GA: 63.04±8.24 ng/mL; $p<0.01$) and β-crosslaps (1.47±0.12 ng/mL vs GA: 1.07±0.11 ng/mL; $p<0.05$). **Conclusion:** This significant increase in both markers suggests a higher bone turnover that should be considered in order to prevent bone demineralization in TS patients carrying GG Cdx-2 VDR genotype.

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Potential Use of Propeptide of Type 1 Procollagen (P1np) as a Monitoring Marker in Pediatric Patients with X-linked Hypophosphatemic Rickets

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Introduction: Total Alkaline Phosphatase (TAP) is the classic marker used to monitor the patients with X-linked Hypophosphatemic Rickets (XHR). The P1NP is a more specific and precocious bone formation marker than TAP. **Aim:** To determine the correlation between TAP and P1NP serum levels in XHR pediatric patients, beyond that verify possible differences between pubescent and impubescent patients. **Method:** Eighty-nine TAP and P1NP morning blood samples were obtained from 17 pediatric patients (14 girls and 3 boys) with XHR. In each blood sample, the patients were classified according to Tanner & Marshall's stages (Tanner 1: 50 samples and Tanner2-5: 39 samples). For the statistics, the Pearson´s correlation was accomplished. **Results:** A mild positive and significant correlation was found between TAP and P1NP serum levels ($r=0.735$; $p<0.001$). This correlation is stronger in the pubescent group ($r=0.881$; $p<0.001$) than the impubescent group ($r=0.505$; $p<0.001$). **Conclusion:** P1NP can be used as a reference bone formation marker in pediatric patients, specially in the pubescent group.

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Endocrine Alterations in Mexican Patients with 22q11.2 Deletion Syndrome

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Introduction and Objective: The del22q11.2 syndrome is the most common microdeletion syndrome and is associated to a wide clinical variability. The objective of our study was to describe the endocrine alterations present in a group of mexican patients with del22q11.2 syndrome. **Methods:** Cross-sectional study. The del22q11.2 was confirmed by FISH analysis in 29 patients. Calcium, parathyroid hormone (PTH), Insuline-like growth factor-I (IGF-1) and thyroid hormones values were measured, as well as annual growth, by determining height and growth velocity. **Results:** 17 out

of 29 patients (58.6%) were female. The median age was 4 years 11 months. The average values were: calcium 8.22 mg/dL, PTH 29.8 pg/mL, TSH 3.9 µU/mL, T3 total 166.1 ng/dL, T4 total 9.4 µg/dL, free T4 1.34 ng/dL, IGF-1 118.6 mU/L. Hypocalcemia was diagnosed in 34.5% of the patients (24.1% latent hypoparathyroidism, 3.4% neonatal transitory hypocalemia, 6.9% transitory hipoparathyroidism); hyperthyrotropinemia in 24.1%, 3.4% had primary acquired hypothyroidism, 37.9% had growth retardation and 17.2% showed failure to thrive with low levels of IGF-1. **Conclusion:** Endocrine alterations can occur at any age in pediatric patients with del22q11.2 syndrome, therefore these patients require a continuous periodic evaluation during childhood and even adulthood.

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Applying Hibridation in Situ Fluorescente (FISH) in Patients with Suspected Clinical Signs of 22q11.2 Deletion Syndrome (DS22q11.2)

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Introduction and Objectives: DS22q11.2 is associated with a wide spectrum of clinical disorders (DiGeorge, velocardiofacial, facioconotrunal and Cayler syndromes) known to arise from the same etiology: microdeletion 22q11.2. The phenotype is variable, including: conotruncal cardiac defect (CCD), facial phenotype, palate anomalies, inmunodeficency and mental. The endocrine manifestations are short stature (ST), neonatal hypocalcemia due to hypoparathyroidism and thyroid dysfunction. Microdeletion is inherited in 6–10% of cases. Objective: To identify by FISH the 22q11.2 microdeletion in patients with apparent DS22q11.2. **Methods:** Population: 32 patients with more than one clinical features of DS22q11.2. Population: 32 patients with more than one clinical features of DS22q11.2. Methods: Cytogenetic and FISH analysis with DNA probes span 4Mb interval, were performed: 1-LSIDiGeorge/VCFS; Vysis. LSI (TUPLE-1) locusHIRA/ARSA (22q13.3); 2-VCF/DiGeorge; LiVe-locusHIRA (Tuple-1)/BCR/S1169; 3-BACs:RP11-22M5/S1169 (22qter). **Results:** The microdeletion 22q11.2 was demonstrated in 14/32 patients (44%). A mother with mild phenotype showed mosaicism. The probes could estimate the size of microdeletion between 3–1.5Mb. The clinical features in this group were: CCD: 100%; facial phenotype: 80%; hypocalcemia: 57% in combination with low and normal PTH; immunodeficiency: 57%; ST: 50%; palates anomalies: 50%; RM: 43%, and microcephaly: 36%. **Conclusion:** Molecular cytogenetics is usefull to confirm the clinical diagnosis in patients with DS22q11.2. We emphasized that conotruncal cardiac defect, facial anomalies, neonatal hypocalcemia, inmunodeficency and short stature, are strong predictor of 22q11.2 microdeletion

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Comparison of Three Diagnostic Definitions of Metabolic Syndrome and their Relationship with the Homeostatic Model Assessment (Homa) Index in Obese Children and Adolescents

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Introduction: Currently there is no consensus for the definition of Metabolic Syndrome (MS) in Pediatrics; however, it is considered that an HOMA index close to three could be useful for diagnosis. **Objective:** To compare the sensitivity (S) and specificity (SPC) of three diagnostic definitions of MS and their relationship with the HOMA index in obese children and adolescents. **Methods:** Cross-sectional study of 30 obese children and adolescents (BMI ≥95th), between 10 and 14 years of age (11.6 ± 1.4 years). We compared definitions from Cook et al., Cruz et al., and the International Diabetes Federation (IDF) of MS, determining sensitivity and specificity based on HOMA index ≥3.1, cutoff value for the diagnosis of MS. For the statistical analysis we calculated frequencies, two-way tables, and differences of proportions. **Results:** The IDF definition showed higher specificity (62.5%) and positive predictive value (PPV) (78.6%), but lower sensitivity (50%) than those from Cruz et al (SPC:50%, S:59.1%, PPV:76.5%) and Cook et al (SPC:37.5%; S:59.1%, PPV:72.2%). **Conclusion:** The IDF definition showed higher specificity and PPV; the definition from Cruz et al. and Cook et al. showed the highest sensitivity for the detection of MS

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Differences in Estrogen Metabolism During the Luteal Phase in Adolescents with Type 1 Diabetes (T1D)

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Introduction and Objectives: Estrogens are metabolized mostly to 2-hydroxyestrone (2OHE), an estrogen antagonist, which may affect the GH-IGF axis. Aim: To determine estrogen metabolites and IGF-I levels in adolescents with T1D. **Methods:** We studied 12 adolescents with T1D and 10 healthy control girls (C). Samples were obtained in follicular and luteal phases. We measured urinary 2OHE (normalized for creatinine) and serum IGF-I, IGFPB3 and SHBG. **Results:** T1D adolescents exhibited higher levels of 2OHE than C during luteal phase (15.7 ± 1.8 and 10.9 ± 1.2ng/ml/mg-creat, respectively, $p < 0.041$). In contrast, serum IGF-I increased during luteal phase in C (315.6 ± 11.3 to 345.2 ± 12.15ng/ml, $p < 0.005$), but not

in T1D adolescents (305.0±22.9 to 306.4±20.4ng/ml, p=0.87). In addition, we observed similar levels of IGF-I, IGFPB3 and SHBG in T1D and C during follicular and luteal phases. **Conclusions:** T1D girls show higher excretion of estrogen antagonists than C, without increasing their serum IGF-1 levels. These findings suggest that T1D girls exhibit a detrimental endocrine profile during the luteal phase, which may affect their metabolic control. This is the first report of differences in estrogen metabolism in adolescents with T1D

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Homocysteine Levels in Obese and Normal Weight Adolescents

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Introduction and Objectives: Homocysteine (He) has become an important risk factor for cardiovascular disease. This study evaluates the homocysteine levels in adolescents. **Methods:** We included 48 obese adolescents (20 males, (BMI≥P97), which were compared to 34 eutrophic ones (17 males, BMI≥P3 and **Results:** The mean age was similar between groups (12.5±2.3 vs. 13.2±2.6 years, p=0.20) as well as the gender distribution (p=0.45). The average He (μmol/L) was higher in obese (5.4±2.3 vs. 4.4±1.9, p=0.03). Males had higher levels of He (5.8±2.4 vs. 4.3±1.8, p=0.001). The stratified analysis according to weight (obese vs. eutrophic) showed a significant difference only for females (p=0.009). There was a positive association between He levels and BMI (r=0.22, p=0.04), WC (r=0.26, p=0.02) and BC (r=0.30, p=0.007). **Conclusion:** The higher homocysteine levels and the positive association with WC and BC suggest that this marker may represent an additional risk factor for cardiovascular disease in obese adolescents.

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Post-Transplant Diabetes Mellitus in Pediatric Renal Transplantation

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Introduction: Post-transplant diabetes mellitus (PTDM) is a complication of renal transplantation may reduce patient survival and graft, and there is limited information in the pediatric population. **Objective:** To determine the frequency, characteristics and risk factors for PTDM. **Methods:** Retrospective analysis of children with renal transplants (2001–2008) who developed PTDM (diagnostic criteria of the American Diabetes Association) to focus on the clinical course, age, body mass index (BMI), type of donor and immunosuppression received. **Results:** Were 302 children, mean age 11.78 (±4.7), 60.8% male. Tacrolimus were 280 (93%), cyclosporine 15 (5%) and sirolimus 7 (2.3%). PTDM occurred in 26 (8.6%) and developing to 87.4 (±129) days after transplantation. 245 (81%) initially received maintenance immunosuppressive corticosteroids. 115 (38%) received corticosteroid therapy down. The multivariate analysis suggest that age> 5 years at transplant, early steroid use, family history and episodes of acute rejection was associated with a higher frequency of PTDM. **Conclusion:** The evaluation of risk factors, early diagnosis of glucose metabolic disorder may prevent the development of long-term consequences and improve the quality of life for our patients

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Paraganglioma Syndrome Type 4 (Pgl 4): Clinical and Genetic Findings

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Introduction and Objectives: Pgl 4 is the second frequent genetic pheocromocytoma/paraganglioma syndrome in children and adolescents. It is an autosomal dominant disease with mutations in SDHB gene. These mutations have been associated with extra-adrenal pheocromocytomas and high malignant potential. Head and neck paraganglioma have been observed less frequently. The aim of this study is to describe the clinical symptoms and genetic findings in 9 patients, 6 aged 12–17 years and 3 adults with Pgl 4. **Methods:** All of them presented symptoms caused by hypersecretion of catecholamines. Biochemical profile showed NA and VMA increase. **Results:** In the younger group tumors were localized in: abdomen(2), thorax(1), urinary bladder(1), unilateral adrenal(3). The adults presented paraganglioma in:urinary bladder(1), organ of Zuckerkandl(1) and neck(1). The SDHB direct sequencing showed missence mutations R217G(2), S198R(1), L65R(1) and a Frameshift g300-304 delCCTCA(5). The frequency of the delecion g300-304delCCTCA was remarkably higher in the population studied than reported so far. The study was then performed in 19 relatives, and 7 carriers were found. **Conclusion:** We conclude that mutations in the SDHB gene should be searched for in patients with paraganglioma or malignant pheocromocytoma as a first step. Thus, the importance of the early diagnosis in these patients becomes critical to allow early treatment that will impove the outcome.

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Adrenal Hypoplasia Congenita with Phenotypic Features Suggestive of Neurofibromatosis Type-1 Among Three African-American Brothers

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Introduction and Objectives: Adrenal hypoplasia congenita (AHC) is a rare inherited condition characterized by primary adrenal

Table 1. Basel and GnRHs stimulated (stim) LH, FSH, testosterone levels indicative of HH; inappropriately low cortisol, aldosterone, DHEA-SO4 levels accompanied by high ACTH levels indicative of primary adrenal failure (for Abstract 46)

	LH (mIU/ml)	FSH (mIU/ml)	T (ng/dl)	LH (stim)	FSH (stim)	T (stim)	ACTH (<70 pg/ml)	Cortisol (μg/dl)	Aldosterone (2-22 ng/dl)	DHEA-SO4 (48-200 μg/dl)
Patient 1	0.02	2.76	5.7	0.21	3.21	9.6	2749	<1	<1	<10
Patient 2	0.16	0.99	<3	2.07	6.75	<3	4755	<1	<1	<10
Patient 3	<0.01	0.17	607	NA	NA	NA	258	<1	<1	<10

failure and hypogonadotropic hypogonadism (HH). Most cases arise from mutations in the NR0B1 gene. We report AHC with phenotypic features of Neurofibromatosis Type-1 (NF-1). **Methods**: Oldest brother, now 21 yo, was diagnosed with adrenal insufficiency at age 5 years. Decrease in growth velocity, lack of puberty, and skeletal immaturity were observed. DHEA-S and testosterone were undetectable. Gonadotropin levels failed to rise after GnRHa stimulation. The other brothers were diagnosed with AHC due to family history. Two required androgen replacement while the youngest is having spontaneous pubertal progression. They have multiple café-au-lait macules, facial freckles; with the youngest having mild scoliosis. **Results:** Micro-Array: Nullizygous for a deletion within cytogenetic band Xp21.2. The deleted interval includes the NR0B1 and MAGEB genes, excluding IL1RAPL1 gene. **Conclusion:** To our knowledge this is the first report with three brothers being affected by AHC with manifestations of NF-1. This study further expands the present knowledge about the disease and emphasizes different phenotypic presentations with variable severity even in biological brothers. "Genome-wide copy number analysis may be useful in patients with NF-1 like features who are negative for mutations at NF-1 and NF-2".

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Multifollicular Ovaries (MFO) During Adolescence: A Physiologic Finding with Normal Hormonal Profile –

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Introduction: MFO is defined by the presence of 6-11 follicles between 4–10mm with ovarian volume <10ml. The significance of this ovarian pattern is not clear. **Aim:** To compare hormonal profile in girls with MFO and polycystic ovaries (PCOM) with those girls without either (NOM). **Methods:** We studied 74 non-obese non-hyperandrogenic adolescents with regular menstrual cycles. Subjects were divided in 3 groups according ovarian morphology: MFO, PCOM by Rotterdam criteria and NOM (girls who not fulfill previous criteria). Transabdominal ultrasound and hormonal profile (androgens, AMH, Inhibin-B, gonadotropins) in follicular phase. **Results:** MFO, PCOM and NOM were observed in 36.5%, 33.8% and 29.7% of the girls, respectively. AMH levels were similar in girls with MFO compared to those with NOM, but lower than with PCOM (34.4±3.8, 32.1±3.6 and 72.5±6.1 pmol/l respectively, $p<0.0001$). Inhibin-B, gonadotropins and androgens were similar between the three groups. **Conclusion:** MFO in healthy adolescents was prevalent and is not associated with hyperandrogenism. The difference in AMH levels in PCOM and MFO, suggests that MFO is not associated with elevated number of small antral follicles. The similar hormonal profile in MFO and NOM, suggests that MFO corresponds to a physiologic finding during this stage of life.

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High Waist Circumference Is Independently Associated With Adrenarche In Chilean Children

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Introduction/Objectives: It is unclear how different indicators of total and central adiposity relate to prepubertal DHEAS and which factors mediate this association. **Methods:** We assessed in 916 prepubertal children (6.8y; 45% girls) the associations between plasmatic DHEAS and weight, BMI = weight/height 2, waist circumference (WC), waist-to-height ratio (WHR), skinfolds and %fat (bio-impedance); and whether these associations were mediated by insulin/IGF1, and leptin. **Results:** Mean DHEAS was 35.2 μg/dl ±21.8; 19.7% had ≥50 μg/dl). Obesity (BAZ ≥ 2SD, WHO 2007) was 15.1% and central obesity (WC ≥ 75thpctle, Cook) 24%. In both sexes, total and central adiposity indicators were similarly associated with DHEAS (i.e. BMI= βstd: 0.22 95% CI (0.16–0.29); WC= βstd: 0.23 (0.16–0.30)), except WHR that had a slightly weaker association (βstd: 0.19 (0.13–0.26)). Obese and centrally obese children had twice the risk of high DHEAS (OR= 2.06 (1.37–3.11) and 1.99 (1.39–2.84)) but only WC was independent (OR= 1.36 (0.75–2.45), 1.65 (1.0–2.77)). These associations were only partially mediated by IGF1 and leptin. **Conclusion:** WC is independently associated with prepubertal DHEAS and adrenarche; causal mechanisms of this association remain to be elucidated.

Posters Presentation

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Does Co-administration of Growth Hormone (rhGH) and a Gonadotropin Releasing Hormone Analog (GnRHa) Improve the Growth Outcome of Adolescents with Idiopathic Short Stature (ISS) and Growth Hormone Deficiency (GHD)

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Introduction: To evaluate the effect of rhGH associated to a GnRHa on the predicted adult height (PAH) after treatment and on the near final height (NFH) of ISS and GHD adolescents. **Methods:** We treated 20 ISS and 9 GHD adolescents with combined therapy for 24 months (CA of 12±1.6 and 11.4±1.1 yrs, Tanner 2–3). Twelve ISS and 10 GHD children treated with rhGH for 24 months, served as controls. **Results:** ISS and GHD patients treated with rhGH improved their PAH following 2 years of treatment ($p<0.042$) and their NFH ($p<0.046$). Combined therapy in ISS and GHD children did not further improve their PAH (an increase of 7.9±4.9 cm with combined therapy vs. 7.3±6.0 cm with rhGH in ISS and of 6.1±7.6 cm vs. 6.4±6.6 cm in GHD), nor their NFH. The NFH reached by patients treated with rhGH or with combined therapy was lower than the PAH calculated at the end of 2 years of therapy. **Conclusion:** Although 2 years of combined treatment improved the PAH and the NFH of ISS and GHD patients in early puberty, this increase was not superior to that observed in similar subjects treated with rhGH.

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IGF-I Levels in Children on rhGH Treatment Is Strongly Dependent of IGF-I Assay: the Effect of Sample Pretreatment

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Introduction: It has been suggested that monitoring IGF-I after rhGH treatment could be useful to ascertain both compliance and safety. Hence, its measurements must prove reliable. **Aim:** To compare two IGF-I assay's performance in monitoring rhGH treatment in children. **Methods:** IGF-I concentration by extracted in house RIA and by ICMA (IMMULITE 2000, Siemens) was measured in 134 serum samples from children after 0.5 to 3 years on rhGH. In addition, 63/134 samples were also measured after alcohol-acid extraction (followed by cryoprecipitation) by ICMA (eICMA). **Results:** Unextracted ICMA results were positively biased compared to RIA ($y=1.608x-8.2$, $r=0.96$) and showed higher divergences at higher IGF-I-RIA values. However, in 63 samples eICMA results were similar to those obtained by RIA ($y=1.036x-16.4$, $r=0.88$), with recovery >90%. Considering a theoretical IGF-I optimal target on rhGH treatment between 0 to +2.0 SDS, 17 samples by RIA were within –2.0 to 0 SDS, but by ICMA 7/17 (41%) showed IGF-SDS >0. Thirty six samples by RIA were within 0 to +2.0 SDS, but by ICMA 11/36 (31%) showed IGF-SDS >+2.0. Overall ICMA without extraction misinterpreted 18/53 samples (34%). **Conclusion:** Our findings stress the need of extraction procedures prior to ICMA measurement in GH treated children to properly interpret IGF-I results

Table 1. Auxological data of ISS patients before therapy, after treatment with combined therapy or with rhGH alone and at near-final height (for Abstract 49)

	Baseline		After 2 years		Near final height	
	rhGH+GnRHa	rhGH	rhGH+GnRHa	rhGH	rhGH+GnRHa	rhGH
n	20	12	20	12	20	12
CA (yrs)	12±1.6	12.2±1.6	13.8±1.6	14.2±1.6	17.8±2.9	17.4±3.1
BA (yrs)	11.4±0.9	10.9±1.9	12.9±0.9 [a.1]	12.6±1.5 [a]		
Height SDS CA	–2.3±1.1	–2.3±0.9	–1.4±1.4 [a.1]	–1.2±0.9 [a]	–1.6±1.5	–0.1±1.9
Height SDS BA	–1.6±1.1	–0.5±1.1	–0.9±0.9 [a.1]	0.3±1.2 [a]		
HV (cm/yr)	6.5±1.9	3.6±0.6b	6.1±1.8	8.1±2.2 [b]		
BMI SDS	–0.2±1.3	–0.1±0.9	0.4±2.1	0.4±1.6		
PAH (cm)	153.7±10	160.8±10.2	159.7±7.3 [a.1]	167.1±13.6 [a]	157.8±7.4	164.3±12.1
PAH SDS	–2.5±1.5	–0.8±1.5	–0.9±1.3 [a.1]	0.6±1.9 [a]		
Δ PAH (cm)	–	–	7.9±4.9	7.3±6		
Target Height (cm)	163.8±6.4	162±9.1	–	–		

Data are mean±SD.
[a] $p<0.05$ compared to start . [b] $p<0.05$ between rhGH+GnRHa and rhGH
CA Cronological age, BA Bone age, HV Height velocity, PAH Predict adult height

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Catch Up Growth in Height and Weight in Preterm VLBW (< 1500 gms) Infants During a Follow Up Program Until 20 Months Old and the Relation to Maternal Age

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Introduction/Aim: Maternal age is linked to catch up in SGA. To describe the catch up on Height and Weight in Preterm VLBW (<1500 gms) infants during 20 months of follow up and the association with maternal age. **Methods:** We review 36 Medical records. Data for Birth-weight and length were recorded and classified according to Usher McLean; after 40 weeks of post conceptional age and until 20 months old according to WHO charts. We defined catch-up ±2 SDS at the chronological age. The maternal age was divided in two groups <20 years old and > 20 years old. We used Fishers Test. **Results:** We found SGA for length 9(36) and SGA for weight 5(36). At 20 months of age the height and weight >-2 SDS in 4(36) and 5(36) respectively. Catch up in Height was 31(36) with p:0.009 and weight 32(36) with p:0.005. When analyzed it with maternal age, p: 0.39. The mean age for catch up in height and weight was 8.5 and 8 months respectively **Conclusion:** Catch up in height and weight at the age of 20 months old in VLBW infants has statistical significance association with the length and weight at birth and there is no association to maternal age

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Effect of the Parental Origin of the X-chromosome on the Clinical Features, Associated Complications and the Two-year-response to Growth Hormone (rhGH) of Patients with Turner Syndrome (TS)

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Introduction: To determine the influence of the parental origin of the X-chromosome on phenotypic variability, metabolism and response to rhGH in patients with Turner syndrome (TS). **Methods:** This was a Latin American prospective, multicenter, correlational study. Unrelated TS 45,X karyotype patients (n=93; 18.4±7.8 years) and their mothers were enrolled. DNA profiles of patients and their mothers were compared to determine the parental origin of the retained X-chromosome through 10 polymorphic X-chromosome-STRs and was correlated with clinical features, congenital malformations, biochemical profiles and

Table 1. Influence of the parental origin of the retained X-chromosome and of the parental height on growth of TS patients in different developmental groups (for Abstract 52)

Developmetal stages	Total (n=93)			Patients height correlation with					
				Maternal Height		Paternal Height		Mid-parental Height	
	Xm=67	Xp=26	p	Xm=67	Xp=26	Xm=67	Xp=26	Xm=67	Xp=26
Neonatal [xxx]	–1.2±0.8	–1.34±0.9	0.58	r=0.341 p=0.24[a]	r=0.282 p=0.45[a]	r=0.233 p=0.82[a]	r=0.182 p=0.93[a]	r=0.263 p=0.44[a]	r=0.192 p=0.93[a]
Early Childhood [xxx]	–2.5±1.2	–2.63±1.6	0.15	r=0.527 p=0.05[c]	r=0.483 p=0.11[a]	r=0.301 p=0.16[a]	r=0.281 p=0.53[a]	r=0.465 p=0.09[d]	r=0.398 p=0.11[a]
Prepuberty [xxx]	–3.3±1.1	–3.5±0.8	0.12	r=0.606 p=0.02[c]	r=0.510 p=0.09[d]	r=0.381 p=0.23[a]	r=0.241 p=0.43[a]	r=0.483 p=0.07[d]	r=0.415 p=0.11[a]
Puberty [xxx]	–5.5±2.3	–5.4±2.6	0.87	r=0.231 p=0.22[a]	r=0.181 p=0.63[a]	r=0.211 p=0.58[a]	r=0.113 p=0.95[a]	r=0.245 p=0.48[a]	r=0.201 p=0.54[a]
Postpuberty [xxx]	–3.5±1.2	–3.7±1.6	0.11	r=0.617 p=0.01[b]	r=0.598 p=0.08[d]	r=0.362 p=0.32[a]	r=0.213 p=0.52[a]	r=0.521 p=0.02[c]	r=0.401 p=0.07[d]
Maternal Height SDS [xxx]	–1.1±0.9	–0.9±0.7	0.69						
Paternal Height SDS [xxx]	–0.8±0.6	–0.9±0.8	0.75						
Mid-parental Height SDS [xxx]	–0.9±1.0	–1.1±0.9	0.64						

Values are expressed as group means±SD, sample sizes as Xm= or Xp=; and number of measures (in brackets). Values are correlations of patient and parental height (Pearson´s correlation coefficient). [a]p>0.10; [b]p ≤ 0.01; [c]p≤0.05; [d] p≤ 0.10

anthropometric data at the beginning and after two years of rhGH treatment. **Results:** Sixty-seven (72%) patients retained the maternal X chromosome (Xm). A significant correlation between maternal height and patient's height ($p \leq 0.05$) in subjects 45,Xm was observed. There was no correlation between paternal height and patient's height at different developmental stages. No differences were detected between groups (45,Xm vs. 45,Xp) in regard to dysmorphic features, classical malformations or increase in the height-SDS after rhGH. There were higher levels of triglycerides, total cholesterol and LDL in patients >20 years who retained the Xm. **Conclusion:** It is possible that the parental origin of the retained X chromosome influences linear growth and lipid metabolism in TS patients.

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TYPE-IA Isolated Growth Hormone Deficiency (IGHD) Resulting from Compound Heterozygous Deletion of 6.7 and 7.6 Kb at the GH1 Gene Locus

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Introduction: IGHD may result from deletion/mutations in the GH1 gene. **Objective:** to characterize the molecular defect in a girl presenting IGHD. **Methods:** The patient was born at 41 weeks of gestation from non-consanguineous parents. Clinical and biochemical evaluation included anthropometric measurements, arginine stimulation tests, IGF-I and IGFBP-3 levels. Molecular characterization included PCR amplification of GH1 gene and SmaI digestion of two homologous flanking fragments, using genomic DNA from the patient and her parents as templates. **Results:** At 1.8 years of age the patient presented severe growth retardation, trunk obesity, frontal bossing, puppet-like face and acromicria. MRI showed pituitary hypoplasia. Laboratory findings confirmed IGHD (Table). GH1 gene did not amplified by PCR in samples from the patient (suggestive of gene deletion), while her parents showed one band of the expected size. SmaI digestion was compatible with the patient being a compound heterozygous for 6.7 and 7.6 Kb deletions, while her parents appear to be heterozygous carriers for either the 6.7 or the 7.6 Kb deletions. **Conclusion:** We have characterized type-IA IGHD caused by compound heterozygosity for two different GH1 gene deletions, suggesting that this condition should be suspected in severe IGHD, even in non-consanguineous families

Table 1.

Auxological evaluation	At birth	10 months	1.8 years
Height, cm (SDS)	44 (–3.7)	57 (–5.9)	61.2 (–7.4)
Weight, g (SDS)	2460 (–2.0)	5100 (–3.6)	6680 (–3.7)
Head circumference, cm (SDS)	34.1	42.1 (–2.0)	43.2 (<–2.0)
Body proportions, cm (percentile)		37.0 (25th)	39.2 (25th)

Endocrinological evaluation at 1.8 years	Value	Reference values
Prolactin (ng/ml)	21	3–15
Cortisol (g/dl)	43	6–21
ACTH (pg/ml)	40	10 – 50
GHBP (nmol/L)	1.62	1.04–6.17
TSH (mUI/ml)	2.81	0.5–6.5
FT4 (ng/ml)	1.28	0.8–2.0
GH (ng/ml), basal	<0.05	0.1–3.0
maximal response post arginine	<0.05	> 6.0
IGF-I (ng/ml)	<25	56–140
IGFBP-3 (µg/ml)	<0.50	2.0–4.4

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The Evaluation of Hypothalamic-pituitary Axis by Magnetic Resonance Imaging (MRI) is Necessary Even with Normal Response of GH Stimulation Test

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Introduction: In our department, since the standardization of MRI of hypothalamic-pituitary region, the initial investigation of patients with short stature (SS) consists of anthropometric assessment, determination of IGF-1 and MRI. **Aim:** To evaluate patients with SS who underwent MRI regarding GH response to stimulation tests and height pattern. **Methods:** From all patients who underwent this investigation protocol, 72 had SS and ectopic posterior pituitary (EPP), and their following data were analysed: chronological age (CA) at diagnosis, target height (TH), initial height and after 1 year of treatment with GH (Ht SDS), serum IGF-1 (Z score), measurement of anterior pituitary area on MRI (mm). It was considered normal response to stimulation test (clonidine or ITT) GH> 5 ng/mL (chemiluminescence). **Results:** 15/72 (20.8%) patients had normal GH response after stimulation. Comparing groups with normal response and with no response to stimulation test, we found no significant difference with respect to: CA; initial Ht SDS, variation in Ht SDS, IGF1 and adenohypophysis area (table). **Conclusion:** Despite of normal GH response after stimulation, these patients already had low levels of IGF1 and SS at diagnosis. Therefore, normal values of GH to stimulation tests do not rule out GHD associated with EPP. We suggest that MRI should be performed early in the investigation of these children.

Table 1.

Variables	GH response <5 (n=56)	GH response > 5 (n=15)
Chronological age	7.6 (4.3)	6.2 (3.1)
TH SDS	–0.4 (0.9)	–0.4 (0.6)
Initial Ht sds	–3.8 (1.4)	–3.2 (1.5)
Ht SDDS variation	1.1 (0.6)	0.9 (0.5)
IGF1 SDS	–2.3 (0.3)	–2.1 (0.6)
Adenohypophysis area	23.3 (10.2)	26 (10.3)

Student t test: p> 0.05

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Noonan Syndrome: Assessment of Bleeding Disorders

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Introduction: Noonan syndrome (NS) is an autosomal dominant disease characterized by facial dysmorphism, short stature, pubertal delay, cardiac defects, cryptorchidism and bleeding disorders. However, the prevalence of hematologic abnormalities varies from 20 to 74%. Since NS patients are frequently submitted to surgical procedures for co-morbidities, it is essential to assess hemostatic function. **Aim:** To describe and characterize hemostatic disorders in NS patients. **Methods:** We studied 13 patients (9 female, 9.7 yr) with Van der Burg criteria (6 with PTPN11 mutations). History of bleeding disorders was assessed with a questionnaire. Hematologic laboratory assessment included: protrombine time (PT), partial thromboplastin time (PTT), clot retraction, platelet count and function, bleeding time and factors levels. **Results:** Hematologic assessment was normal in 12 of 13 patients, despite a history of frequent hematoma (46%), epistaxis (15%) and gingival bleeding (39%). One patient had a platelet function disorder (storage pool disease). None of the patients submitted to surgery presented hematologic complications. **Conclusion:** Bleeding signs do not seem to be due to coagulation disorders in the NS patients reported in this study.

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Spontaneous Pregnancy in a Patient with Vaginal Agenesis and a Complex Cloacal Malformation

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Introduction: Most children with complex urogenital anomalies can be successfully reconstructed and develop into socially well-adjusted young adults, however future fertility and pregnancy outcomes are not well described. **Methods:** We report a 31-year-old patient giving birth after successful genital reconstructive surgery at 11 years. **Results:** Imperforate anus and cloacal malformation were found at birth. Surgical correction of the imperforate anus was carried out 48 hours after birth, and bilateral vesico-urethral reimplantation at 18 months. At age 11 she complained of several hematuric episodes of uncertain etiology that were found to be menstrual discharges through a single vulvar orifice, as she had complete sexual development, but no vaginal opening. During corrective surgery 2 hemiuterus were observed. The left atrophic one was removed. The right one communicating with the bladder, was disconnected and attached to a neovagina created by sigmoid reconstruction. At age 26 spontaneous pregnancy was confirmed, but resulted in miscarriage at 8 weeks. At age 31 she became pregnant again. After a 34-week-pregnancy, a C-section was performed to prevent uterine rupture. The newborn was a healthy girl. **Conclusion:** This case demonstrates that it is possible to conceive and to carry on pregnancy after significant vaginal reconstruction with impaired uterus.

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Testicular Function in Pubertal Boys with Type 1 Diabetes Mellitus (T1DM)

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Background: The effect of type 1 diabetes on Leydig and Sertoli cells function is not clear. **Aim:** To assess testicular function in pubertal boys with T1D. **Methods:** Pubertal boys with T1D (n=69, 14.5±0.3 yr) and healthy controls (C) (n=100, 14.3±0.2 yr) were studied. Inclusion criteria were Tanner stage 2 to 5, up to 18 years of age, lack of chronic comorbidities. Both groups were matched by age, BMI and Tanner stage. We measured total testosterone (TT), SHBG, inhibin B, anti-mullerian hormone (AMH) and gonadotropin levels. Free androgen index (FAI) and calculated free testosterone (cfT) were estimated. **Results:** TT, FAI and cfT were higher in T1D compared with C. Both group had similar inhibin B, AMH and gonadotropins levels. **Conclusion:** Children with T1D exhibit elevated androgen levels but normal Sertoli cell function during puberty. These data suggest involvement of Leydig but not Sertoli cells during puberty in T1D

Table 1.

DM1 (n=69)	C (n=100)	
TT (ng/dl)	422.5±30	333.5±30*
SHBG (nmol/L)	47.2±3.6	35.6±1.4***
cfT (pmol/L)	324.5±27.7	251.7±15.9**
AMH (pmol/L)	132.8±14.4	128.7±15.9
Inhibin-B (ng/L)	218.1±8.8	214.7±6.5

*P=0.008
**P=0.001
***P=0–01

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Novel Mutation in Rspo1 in Patient with Disorder of Sexual Development 46, XX Testicular Associated to Hiperceratose Palmoplantaris

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Introduction: There are only two descriptions of RSPO1 mutation related to Disorder of Sexual Development (DSD) 46, XX Testicular: a family with four affected members and one sporadic case. In both, complete XX sexual reversal was associated with palmoplantar keratoderma and predisposition to squamous cell carcinoma. **Objective:** Search for RSPO1 mutations in a patient with SRY-negative DSD 46,XX Testicular and palmoplantar keratoderma. **Methods:** Genomic DNA was isolated from peripheral blood. The coding exons were amplified and sequenced. **Results:** We found the homozygous nucleotide change NM_001038633.2:c.1093G>A in the sixth exon that led to amino acid substitution (Cys102Tyr). This alteration is absent in 100 normal controls. Discussion: RSPO1 gene is involved in WNT4 regulation and β-catenin activation, both important in the sexual determination. In addition, it participates in the keratinocytes growth and development regulation. The R-spondina1 has two furin-like domains, which are essential for Wnt signaling pathway amplification. The amino acid change is located in a highly conserved region, within the second furin-like domain and potentially affects protein function. **Conclusion:** We described the new c.1093G>A change which probably cause DDS 46, XX Testicular and palmoplantar keratoderma in our patient. Functional analysis of the mutation is now under investigation.

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Anti–Müllerian Hormone (AMH) in Patients with Congenital Adrenal Hyperplasia (CAH)

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Introduction: Hyperandrogenism in prepubertal and pubertal girls is a risk factor for polycystic ovary syndrome (PCOS). Women with CAH, the most frequent cause of hyperandrogenism, may develop PCOS. AMH is elevated and represents a useful marker for the diagnosis of PCOS. **Objective:** To determine if serum AMH levels are elevated in girls with CAH **Methods:** A cross-sectional study in 38 patients with non classical (NC) CAH (6 prepubertal [PP], 32 pubertal [P]) and 39 patients with classical (C) CAH (18 PP and 21P) was done. AMH levels were determined by ELISA and compared with AMH levels of normal girls (69 PP and 223 P). **Results:** AMH levels (pmol/l) are showed in the table. **Conclusion:** AMH levels are elevated in patients with non classical CAH, suggesting an increased mass of early antral follicles probably due to an increased androgen milieu. In patients with classical form of CAH this increment is not observed. A longitudinal study would be necessary to evaluate the usefulness of this increment to predict evolution to PCOS.

Table 1.

	Non classical CAH (NC)	Classical CAH (C)	Normal (N)	
Prepubertal girls	41.9±21.9	25.7±24.8	22.4±15.6	ANOVA P=0.003 Tukey P<0.05 NC vs N
Pubertal girls	36.9±38.2	23.4±19.7	21.1±16.3	Kruskal-Wallis P=0.005 Dunn P<0.01 NC vs N

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Characterization of the Population of 46,XX DSD Patients Followed in the Garrahan Pediatric Hospital

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Introduction: Disorders of sexual development (DSD) are those congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical. **Aim:** The main aim of this study is to characterize a cohort of 46,XX DSD patients followed at the Garrahan Pediatric Hospital. **Methods:** Medical records of all patients seen at the endocrinology department because of DSD between January 1, 2000 and January 1, 2011 in whom laboratory tests were requested were reviewed. We analyzed the records of 151 patients with 46,XX Karyotype. One patient was excluded because of insufficient studies for the etiological analysis. **Results:** In 133 patients (88.1%) the final diagnosis was congenital adrenal hyperplasia (CAH) due to 21-hydroxilase deficiency. The final diagnoses of the remaining 18 patients were the following: ovotesticular DSD in 5 patients (3.3%), testicular DSD in 4 (2.6%), aromatase deficiency (CYP19) in 4 (2.6%), oxidoreductase deficiency (POR) in 2 (1.3%), CAH due to 11-hydroxilase deficiency in 2 (1.3%), and CAH due to 3βhydroxysteroid dehydrogenase in 1 patient (0.7%). **Conclusion:** As has been previously described, the diagnosis of CAH is the most common in patients with DSD 46, XX.

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Effects of GH Over Androgen Production in Adolescents with Polycystic Ovarían Syndrome (PCOS): Preliminary Results

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Introduction: Hyperandrogenism has been reported in adolescent girls with GH insensitivity during IGF-I treatment, which reverts after discontinuing treatment. We analyzed changes in the levels of gonadotrophins and androgens in adolescents with PCOS after short-term GH administration. **Methods:** We studied six adolescent girls, at leat three years after menarche, with PCOS according to the Rotterdam criteria. We performed a complete physical exam, pelvic ultrasound and measured serum testosterone, SHBG, androstenedione (A2), 17 OH progesterone (17OHP), DHEA-S, LH, FSH, Insulin, IGF-I e IGFBP-3 basally and after administration of GH (of 0.1 U/kg/day) for 3 days. **Results:** Mean age 16.9±0.7 years, z-height 1.6±0.1, z-BMI 1.0±0.3, waist/hip 0.8±0.1, Ferriman score 12±3 and ovarian volume 9.4±1.2cc. Serum IGF-I increased by 84.2±23.2 ng/ml Two girls with the lowest BMI increased A2 by 0.9±0.3 and17OHP by 0.7±0.4ng/ml associated. with a decrease in insulin -2.7 uUI/ml and LH -2.0±0.9mUI/ml after GH. **Conclusion:** A group of lean girls with PCOS shows evidence of an increase in their circulating androgens after short-term administration of GH. These findings suggest that the somatotrophic axis may be involved in the development

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Analysis of Rspo1 in Patients with Disorder of Sex Development 46,XX Ovotesticular

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Introduction: The majority of Ovotesticular (OT) Disorders of Sex Development (DSD) patients have 46,XX karyotype and only 10% of them are associated to SRY translocations. Recently R-spondin1 (RSPO1) mutations were described in a family with cases of SRY-negative 46,XX Testicular DSD and in an isolated case of SRY-negative OT DSD. DSD was associated with palmoplantar keratoderma in both cases. Objective: Search for RSPO1 mutations in patients with SRY-negative 46,XX DSD OT without SOX9 amplification. **Methods:** Fifteen SRY-negative 46,XX DSD OT patients were included and none of them was found to have palmoplantar keratoderma. Genomic DNA was isolated from peripheral blood. The coding exons were amplified and sequenced. **Results:** No mutations were identified. Seven known single nucleotide polymorphisms were found: rs12046650, rs12039431, rs36043533, rs11588571, rs4652964, rs79760013, rs66697849. Discussion: The balance between the opposing pathways Fgf9/Sox9 and Wnt4/β-catenin directs to a male or female fate during the sex determination. R-spondin1 is essential for WNT4 expression in XX gonads and acts as β-catenin key regulator. RSPO1 loss-of-function mutation could induce testis development in the absence of SRY. **Conclusion:** Our findings suggest that RSPO1 mutation is not a common cause of SRY-negative 46,XX DSD OT in the absence of palmoplantar keratoderma

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Long Term Follow-Up of Thyroid Function and Morphology in Children with Transient Central Hypothyroidism Born to Mothers with Inadequately Treated Graves' Disease

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Introduction: Transient Central Hypothyroidism (CH) in infants born to mothers with inadequately treated Graves 'disease (GD) due to high T4 levels in utero suppressed fetal TSH by pituitary feedback usully need T4 supplementation until pituitary TSH secretion is restored. Until now, only one report analyzed the long term effects on the function of the thyroid axis after T4 withdrawal. Kempers described primary hypothyroidism with"desintegrated" thyroid gland in some neonatal CH in later childhood, as ocurred in animals with lack of type 3 deiodinase. **Methods:** We present 7 CH dignosed by routine tests of thyroid function in newborns whose mothers had GD. All neonates had decreased FT4 (range: o.2–0.9ng/dl) with decreased or inadequately normal TSH (o.29- 7.04 UI/l) at diagnosis. Their mothers had active uncontrolled hyperthyroidism during gestation. Five patients needed T4 treatment during 7–24 months. In one patient (1year-old) thyroid supplementation has not been withdrawn yet. Follow-up from T4withdrawal was mean 6.3 y (range 0.8–10.2 y). At last visit TSH, T4, FT4, TG (ECLIA) were measured (n:6), ultrasound imaging (n:7) and Tc99 thyroid scintigraphy were performed (n:6). **Results:** Normal TSH (1.04–2.3UI/l), T4(7.7–10.9 ug/dl), FT4 (1.2–1.4ng/dl) were found. Tg was found within their reference range. TPO-Ab and Tg-Ab were not demonstrated in any of the patients. Thyroid volume, echogenicity, echotexture and TC 99 scan were normal in all the patients studies. **Conclusion:** In conclusion, our normal findings suggest that besides insufficient fetal TSH secretion, the thyroid receptor stimulating antibodies transferred from the mother allow the development of the thyroid gland.

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Prevalence and Sonographic Characteristics of Thyroid Nodules in Pediatric Patients with Hashimoto's Thyroiditis

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Introduction: A higher prevalence of thyroid nodules has been documented In adults patients with Hashimoto's thyroiditis (HT). **Aim:** The aim of our study was to assess the prevalence of thyroid nodules in pediatric patients with HT, and it´s ultrasonographic characteristics. **Methods:** This is a transversal descriptive study. We included 72 children diagnosed with HT. Thyroid US was made in all patients. **Results:** In our sample, 90.3% (n=65) were female patients, with a mean age of 12.9±2.9 years. By ultrasound we found 69.4% (n=50) had thyroid nodules, 60% (n=30) of them were multinodular and 19.4% was solitary nodules. The average diameter of thyroid nodules was 4.8±2.7 mm. The nodules´characteristics were variable: 80% were solid, 90% hypoechoic and 10% had calcifications. a surrounding halo was observed in 96%, and 78% had well delimited margins. Finally, the vascularity in nodules was central in 34% and in 66% peripheral. **Conclusion:** Pediatric patients with HT had a high prevalence of thyroid nodules. The ultrasonographic characteristics of thyroid nodules are variable and are mostly benign characteristics.

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Calcitonin in the Tumor Development of Hereditary Marrow Thyroid Cancer in Two Children Diagnosed by Molecular Biology

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Introduction: Children diagnosed by molecular biology MEN2 should be treated by early prophylactic thyroid surgery and at determined times by the type of mutation affecting the ret proto-oncogene. Early stages such as cell hyperplasia C (HcC) or micro shapes of marrow thyroid cancer (MTC) have high stimulated levels of calcitonin (CT) which correlate with the tumor mass. The HCC is the earliest histological finding, prior to the development of a microcarcinoma in patients with MEN2. The HCC is presented soon after birth, and at this stage of the disease, basal CT may be normal. Therefore, a normal basal CT result does not rule out the C-cell pathology at the earliest stages. **Objective:** To evaluate the response over the time of the stimulated CT in two girls of 7 and 8 years old carriers of mutations in the RET proto-oncogene. **Méthods:** Two five year old girls (A and B) members of two different families affected by MEN 2A, and whose molecular biology diagnosis detected the RET proto-oncogene mutations. Due to their early age, parents of both girls were oppossed to an immediate thyroid surgery. This situation resulted in the possibility of keeping track of the possible development of the CMT through the evaluation of CT values for the combined stimulus of Pentagastrine (Pg) and Calcium (Ca). Utilizing CT through a RIA evaluation and intravenous combined stimulation with a sequence of 2.0 mg/kg of calcium gluconate in 1 minute and pentagastrine at the rate of 0.5 µg/kg in 5 seconds. The evaluation periods were: -5; 0; and post stimulus + 1; + 2; +3 and +5 minutes. **Results:** In the first evaluation, the girls showed normal CT values, both basal and stimulated. After a year, the values of patient A showed a basal normal CT (<10.0 pg/ml) and an increase of CT in response to the stimulus, within the normal range response (<200.0 pg/ml). In the second year, the basal stimulation test remained normal and the response continued to increase but always below 200 pg/ml. At that time, in virtue of an increasing stimulation curve, parents agreed to surgical treatment and histology showed C cells hyperplasia and a microcarcinoma. Likewise, patient B showed a basal normal CT (<10.0 pg/ml) and also an increase of CT in response to the stimulus, within the normal range response (<200.0 pg/ml). In the second year of stimulation test, the CT basal remained normal but the response increased beyond the cutting range and reaching 285 pg/ml. Nevertheless, her parents did not want to treat her at the time and it was decided to have a new stimulation on the following year. The new test again showed a normal CT but its higher value of stimulated CT grew to 680.0 pg/ml. Just then their parents accepted the surgical treatment and histology showed only C- cell hyperplasia. **Conclusion:** The CT values keep an increase with the development of the CMT. Each particular individual responds with its own and different CT levels to the state of the tumor´s development.

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A Case of Complete Deletion of 18p Associated with No Previous Reported Thyroid Hemiagenesis, and Immunoglobulin G (IgG) Deficiency

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Introduction: Deletion 18p is one of the most frequent autosomal monosomies. Clinical features are short stature, holoprosencephaly spectrum, and mental retardation. Hypopituitarism, autoimmune disease and IgA deficiency can be present. We report a patient with 18p- with thyroid hemiagenesis and immunodeficiency. **Methods:** A 4 year old boy born from healthy unrelated parents who was referred for short stature. Dysmorphic features, tetralogy of Fallot, length 85cm (-4DSD) and developmental delay were found. History of recurrent suppurative otitis, respiratory, urine and skin infections. Delay of 30 months on BA. **Results:** Laboratory:TSH:12.83mUI/ml (0.7–6.4); free T4:1.06ng/dl (0.72–1.72); T4:6.87ug/dl (5–12.5); T3:191ng/dl (80–260); basal GH:2.98ng/ml (<5); IGF1:115ng/ml (49–283); IGFBP3:3.3ug/dl (1.1–5.6), normal cortisol and prolactin levels. IgG: 371mg/dl (701–1157). Thyroid ultrasound showed a right lobe of 1.15cc and absence of the left lobule confirmed by 99mTc scan. Brain MRI showed ventricular dilatation. Cytogenetic and FISH analysis were performed using centromeric (18p11.2) and subtelomeric (18p11.32) Live probes. Karyotype: 46,XY,del(18)(p11.1).

Conclusions: The finding of thyroid hemiagenesis and IgG deficiency previously not reported in a patient with complete deletion 18p is a contribution to the genotype/phenotype characterization of this syndrome, and to the study of thyroid dysgenesis.

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Monogenic Hyperinsulinism: Hyperinsulinism/Hyperammonemia Syndrome. A Case Report

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Introduction: Monogenic Hyperinsulinism (HIM) represents a group of heterogeneous clinical disorders, which is a common cause of severe persistent hypoglycemia originated by single gene mutations. Hyperinsulinism hyperammonaemia (HI/HA) is the second most common cause. The diagnosis is based on finding hyperinsulinemic hypoglycemia associated with hyperammonemia, originating by activating mutations of Glutamate Dehydrogenase, 80% Novo, and 20% for autosomal dominant inheritance. This study presents the relationship between GLUD1 mutation and the hypoglycemia/hyperammonemia. **Methods:** A case report of male infant, 18 months, with first convulsive episode at 2 months, presenting glucose value of 18 mg/dl. After correction, patient presented again a convulsive episode, with glucose value of 22 mg/dl, Insulin: 60.5mUI/ml, Ammonium: 226 umol/l. Diagnosis arises HI/HA; begins diazoxide 12mg/kg/day achieving glycemic control without new convulsions. Discard test is made for glycogen disease type III and IB-C being negative, and molecular study. **Results:** study reported Novo heterozygous mutation in Gene GLUD1 exon 12, consistent with HI/HA. Currently, with nutritional management and diazoxide 14mg/kg/day, persists mild hyperammonemia, no convulsions, proper weight and height development, psychomotor retardation and glycemic control. **Conclusion:** Early diagnosis and treatment of HI/HA is very important for the initiation of appropriate therapy to decrease brain damage seconday to hypoglycemia and perform genetic counseling.

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Prevalence of Metabolic Syndrome in Colombian Obese Children

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Introduction: The Metabolic syndrome (MS), begins to be described in pediatric populations. In Colombia, childhood prevalence of MS rest unknown. This study assesses the frequency of MS and other risk factors (RF) in a pediatric high-risk population (Obese). **Methods:** 2461 children (1575 girls & 886 boys) with overweight and obesity, between 6–18 years, where analyzed by sex and age according to guidelines by of the IDF for MS. **Results:** We found BMI >90th percentile in 37.9% of boys and 28% of girls. Systolic blood pressure> 90th percentile in 40.1% of males and in 39.4% of girls, HDL cholesterol values <40 mg / dl in 36.0% of boys and in 18.8% of girls, and Triglycerides > 110 mg/dl by 26.4% in boys &.4% in girls, basal blood glucose> 100 mg/dl in 7.1% of boys and 2.5% of girls. 36% of the population had no RF, 40% 1 RF, 17.7% RF, 6.4% 3 RF, being this two last ones those accepted to define MS. Only 1 child was associated with 4 RF. **Conclusion:** A third of obese children present 1 or more risk factors but only 6.4% where diagnosed as MS.

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Neonatal Diabetes

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Introduction: Neonatal diabetes is a very rare disease with an estimated frequency of one per 500,000 live births. Metabolic control is difficult, is necessary to consider changes in food intake, recurrent infections and increased susceptibility to neurological sequelae secondary to hypoglycemia. **Methods:** Case report: women's product of the second pregnancy, non-consanguineous young parents, normal pregnancy, normal childbirth to the 40 week, birthweight unknown, psychomotor delay. Enter 3 months with diarrheal, severe dehydration and breathing of Kussmaul, blood sugar of 600 mg/dl, positive ketonuria began insulin infusion to 0.05 U/Kg/hour, then management with insulin NPH made numerous hypoglycemia, then became changed to insulin Glargine. When the diagnosis was confirmed progressive overlap to glibenclamide 2.5 mg/day was initiated. **Results:** Glycated haemoglobin 11.1 %, insulinemia 0.72 uUI/ml/ml, triglycerides 245 mg/dl, cholesterol 150 mg/dl. Molecular genetics: heterozigosis for the mutation in the KCNJ11 gene. Mother has mosaicism for the same mutation. **Conclusion:** In the presence of persistent hyperglycemia in a child younger than 6 months, it is imperative to do the diagnostic of neonatal diabetes with molecular genetic studies to prevent iatrogenic therapeutic behavior with relevant consequences in the life of the patient.

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Reference Values of Waist/Stature Ratio in Chilean Children Between Ages 6 and 14 Year

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Introduction: Waist to height ratio (WtHR) has advantages over isolated waist circumference and body mass index. **Aim:** To determine cardiometabolic risk independent of age and sex. **Methods:** We conducted a population-based study to describe WtHR distribution in 2983 school children (6–14 years) belonging to mid- low socioeconomic population. We determined on 3 consecu-

tive occasions waist circumference, weight and height according to standardized procedures by the WHO, and calculated WtHR. We recorded the average of 3 determinations. Results are expressed as percentiles distributed between 10 and 90 and divided by sex and age **Results:** The sample consisted of 51.5% males. Prevalence of overweight and obesity was 24.4% and 20.7% respectively. General WtHR was 0.49±0.05 **Conclusion:** 1) We present WtHR reference values for Chilean children according to age and sex, of a representative sample of mid- low socioeconomic population. 2) Although this is a population with higher obesity, this corresponds to the actual nutritional situation in Chilean children. 3) This reference according to our studies is not available until today in Chile.

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Effect of 6-Month Metformin Intervention on Endothelial Function Markers in Mexican Adolescent Patients with Polycystic Ovary Syndrome

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Introduction: Cellular adhesion molecules (CAMs), asymmetric dimethilarginine (ADMA) and carotid intima media thickness (CIMT) are markers of endothelial function. Metformin has proven beneficial effects in metabolic and clinical outcome in women with polycystic ovary syndrome (PCOS). Some studies have evaluated its effect on measured CAMs in adult patients, but little has been reported about its effect in adolescents with PCOS. The aim of this study was to determine if there is a difference in measured CAMs, ADMA and CIMT in adolescents with PCOS after metformin treatment. **Methods:** Twenty adolescents with PCOS were studied. Anthropometry, metabolic and hormonal profile, CAMs (s-ICAM, sE-selectin), ADMA and CIMT (measured by carotid-USG) were obtained before and after 3 and 6 months of treatment with 1g/daily metformin. **Results:** A significant decrease in weight, BMI, waist, waist to height ratio, insulin levels and HOMA index was found after metformin treatment. No significant difference was found in CAMs, ADMA, or CIMT after treatment. **Conclusion:** Metformin treatment in adolescent patients with POS has beneficial effects on some metabolic parameters by improving insulin resistance. An effect on endothelial function after treatment was not evidenced by the measurement of CAMs, ADMA and CIMT in this 6 month trial.

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Type 2 Diabetes Mellitus in Childhood: Clinical and Biochemical Characteristics at the Time of Diagnosis

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Introduction: The aim was to evaluate the clinical and biochemical diagnosis of Type 2 Diabetes Mellitus in pediatric patients. **Methods:** We reviewed the medical records of the 187 registered patients with diabetes mellitus and identified 17 (9%) with T2DM. The following data were recorded: age, sex, perinatal history, family history of diabetes, associated diseases, anthropometry, pubertal stage, main symptoms and signs and biochemical data, such as urine glucose, glycosylated hemoglobin, C-peptide, lipid profile, anti-islet antibodies, insulin and Glutamic Acid Descarboxylase (GAD) antibodies. **Results:** The average age at diagnosis was 12.8±3 years, 11 were male (65%) and 6 female (35%). All were born at term and 17.64% were macrosomic. Fourteen patients (82%) had a family history of T2DM. The most frequent symptoms were polyuria, polydipsia, polyphagia and weight loss; 35% were overweight, 42% were obese and 65% presented acanthosis nigricans. Some component of the lipid profile was abnormal in 60%. Anti-insulin antibodies, anti-GAD and Islet cell antibodies (anti-ICA) were negative in 86% and14.28% of the patients had any of them positive **Conclusion:** We found that most have a family history of T2DM. 75% of them showed the classical signs and symptoms of this disorder, with overweight or obesity, and dyslipidemia.

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Evaluation of Central Precocious Puberty Treatment with GnRH Analog in the Triângulo Mineiro School of Medicine

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Introduction: GnRH analog is provided by State Health Departments upon protocol for central precocious puberty (CPP). **Aim:** The aim of this study was to report our experience since 1995. **Methods:** Retrospective analysis of CPP children at the Endocrinology Unit from 1991–2010. Treatment was discontinued when bone age (BA) reached 12 years. Follow-up until final height (FH): growth velocity <1cm/year, BA 16 years. **Results:** Forty three patients divided into two groups. Subgroup 1A, n=20: among patients that reached final height (FH), 17 reached target height (TH) while 3 did not; TH did not differ from FH (p=0.090); initial final height prediction (IFHP) was similar to FH. Subgroup 1B, n=11: did not reached FH; IFHP, TH, height prediction after treatment were not different (p=0.872). These two subgroups showed that initial height z score was significantly higher after treatment. In group 2, 12 untreated patients, control group, only 6 reached TH (50%); FH did

not differ from TH (p=0.770) and IFHP (p=0.679). FH was higher in group 1A (p=0.015), and BMI in the untreated group (p=0.045). **Conclusions:** GnRH analog therapy for CPP was effective in decelerate pubertal growth. After discontinued, growth spurt was 18.55 cm (median). FH was greater in treated group in which the majority reached genetic height.

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Adrenocortical Function in a Pediatric Population with Type 1 Diabetes Mellitus (DM1)

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Introduction: Adults with DM1 reports show 25% of hypocortisolism during low doses ACTH test with negative antibodies suggesting other causes such as non autoimmune alterations in axis HPA. **Aim:** To evaluate adrenal function in pediatric patients with DM1, through low dose ACTH test and correlate the results with the frequency of severe hypoglycemia (SH) and metabolic control. **Methods:** Low dose ACTH test (1ug) in DM1 patients <18 years. Basal and stimulated cortisol was measured, in addition DHEAS and plasma Renin activity (PRA). We considered subnormal cortisol response post ACTH <18 ug/dl. **Results:** 44 patients DM1, age 12.3 years (5.7–18), 30 boys. Thyroiditis and celiac disease: 18%. HbA1cX :8.4%. InsulinX:1 U/kg/day. SH 43%. Altered results of ACTH test: 52%. SH and altered cortisol response: 53 %. High PRA: 45%. High PRA and subnormal responders: 48%. Normal DHEAS: 93% group **Conclusion:** Considerable high percent of pediatric patients with DM1, have a subnormal response of cortisol. High PRA suggests a primary defect. We did not find correlation with metabolic control, perhaps due to good metabolic control of this group. Half of the patients with hypoglicemia have a subnormal cortisol response. These results stimulates the search of subclinical hypocortisolism. Adrenal antibodies should performed.

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CAG Repeats of Androgen Receptor (AR) and Gene Expression in Women with Alopecia

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Introduction: The AR gene has highly polymorphic region consisting of the CAG repeat in exon 1. About 10% of women were homozygous for the number of repeats and it is believed that there is a correlation between AR gene expression and the number of repeats. **Aim:** To evaluate tissue-specific of AR gene in women with alopecia as well as to correlate this expression with the number of CAG repeats in exon 1 of AR gene. **Methods:** We analyzed 30 patients with alopecia and 22 control women. We obtained from the same individual RNA samples from hair follicles, both of the region around the area affected by alopecia (fronto-parietal) and in the control area (parietal-occipital). All samples were subjected to RT-PCR and genotyping in order to establish AR gene expression and the number of CAG repeats respectively. **Results:** There was no difference in AR expression in fronto parietal and occipital regions observed in patients or controls. There was no difference in the number of CAG repeats between patients and controls. There were more women homozygous for the number of CAG repeats in both groups (x/30 in patients group and y/22 in control group) compared to literature. Heterozygous patients had higher gene expression compared to homozygotes (p=0.038). There was no correlation between the number of repetitions and AR expression. **Conclusion:** AR gene expression is affected and unaffected areas showed no difference in both groups, suggesting that AR expression does not interfere in installation of alopecia. There was a difference in number of homozygous women, suggesting an imprinting mechanism. The highest gene expression in heterozygous patients may suggest impaired methylation pattern of AR gene with consequent expression of both alleles.

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Evaluation of Growth During the First Year of Life in Children with Salt Wasting Congenital Adrenal Hyperplasia (SW-CAH) Under Two Different Therapeutic Schemes of Hydrocortisone

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Introduction: Linear growth is the best clinical parameter for monitoring treatment of children with SW-CAH. To analyze growth pattern during the first year of life in patients with SW-CAH treated with hydrocortisone either twice (TID) or three times daily (TID). **Methods:** Growth velocity (GV) and hydrocortisone dose were evaluated at 0.53±0.1 and at 1.03±0.1 year in 17 patients (12F) treated BID (G1) and in 8 (4F) treated TID (G2). **Results:** Baseline clinical characteristics and hormonal control were similar between both groups. GV (cm/year) at 6 months was (mean±SD) 30.2±7.6 in G1 vs 30.8±6.2 in G2 (P=NS), and at 12 months was 14.8±5.4 (G1) vs 14.6 ±4.4 (G2) (P=NS). Height at 12m (mean±SD) G1=-0.75±1.16 vs G2=-1.38±0.76 (p=NS). Mean hydrocortisone dose (mg/m2/d, mean±SD) in G1 and G2 were 22.6±2.7 vs 32.3±9.3 (P=0.02) at baseline, 14.14±2.51 vs 18.4±3.05 (P=0.001) at 6m and 13.6±4.2 vs 17.3±3.0 (P=0.04) at 12m, respectively. **Conclusion:** Despite the use of different therapeutic schemes of hydrocortisone, no significant differences were observed in GV or height during the first year of life in patients with SW-CAH.

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AMH and Inhibin B in Pubertal Girls with Classical Congenital Adrenal Hyperplasia

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Introduction: Previous studies found increased AMH levels in daughters of PCO women, suggesting disorders in folicular development. Objective: To evaluated AMH and Inhibine B, androgens (total testosterone, DHEA-S, 17 OH progesterone and FAI) in puberal girls with Clasic Adrenal Hiperplasia, and correlates it with ovaric size. **Methods:** We study 15 puberal girls with classic CAH (12.0 + 1.9 años) and 26 control girls (11.7 + 1.3 años) matched by age, Tanner stage and BMI. 17 OH Progesterone, Testosterone, DHEA-S, Free androgen Index, AMH and Inhibina B were done, basal in controls and under adrenal supresión suprarrenal con Dexametasona supression with Dexametasone (2 mg/day, 4 days before study) in CAH girls; ginecologic ecotomography was also done. **Results:** See Table 1. There wasn´t difference on LH, FSH, AMH, DHEA-S levels, nor in ovaric size. CAH girls had higher levels of Inhibine B and less 17 OH P, testosterone and FAI. **Conclusion:** Puberal girls with Classic Congenital Adrenal Hyperplasia have increased levels of Inhibine B, with no correlation with ovaric size

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Novel Mutations in Vitamin D 1-αhydroxylase Gene in Patients with Vitamin D-dependent Rickets Type 1

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Introduction: Vitamin D-dependent rickets type 1 (VDDR1), is characterized by early onset of rickets with hypocalcemia. **Objective:** The aims were to detect CYP27B1 mutations in VDDR1 patients and to characterize clinical and endocrinological features. **Methods:** Three patients with clinical and radiographic features of rickets were studied. **Results:** First symptoms appeared within the first year of life. In two patients the laboratory abnormalities were typical of VDDR1, but in one they were unusually mild (normal calcemia and serum 1,25-(OH)2D3 but elevated serum alkaline phosphatase activity and PTH). All patients responded to treatment with 1,25-(OH)2D3. Two novel mutations (c859-860ins C, p.R432C) were identified in the two patients with typical laboratory abnormalities suggesting that these mutations would be severe. It would be predicted that c859-860ins C leads to a truncated protein if translated while p.R432C was predicted to affect protein function using the sequence homology based SIFT tool and by the structure based approach PolyPhen. The previously described p.A129T mutation was found in the patient with mild laboratory abnormalities, suggesting that such mutation might confer partial enzyme activity. **Conclusion:** These findings show the phenotypic variation in patients with VDDR1 and that classical laboratory criteria may fail to detect patients with mild abnormalities.

Table 1. (for Abstract 77)

	HSRC-C	Controles	P
N	15	26	
17 OH Progesterona (ng/dl)	0.72+0.63	1.38+0.65	0.04
Testosterona (ng/dl)	0.11+0.08	0.24+0.14	0.01
FSH (mUI/ml)	4.03+1.86	3.57+1.85	0.46
LH (mUI/ml)	2.85+4.62	1.87+1.87	0.34
SHBG (nmol/L)	67.3+29.3	40+12.8	0.0002
IAL	0.77+0.83	2.21+1.37	0.0007
DHEA-S	604+446	524+366	0.54
Hormona Anti-Mülleriana	28.93 (± 14.98)	23.80 (± 23.53)	0.20
Inhibina B	102.41 (± 47.76)	71.13 (± 40.64)	0.021
Volumen ovárico mayor	4.08 (±2.33)	4.27 (± 3.40)	0.42
Diámetro uterino longitudinal	5.12 (± 1.27)	4.92 (± 1.60)	0.34
Volumen uterino	11.13 (± 9.24)	15.07 (± 12.05)	0.13

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Identification of Three Novel PHEX Mutations in Brazilian Pediatric Patients with X-Linked Hypophosphatemic Rickets

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Introduction: Inactivating mutations of the PHEX gene are the X-Linked Hypophosphatemic rickets (XLH) molecular basis, resulting in elevation of the FGF23 serum levels and causing phosphate wasting. **Aim:** To evaluate XLH pediatric patients' phenotype and genotype. **Methods:** A review of medical records and mutational analyses of the PHEX gene were performed on eight Brazilian children (6 girls and 2 boys) with XLH; 3 of them belong to the same family. **Results:** Initial laboratory tests and clinical data revealed typical features of XLH. The serum levels of bone formation markers (alkaline phosphatase and P1NP) were increased, as well as the bone reabsortion marker (CTx) at diagnosis, decreasing during treatment. The FGF23 measurements were always elevated. Six different mutations were found: 3 nonsense, 1 missense, 1 small insertion and 1 small deletion being three not described at the literature. **Conclusion:** The molecular analysis confirms the clinical and laboratorial XLH diagnosis, allows the hypophosphatemic rickets with FGF23 high levels differential diagnosis and provides an accurate genetic counseling.

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Bone Mineralization in Children with Motor Disabilities (MD): Determination of Bone Mineral Density (BMD) in the Legs by Dual-emission X-ray Absorptiometry (DXA) Can Be a Useful Tool

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Introduction: Children with MD often suffer from osteoporosis and pathologic fractures. Little is known about their BMD and its relationship to fracture risk. **Aim:** To assess leg and total BMD in this patients by measuring BMD by DXA, in order to detect potential risk zones (legs) for osteoporosis and fractures. **Methods:** We evaluated 11 children, median age 9.3 years. Total body and leg BMD was measured by DXA using a Lunar DPX-L machine. BMD values from patients were compared with those obtained in 91 normal individuals classified according to sex, age (5–6, 7–9, 10–12, 13–15, 16–18 years) and Tanner stage. Results are expressed as mean ± SD. Statistical analysis was performed using one sample T test. **Results:** Patients showed a normal Total Body BMD (-0.2 ± 1.4)(2/11 had BMD less than -2 SD). On the other hand, when legs mineralization was compared to normal values, they showed a significant reduction: -2.8 ± 2.7 SD, p 0.006. (7/ 11 (58%), had legs BMD less than -2.0. **Conclusions:** Children with MD in lower extremities may have less mineralization in their legs. The determination of BMD in the legs can be a useful tool to identify those patients at greatest risk of suffering multiple fractures.

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