HORMONE
RESEARCH IN
PÆDIATRICS

ABSTRACTS

XXVI Annual Meeting of the Latin American Pediatric Endocrinology Society (SLEP)

Buenos Aires, Argentina, November 8–11, 2016

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The Scientific Committee and Dr. Ignacio Bergadá would like to take this opportunity to thank them publicly for their efforts. We are grateful for their help and honored that they are willing to assist us in maintaining high standards.

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Program

November 8, Tuesday

14:00	Registration
17:30–18:30	Sandoz Symposium New tools for the etiological diagnosis of disorder of sexual development Dr. Olaf Hiort (Germany)
18:30–19:00	Opening Ceremony Award "Master in Pediatric Endocrinology" Dr. Fernando Cassorla Introduced by Dr. Ethel Codner
19:00–20:00	Conference "César Bergadá" Dr. Sonir Antonini (Brazil)
20:00	Welcoming Reception

November 9, Wednesday

08:30–09:30	Plenary Lecture 1: New insights into congenital hypopituitarism Dr. Mehul Dattani (UK) Coordinator: Dr. Berenice Mendonca
09:30–10:30	Plenary Lecture 2: Prader Willi Syndrome, insights on the endocrine management Dr. Cheri Deal (Canada) Coordinator: Dr. Ana Keselman
11:00–12:30	Oral Presentations A & B
12:45–13:45	Merck Symposium New horizons in the diagnosis of growth hormone deficiency Dr. Philip Murray (UK)
14:00–15:00	Poster Session
15:30–16:30	Oral Presentations A & B
16:30–17:15	ESPE-SLEP Symposium ESPE: Pathogenesis of craniopharyngioma Dr. M. Dattani (UK) SLEP: Exome sequencing and copy number variation analysis in children with short stature Dr. Alexander Jorge (Brazil) Coordinators: Dr. Mirta Miras and Dr. Germán Iñiguez
18:00–20:30	SLEP Assembly Meeting

November 10, Thursday

08:30–09:30	Plenary Lecture 3: Pediatric thyroid cancer, what's new? Dr. Andrew Bauer (USA) Coordinator: Dr. Patricia Papendieck
09:45 - 10:45	Oral Presentations A & B
10:45 - 11:15	Break
11:15 - 12:15	Poster Session
12:30 - 13:30	Novonordisk Symposium Addressing challenges of GH therapy in children born SGA Early referral of children born small for gestational age (SGA) to the specialist: is it still an issue? Dr. Alejandro Fainboim Key challenges regarding evaluation and management of children born SGA Dr. Durval Damiani Coordinator: Dr. Ana Keselman
13:30 - 14:30	Symposium: Global pediatric endocrinology and diabetes (GPED): accessing essential medicines in pediatric endocrinology and diabetes in Latin America The World Health Organization and the National Model lists of essential medicines Dr. Jean-Pierre Chanoine (Canada) Addressing complex pediatric endocrine problems when faced with limited resources Dr. Margaret Zacharin (Australia) Laws and regulations: understanding the challenges of accessing essential medicines. Dr. Raul Calzada (Mexico)
15:00 - 15:30	Break
15:30 - 16:30	Oral Presentations A & B
16:30 - 18:30	Satellite Mini-Symposium: Rare diseases 1. Hypophosphatasia Dr. Wolfgang Hogler (UK) 2. X-linked hypophosphatemic rickets Dr. Thomas Carpenter (USA) Coordinators: Dr. Gisela Viterbo and Dr. Hamilton Cabral

November 11, Friday

08:30–09:30	Plenary Lecture 4: Update in immunopathies and adrenal disorders in pediatrics Dr. Cheri Deal (Canada) Coordinator: Dr. Marco Rivarola
09:30 - 11:00	SEEP (Sociedad Española de Endocrinologia Pediatrica)-SLEP Symposium Gender dysphoria Dr. Itxaso Rica (Spain) Endocrine hypertension in pediatrics Dr. A. Martinez Aguayo (Chile)
11:00 - 11:30	Break
11:30 - 12:30	Oral Presentations A & B
12:45 - 13:45	Pfizer Symposium 2016 update to management guidelines for estrogen treatment in combination with GH in girls with Turner syndrome Dr. Judith Ross (USA)
14:00 - 15:00	Poster Session
15:00 - 15:30	Break
15:30 - 16:30	Oral Presentations A & B
16:30 - 17:30	Plenary Lecture 5: Approach to the pediatric patient with Graves' disease Dr. Andrew Bauer (USA) Coordinator: Dr. Gil Guerra
20:00	Closing Ceremony and Awards

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Abstracts

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Presenting authors are underlined

O-1

Whole-Genome Sequencing Identifies Genetic Alterations in Pediatric Adrenocortical Tumors

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Pediatric adrenocortical tumors (ACTs) are very rare, with an unique biology and frequently arise in the context of Li-Fraumeni and other constitutive genetic syndromes. Thirty-seven pediatric ACTs were studied by molecular profiling, including whole genome, whole exome and transcriptome analysis. The cohort comprise a large number of ACTs (25 out 37) from patients with a germline TP53 mutation including cases with the Founder R337H prevalent in Brazilian population and 2 patients with a clinical diagnosis of Beckwith-Wiedemann syndrome. The tumors were clonally heterogeneous and chromosomal instability was a hallmark. Copy-neutral loss of heterozygosity for chromosomes 11 and 17 was prevalent and observed during early tumorigenesis, indicating likely driver events. ACTs associated with germline TP53 mutations showed a complex spectrum of genomic alterations whereas those with wild-type TP53 were more stable. Recurrent chromosomal translocation and fusion protein were not observed. Recurrent somatic mutations with prognostic implications include those in ATRX and CTNNB1. A dismal outcome is predicted by concomitant TP53 and ATRX mutations and associated genomic abnormalities, including high background mutation rate and massive structural variations. Alternative lengthening of telomeres was associatedwith the presence of ATRX and TP53 mutations. Overexpression of genes associated with mitosis and chromosomal segregation was also prevalent in this group. Remarkably, integration of human herpesvirus-6 in the chromosome 11p15 region in two cases suggests an alternative etiologic mechanism for this tumor. Collectively, these findings demonstrate the nature, timing and potential prognostic significance of key genetic alterations in pediatric ACT and outline a hypothetical model of pediatric adrenocortical tumorigenesis and potentially other embryonal tumors.

O-2

Mutation in SGPL1, Causing Sphingosine-1-Phosphate Lyase Deficiency, Leads to a Novel Form of Primary Adrenal Insufficiency with Steroid Resistant Nephrotic Syndrome

Braslavsky, D.[1]; *Barbagelata, E.*[2]; *Prasad, R.*[3]; *Cassinelli, H.*[1]; *Maharaj, A.*[3]; *Piantanida, J.J.*[2]; *Wainberg, E.*[2]; *Vallejo, G.*[2]; *Metherell, L.*[3]; *Bergadá, I.*[1]

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Background: Primary adrenal insufficiency (PAI) is most commonly congenital in children and genetically heterogeneous. A third of patients have no genetic diagnosis, meaning their prognosis is uncertain. The association of PAI and nephrotic syndrome (NS) was observed in four families.

Aim: To discover the genetic defect underlying this syndrome.

Methods: Whole exome sequencing was performed in two families and Sanger sequencing to confirm segregation and screen further families.

Case Reports: Argentinean siblings with PAI and NS born to consanguineous asymptomatic parents. The boy was admitted at 0.9 yrs with seizures and myocardial dilatation due to hypocalcemia. Weight and height in 25th centile. He had skin hyperpigmentation, generalized ichthyosis and café au lait spot, micropenis, unilateral cryptorchidism and neurosensorial deafness. NS rapidly turned into chronic renal failure (CRF) stage V (biopsy: NS from first year). Lab: Cortisol 11.4 μg/dL, ACTH >1250 pg/mL, Aldosterone 182 pg/ml, LH 36 IU/L, FSH 58 IU/L, testosterone <10 ng/dL, antimüllerian hormone 40 pmol/L, TSH 12.9 mU/L, fT4 0.9 ng/dL, calcium 2.87 mg/dL, phosphate 11.2 mg/dl, PTH 366 pg/mL. Kidney transplantation at 7 yrs. He developed growth retardation and progressive neurodevelopmental delay. The younger sister was born with bilateral cataracts, ichthyosis and café au lait spots. She developed hyperpigmentation and proteinuria at 1 month. NS was diagnosed (confirmed by biopsy). At 4 months she suffered an adrenal crisis (serum sodium/potassium 108/6 meq/L respectively, cortisol 1.9 μg/dL, ACTH >1250 pg/mL). She developed CRF awaiting for kidney transplant. Presently (2 yrs) she has mild neurodevelopmental delay. Ultrasound showed bilateral enlarged adrenal glands with unilateral hyperecogenic image inside in both patients. Sanger sequenciation revealed an homozygous canonical splice site change [c.261+1G>A; p.?] in SGPL1 (gene encoding sphingosine-1-phosphate lyase) in both patients and the same SGPL1 heterozygous mutation in their parents.

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Conclusions: We have identified a novel, potentially progressive disorder, incorporating PAI and NS amongst other features. This novel syndrome highlights the importance of the sphingolipid metabolic pathway in adrenal function. A genetic diagnosis for patients with this form of PAI is important for correct treatment, genetic counselling and screening for co-morbidities. Functional characterization of this molecular variant is ongoing.

O-3

Vitamin D Receptor (VDR) Is Underexpressed in Pediatric Adrenocortical Tumors and 1,25(OH)$_2$D$_3$/VDR Plays Antiproliferative Effects via Suppression of Beta-Catenin and Cell Cycle Arrest in Adrenal Cells

Bueno, A.C.[1]; *Leal, L.F.*[1]; *Gomes, D.C.*[2]; *Montaldi, A.P.*[3]; *Brandalise, S.R.*[4]; *Masterallo, M.J.*[4]; *Cardinalli, I.A.*[4]; *Yunes, J.A.*[4]; *Martinelli Jr, C.E.*[1]; *Tone, L.G.*[1]; *Scrideli, C.A.*[1]; *Moreira, A.C.*[5]; *Molina, C.A.*[6]; *Ramalho, F.*[7]; *Ramalho, L.N.Z.*[7]; *Tucci Jr, S.*[6]; *Castro, M.*[5]; *Antonini, S.R.*[1]

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Wnt/Beta-catenin pathway is activated in pediatric adrenocortical tumors (pACTs). The vitamin D_3 (calcitriol-1,25(OH)$_2$D$_3$) receptor (VDR) was shown to be underexpressed in adult adrenocortical carcinomas (ACCs). It is possible that 1,25(OH)$_2$D$_3$/VDR interacts with beta-catenin in adrenal cells.

Aim: To investigate the role of 1,25(OH)$_2$D$_3$/VDR in pACTs tumorigenesis and its interaction with beta-catenin and adrenocortical cell proliferation.

Methods: Clinicopathological features and VDR expression were evaluated in 72 pACTs, 33 fetal (FAs) and 12 pediatric adrenals (pNAs) by qPCR and immunohistochemistry. In vitro, we evaluated in NCI-H295 cells the effects of VDR activation by 1,25(OH)$_2$D$_3$ (10^{-7} M) or inhibition (siRNA knock-down) on vitamin D pathway (CYP27A1 and CYP24A1), beta-catenin, and cell cycle markers (CTNNB1, MYC, CCND1, CDK4, CCNE1, and CDK2) mRNA expression (qPCR); protein expression (western blot), cell localization (immunofluorescence-IF), cell cycle (flow cytometry) and cell viability (MTS).

Results: VDR expression was observed mainly in the nucleus of FAs subcapsular cells (20th week) and progressively increased, extended to the cytoplasm and spread throughout the cortex in late gestation and postnatal adrenals. In pACTs, VDR staining was absent in 4.3%, nuclear/cytoplasmatic in 28.3% and cytoplasmatic in 67.4%. Strong VDR staining inversely associated with Weiss score ($p < 0.001$). Compared to pNAs, VDR mRNA expression was decreased in pACTs ($p = 0.01$), especially in carcinomas ($p < 0.05$). In vitro, the activation of VDR by 1,25(OH)$_2$D$_3$ (48 h) was confirmed by decreased CYP27A1 ($p < 0.0001$) and increased CYP24A1 ($p < 0.001$), VDR expression (mRNA: $p = 0.001$; protein: 87%) and nuclear cell staining. 1,25(OH)$_2$D$_3$/VDR activation arrested cell cycle in GO/G1 (53 to 60%; $p < 0.01$), decreased G2 (25 to 19%; $p < 0.05$), and reduced the mRNA expression of G1-S markers CCND1 ($p < 0.0001$), CDK4 ($p = 0.001$), CCNE1 ($p < 0.0001$), CDK2 ($p = 0.001$). MYC ($p < 0.001$) and CTNNB1 ($p < 0.001$) mRNA expression were also reduced and beta-catenin staining (IF) was impaired. Cell viability was reduced after 96 h of 1,25(OH)$_2$D$_3$ treatment (–8.7%; $p < 0.001$). VDR knockdown (–77%; 48 h) increased beta-catenin expression (79.5%; $p = 0.01$). When activated by 1,25(OH)$_2$D$_3$, remaining VDR (23%) reduced MYC (–23%; $p = 0.01$) and CCND1 (–28%; $p = 0.01$) expression.

Conclusions: VDR plays a role in adrenocortical differentiation and is underexpressed in pACTs, mainly in pACC. In vitro, 1,25(OH)$_2$D$_3$/VDR inhibits beta-catenin, reducing adrenal cell proliferation and may emerge as a new antitumor target.

O-4

Neonatal Screening of Congenital Adrenal Hyperplasia: Results after 24 Months of Its Implementation in the Public Health System of Rio Grande do Sul, Brazil

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Congenital Adrenal Hyperplasia (CAH) is characterized by failure in the metabolism of steroids, with high rates of morbidity and mortality. The deficiency of the enzyme 21-hydroxylase cause 90–95% of cases of hyperadrenocorticism and leads to the accumulation of 17-hydroxyprogesterone (17-OHP). Early diagnosis in neonatal screening allows adequate treatment and reducing mortality.

Objective: To describe the results obtained in the CAH NS in the public health program in the state of Rio Grande do Sul (RS), Brazil.

Methods: The database of the local Reference Service was analyzed and the newborns (NB) with suspected CAH by changing the

17-OHP, measured in dried blood spots by fluoroimmunoassay technique and adjusted for birth weight (BW) were selected. The 17-OHP cutoff levels used were those recommended by the CAH Neonatal Screening National Program for 4 birth weight (BW) ranges: ≤1,500 g; 1,501–2,000 g; 2,001–2,500 g; >2,501 g and 99th percentile (P99) cutting 17-OHP to diagnose CAH was 110.4; 43.0; 28.2 and 15.1 ng/mL, respectively. Classic CAH (salt wasting and simple virilizing) was diagnosed by an increase in 17-OHP confirmed in the retest and by clinical evaluation and genotype done by PCR, Snap-Shot and MLPA (Multiplex ligation-dependent probe amplification).

Results: In the 1st year, 108,409 infants were screened, 8 cases of CAH were diagnosed, with an estimated incidence of 1:13,551. In this period, the positive predictive value (PPV) of the initial screening (before diagnostic confirmation) was 1.6% and an overall rate of false positives (FP) was 0.47%. The FP results were higher among infants with BW <2,000 g. After 24 months, 15 cases were diagnosed, from a total of 217,965 NB, with an estimated incidence of 1:14,531, with a good genotype-phenotype correlation. The most frequent mutation was IVS2-13A/C>G (40% in homozigosis), followed by V281L, deletion, conversion or rearrangement events.

Conclusion: The results underscore the need for CAH neonatal screening in the public health system and show that the strategy adopted was appropriate. Incidence, PPV and FP results were similar to those reported by other states of Brazil.

O-5

Elevated 17-Hydroxyprogesterone Levels in the Neonatal Screening as the First Clue of a Congenital Adrenocortical Tumor in an Asymptomatic Girl

Elamid Costa, M.[1]*; Manso de Lima, G.*[1]*; Sarti, M.T.*[1]*; Tucci, S.*[2]*; Costa Silva, R.J.*[3]*; Castro Barros, M.V.*[3]*; Muglia, V.*[4]*; Elias Jr, J.*[4]*; Castro, M.*[5]*; Scrideli, C.A.*[1]*; Antonini, S.R.*[1]

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Background: Congenital adrenocortical tumors (ACT) are rare. Herein we report on an otherwise healthy newborn with the diagnosis of congenital ACT carried out due to increased 17-Hydroxyprogesterone (17OHP) levels in routine neonatal screening and an unusual adrenal steroid profile.

Case Description: Patient was a full term AGA girl, born to non-consanguineous parents after an uneventful pregnancy, with normal external female genitalia and no other signs of hyperandrogenism or adrenal insufficiency in the neonatal period. Increased blood 17OHP level measured on paper filter was detected in the 1th week of life (35.5 ng/mL-107 nmol/L) with normal Na e K. In the 3rd week of life plasma 17OHP remained elevated (24 ng/mL–72 nmol/L) and modestly increased Androstenedione (1.4 ng/mL–4.9 nmol/L) and Testosterone (76 ng/dL–2.6 nmol/L) but extremely high level of DHEAS (3,163 mcg/dL–82 umol/L) was detected and later confirmed. This unusual steroid profile, particularly very high DHEAS levels, in addition to the absence of ambiguous genitalia, raised the possibility of adrenal tumor. MRI confirmed the presence a round solid heterogeneous tumor measuring 1.6x3.2x1.9 cm on the left adrenal. In addition, 7 similar lesions, the largest measuring 1.9x1.5 cm, were found in the liver but no metastases were found in the lungs or bones. Alfa-feto protein and beta-HCG levels as well as flow cytometric immunophenotyping were normal. Liver and adrenal percutaneous tumors biopsies confirmed their adrenal origin by morphology and immunohistochemistry (positivity for Inhibin A and Vimentine), with high Ki67 proliferative index (15% and 5%, respectively) and Weiss score 3. Tumor stage (IAPATR) was IV. Liver metastases were not resectable and neo adjuvant Mitotane and Etoposide/Cisplatin/Doxorubicin therapy was started. Molecular analysis detected a novel heterozygous germline TP53 mutation (c.455C>T/p.Pro152Leu) predicted to be pathogenic by in silico analysis. Family history indicated the existence of one 4th-degree cousin with adrenocortical tumor in childhood but no other criteria for Li-Fraumeni Syndrome were found.

Conclusion: Neonatal ACT is rare but this diagnosis should be suspected in children with elevated neonatal 17OHP, atypical androgen profile and absence of ambiguous genitalia in females. In addition to classic confounding factors (prematurity and low birth weight) ACTs can be a cause of 'false positive result' in the neonatal screening of CAH.

O-6

MHC-Class II Expression in Pediatric Adrenocortical Tumors: Prognostic Significance

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Adrenocortical tumors (ACTs) are rare in children accounting for approximately 0.2% of all pediatric malignancies. Currently, prognosis is based on tumor size, surgical resectability, and metastasis at diagnosis. Adrenocortical adenomas carry a good prognosis; however, the outcome is variable for the 80% of cases classified as carcinomas. Many small, completely excised adrenocortical carcinomas later relapse, while others are cured. Our previous study suggested that expression of Major Histocompatibility Complex (MHC) class II molecules was associated with histology of pediatric adrenocortical tumors (ACT). Because ACT cases with adenoma histology is associated with an excellent prognosis, we expand

our study to determine prognostic implications of the differential MHC class II gene expression in a uniformly managed cohort of patients with adrenocortical carcinoma and whether the MHC class II-expressing cells were derived from tumor cells or infiltrating hematopoietic mononuclear cells. We analyzed the expression of MHC class II and a selected cluster of differentiation (CD) genes in 63 pediatric ACTs by Affymetrix Human U133 Plus 2.0 or HT HG-U133+PM gene chip analyses. Five of the 38 probe-sets, were considered for prognostic factor analysis in a cohort of 34 cases histologically defined as carcinoma that had been uniformly treated (COG cohort). Cells expressing MHC class II were identified by morphologic and immunohistochemical assays using antibodies against HLA-DR, HLA-DPA1, CD3, CD4, CD8, CD68 and CD163. Total MHC class II expression was significantly greater in adrenocortical adenomas than in carcinomas ($P = 4.8 \times 10^{-6}$) and was associated with a higher progression-free survival (PFS) estimate ($P = 0.003$). Specifically, HLA-DPA1 expression was most significantly associated with PFS after adjustment for tumor weight and stage. HLA-DPA1 was predominantly expressed by hematopoietic infiltrating cells and undetectable in tumor cells in 23 of 26 cases (88%). MHC class II expression, which is essentially produced by tumor-infiltrating immune cells, is an indicator of disease aggressiveness. Our results suggest that immune responses modulate adrenocortical tumorigenesis, and may allow the refinement of risk stratification and treatment.

O-7

Premature Thelarche in Girls with a History of Exposure to Endocrine Disruptors

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Given the scarce experience in our setting about the impact of endocrine disruptors (ED) in pubertal development, we present a preliminary study in girls with premature thelarche with a history of exposure to various ED.

Aim: To assess clinical, biochemical and progression data in girls with premature thelarche exposed to ED, who had different clinical courses when instructed to discontinue their exposure to them.

Material and Methods: ED exposure/intake was confirmed in 60 patients with a chronological age (Median and range): 7.08 yr (2.2–7.9 yr) who presented with premature thelarche. Patients were instructed to discontinue exposure and followed up for 2 yr (9 m–8 yr). After ED discontinuation was indicated, exposure to ED and progress were assessed by clinical interview. Clinical data, bone age (BA), gonadotropins, E_2, urocytogram and gynecological ultrasound were evaluated.

Results: ED involved: BPA/Phthalates (plastic heating), parabens (personal care products) and phytoestrogens. Time from the appearance of thelarche to first visit: 6 m (2–18 m); breast development Tanner II: 73.3%, III: 26.7%. Involution of thelarche was confirmed in 44 girls (G1), persistence in 7 (G2) and progression to precocious puberty in 9 (G3). Obesity: G1: 20.45%, G2: 33.33%, G3: 28.57%. First visit (table). Trophic/hypotrophic urinary cytology G1: 43.2%/22.7%, G2: 14.3%/14% and G3: 44.4%/22.7%. Pubertal features on ultrasound examination G1: 27.3%, G2: 14.3% and G3: 33.3%. No significant differences were found in any of the first visit variables (ANOVA).

Discussion: Involution upon discontinuation of ED in G1 would be suggestive of exposure as the most probable etiology. In G2, persistent thelarche with no involution might relate to non-discontinuation of exposure, non-involution after stimulation or premature 'idiopathic' thelarche. Patients in G3 might be considered as central idiopathic precocious puberty, nevertheless, the priming effect of ED cannot be ruled out. Our findings emphasize the importance of considering the exposure as an etiology, and of regular follow-up for evaluating the clinical course, given the absence of clinical-hormonal-imaging differences in presentation, and the impossibility of measuring ED.

O-8

Cytogenomic Characterization of Chromosomal X-1 Translocation to Establish a More Accurate Phenotype-Genotype Correlation in an Adolescent with Primary Ovarian Insufficiency

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X-A translocations usually produce alterations in the gonadal development of both genders. Rearrangements of the X-chromosome in primary ovarian insufficiency (POI) has been document-

Table 1. First visit (for Abstract O-7)

	Height–SDS median (range)	Advanced BA (>1 year)	LH (mIU/ml) median (range)	E2 (pg/ml) median (range)
G1	0.76 (–1.61 to +3.86)	31.81%	0.12 (<0.04–1.4)	14 (<10–60)
G2	1.90 (+0.28 to +2.2)	28.57%	<0.04 (<0.04–0.12)	<10 (<10–26)
G3	1.20 (0 to +3.8)	55.55%	0.42 (<0.04–1)	17 (<10–60)

ed by different balanced and unbalanced X-A translocations, involving critical regions for normal ovarian development: POF1 (Xq26-q28) and POF2 (Xq13.3-q21.1). Microdeletions at these breakpoints have been characterized only in half of the cases. Two mechanisms have been proposed: the XIST-mediated inactivation on the autosomal region translocated, and an epigenetic effect called PositionVariegation that takes place when genes are located near a constitutive heterochromatin resulting in variegated silencing.

We describe how a combination of molecular cytogenetic and STRs analysis allowed us to detect and correlate a novel non-reciprocal translocation (X;1) in an adolescent with POI.

We present a 14-year-old girl diagnosed with hypergonadotropic hypogonadism, without somatic stigmata of Turner Syndrome. At first visit she was 3.1 years old and had short stature and no progressive motor neuropathy. She started spontaneous breast development at age 11 although at 14 she had not pubertal progress. Pelvic ultrasound showed a normal uterus and ovaries. FSH and LH were on menopausal range and low estradiol and AMH levels were observed.

Cytogenetic studies and FISH with whole-painting probes for 1 and X chromosomes, heterochromatin 1q12, and Xq28 probes were performed. Molecular analysis by QF-PCR determined the expansion CGG of FMR1 gene (Xq27.3), and STRs: DXS8091, DXS8377, DXS1068, DXS8069, DXS15 linked to Xq28. Karyotype revealed an apparently balanced translocation 46,X,t(X;1)(qter;q12). However, FISH showed the chromosome translocated without Xq28 signal. STRs linked to Xq27.3 and DXS8091 revealed three alleles, two of maternal and one of paternal origin. The rest of STRs showed only one allele of paternal origin. Late-replication studies revealed the existence of skewed X inactivation in derivative X chromosome.

We characterize a de novo X-1 unbalanced translocation with deletion Xq28 and interstitial duplication Xq27.3q28. POI is caused by: a-Haploinsufficiency of genes in POF1. b-Duplication of FMR1 and FMR2 genes. c-Asynapsis during meiosis leading to apoptosis of germ cells in the ovary. d-An epigenetic effect due to positioning within proximity of constitutive heterochromatin, resulting in silencing of genes in X-chromosome.

O-9

Molecular Analysis of NR5A1 Gene in a Cohort of 96 Brazilian Patients with 46,XY DSD Revealed Nine Novel Mutations

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The term Disorders of Sex Development (DSD) characterizes incomplete or disorganized genital or gonadal development. There are several genes that participate in both sex determination and differentiation processes. Mutations in NR5A1 gene, which encodes the transcription factor SF-1, are responsible for different phenotypes of DSD. Direct sequencing of the 7 exons of NR5A1 gene, including the promoter region and intron/exon boundaries and 3'UTR was performed in 96 patients with 46,XY DSD. The study revealed nine novel mutations in 11 patients (six with Partial Gonadal Dysgenesis and five classified as idiopathic 46,XY testicular DSD). The heterozygous mutations were scattered throughout exons 2 to 7 of the gene; six were within the DNA-binding domain (p.Lys38*, p.Ser32Asn, p.Arg39Cys, p.Cys55Ser, p.Cys65Tyr and p.Leu80Trpfs*8), two at the ligand binding domain (p.Cys247* and p.Lys1187Argfs*34), and one was an intronic nucleotide substitution at intron 6 donor splice site (c.1138+1G>T).

We presume that the anomalous mRNA produced as the result of p.Lys38* and p.Leu80Trpfs*8 mutations will be degraded by nonsense-mediated mRNA decay even before the translation, leading to SF-1 haploinsufficiency. Based on in silico studies, the c.1138+1G>T was predicted to generate an anomalous transcript and a truncated protein. In order to evaluate the impact of the other five mutations (p.Ser32Asn, p.Arg39Cys, p.Cys65Tyr, p.Cys247* and p.Lys1187Argfs*34) upon the protein function, normal and mutated SF-1 were expressed in HeLa cells and the expression efficiency was monitored using Western blot. Their transactivation abilities were tested in vitro using AMH and STAR promoter containing luciferase reporter genes and electrophoretic mobility shift assays (EMSA). The results showed that, the transactivation of AMH and STAR promoters were drastically reduced for all mutants, and in four cases the complex SF1-DNA were not created. The mutation p.Cys55Ser, was recently identified in one patient and, according to in silico analyses, was considered as damaging to the protein function.

The results elucidate the impact of these mutations in protein expression, justifying the DSD phenotype. Those finds highlights the important role of SF-1 in sexual development and demonstrate the significance of NR5A1 molecular analyzes in cases of patients with DSD.

O-10

Menstrual Cycle and Ovarian Function in Young Adolescents Conceived after Assisted Reproductive Techniques (AcART)

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Introduction: Limited data exists about menstrual cycles in young adolescents conceived after assisted reproductive techniques (AcART). Moreover, no information exists about granulosa cell function in these young women.

Aim: The aim of the study was to evaluate menstrual cycle patterns and hormone levels in AcART and compare them with adolescents that were spontaneously conceived (AcSP).

Methods: AcART (n = 12) and AcSP (n = 49) were studied during the first 2 years postmenarche. Hormonal profiles and ultrasonographic studies were performed during the follicular phase. Menstrual disorders were not an exclusion criteria for control adolescents. Oligomenorrhea was defined by cycles more than 45 days. Non parametric statistics was used.

Results: AcART showed similar age at menarche compared with AcSP (12.3 ± 1.1 and 11.9 ± 1.0, p = 0.96, respectively). The cycle length in AcART were not different from those in AcSP (AcART: 36.0 ± 13.7 and AcSP: 33.2 ± 7.8, p = 0.92). The presence of oligomenorrhea was more prevalent in AcART (27% vs. 6.5%, p = 0.044, X^2). In addition, AcART have lower AMH levels (p = 0.024) and higher serum INHB (p = 0.049) than AcSP, without any differences in FSH, LH, estradiol and testosterone levels (Table). AcART were born at a similar gestational age, but had lower birth weights compared with AcSP (3314 ± 608 and 3467 ± 484 g, p = 0.031, respectively). The adolescents in both groups showed similar frequency of acne and hirsutism.

Conclusions: These data suggest that menstrual cycle duration is similar in AcART and AcSP, and girls from both groups undergo menarche at a similar age. In addition, AcART show an increased prevalence of oligomenorrhea, associated with lower serum AMH and higher serum Inhibin B levels. Future studies should investigate whether these preliminary results are indicative of ovarian dysfunction in AcART (Fondecyt 11130240).

Table 1. Hormonal profile en AcART and AcSP (for Abstract O-10)

	AcSP (n = 49)	AcART (n = 12)
AMH (ng/ml)	6.0±3.7	3.1±1.6*
Inhibin-B (pg/ml)	43.7±27.4	67.8±30.7*
FSH (mUI/ml)	5.7±1.6	6.7±1.2
LH (mUI/ml)	2.9±1.4	3.4±1.6
Estradiol (pg/ml)	43.5±15.0	41.7±16.3
Testosterone (ng/dl)	40±18	38±18

* $p < 0.05$.

O-11

Targeted Massively Parallel Sequencing for the Molecular Diagnosis of 46,XY Disorders of Sex Development (DSD)

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Background: Few patients with gonadal dysgenesis (GD) obtain a molecular diagnosis by Sanger sequencing, given the complexity of the genetic defects underlying 46,XY DSD.

Objective: To investigate the underling genetic etiology of 46,XY DSD patients of unknown genetic etiology by using targeted massively parallel sequencing (TMPS).

Materials and Methods: We designed an amplicon-based capture panel of 51 genes for targeted sequencing. Among those, 38 are already associated to human DSD, 8 are involved in gonadal determination pathway, and 3 are associated to DSD in mouse. We studied seventeen 46,XY DSD patients: 13 patients with GD, 3 previously gonadectomyzed (PG), and one patient with a heterozygous CYP17A1 mutation identified by Sanger sequencing. Sequencing was performed in the Illumina MiSEQ platform. The raw data was analyzed using our in house bioinformatic pipelines for mutations (SNVs and indels) and copy number variations.

Results: TMPS identified a likely pathogenic variant in 3 GD patients and in 2 previously gonadectomized patients. All variants were found in genes previously associated to human DSD. Four were missense mutations, 1 frameshift and a copy-number gain found in the patient with 17-hydroxylase deficiency (17OHD). Additionally, we found two variants of uncertain clinical significance in the ESR2 gene. All the allelic variants found are novel, locates in conserved regions of the genes and are absent or in low frequency (<0.0007) in population databases. At least 6 prediction site tools classified them as deleterious. Conclusion: Our NSG-based targeted approach improved the genetic diagnosis of 46,XY DSD. An early genetic diagnosis can help guiding endocrine and imaging tests, limiting potentially unnecessary invasive testing and costs in 46,XY DSD patients.

Table 1. Molecular defects by target massively parallel sequencing in 46,XY DSD patients (for Abstract O-11)

DSD cause	Gene	Mutation	Zygosity
GD	GATA4	p.P407R	Hetero
GD	NR5A1	p.A340V	Hetero
GD	CBX2.2	p.C154fs	Hetero
PG	NR5A1	p.T29R	Hetero
PG	DHH	p.L335P	Homo
17OHD	CYP17A1	Dup. exons 1,2/ p.W406R	Compound hetero

O-12

Lower AMH Concentrations and High Androgens in Girls with Premature Adrenarche at Pubertal Onset

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Background: Premature adrenarche (PA) has been considered a benign condition. Recently, associations with increased androgen levels and PCOS have arisen.

Objective: To determine whether PA in children at pubertal onset (TII) determines a different timing of pubertal events and a different pattern of ovarian and adrenal hormones.

Methods: 583 girls from the Growth and Obesity Chilean cohort Study (GOCS), born ~2002, were followed twice a year with a clinical evaluation, and at TII a complete hormonal profile (androstenedione, 17OHprogesterone, testosterone and AMH). PA was defined by DHEAS >42.0 µg/dl at 6.8 ± 0.6 yr (RIA). Statistics: Generalized linear models were used to assess the relation between PA and hormonal profile, adjusting by chronologic age, HOMA and body mass index (BMI) at DHEAS sampling.

Results: At TII, girls who developed PA (PA+) were slightly younger (by interval censoring, Turnbull), taller and had a higher BMI SDS. In addition they displayed higher androstenedione, higher testosterone and lower AMH levels. No differences were observed in gonadotrophins, estradiol, 17OHprogesterone and SHBG levels.

Conclusions: Girls with history of PA initiated their puberty at an earlier age. At this stage of puberty (TII) they also showed a mild hyperandrogenism in concert with lower concentrations of AMH. Continuous follow-up of this cohort is a unique opportunity to address prospectively whether the interrelationships of PA and ovarian function persist after puberty is completed (Fondecyt 1140447 & 1120326, WCRF:2010/245).

Table 1. Clinical characteristics and hormonal profile in girls with PA (PA+) and without PA (PA–) (for Abstract O-12)

	Girls PA+	Girls PA–
Age (years)	8.80 (95% CI; 7.9–9.3)	9.30 (95% CI; 9.1–9.6)
Height_SDS	0.30±0.9**	0.10±1.0
BMI_SDS	1.10±1.1**	0.80±1.1
Androstenedione (ng/ml)	0.30±0.2**	0.26±0.1
Testosterone (ng/ml)	0.08±0.05*	0.06±0.04
AMH (ng/ml)	3.50±2.1**	4.40±2.5

* $p < 0.05$; ** $p < 0.01$.

O-13

Characterization of Four Latin-American Families Confirms Previous Findings and Reveals Novel Features of ALS Deficiency

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Introduction: ALS deficiency (ALS-D), caused by inactivating mutations in both IGFALS gene alleles, is characterized by diminished levels of IGF-I and IGFBP-3 associated to mild growth retardation. The aim of this study was to evaluate the impact on growth and on the IGF system of seven different IGFALS gene variants detected in four families. Functional in vitro characterization was also performed.

Subjects and Methods: We have diagnosed complete ALS-D in 4 subjects from Latino America, (3 boys), aged 2.4 to 13.8 years, presenting either short (–2.65 and –3.01 SDS) or normal height (–1.28 and –1.67 SDS). Auxological data, biochemical and genetic studies were also extended to all available relatives. Measurements included: basal levels of IGF-I, IGFBP-3 and ALS, IGF generation test in the index cases, serum Western and ligand immunoblot and in vitro ternary complex formation (ivTCF). The IGFALS gene was completely sequenced and the variants found were functionally characterized in vitro.

Results: Four index cases and four relatives were diagnosed as ALS-D (3 homozygous, 5 compound heterozygous), 14 relatives as heterozygous carriers and 3 as homozygous wild type. The following variants were found: p.E35Gfs*17, p.E35Kfs*87, p.L213F, p.N276S, p.L409F, p.A475V and p.S490W. Except one, ALS-D patients presented low IGF-I, undetectable levels of IGFBP-3 and ALS, and did not normalize IGF-I levels in the IGF generation test. Seven out of 8 patients did not form ivTCF. Functional studies revealed that variants p.E35Gfs*17, p.E35Kfs*87, p.N276S, p.L409F and p.S490W were not expressed, while p.L213F was synthetized but not secreted and p.A475V was normally synthetized and secreted, albeit at lower levels.

Conclusion: This study confirms that despite the severe effect on the circulating IGF system, ALS-D has a mild effect on height. The diagnosis of 2 adults with ALS-D suggests that this condition is underdiagnosed in childhood. In addition, we have found a father and son affected with ALS-D, evidence of preserved fertility, a variable response of IGF-I to IGF generation test and, the first case of a compound heterozygous patient retaining some marginal expression of ALS. In vitro expression studies were useful to classify the IGFALS variants as pathogenic or benign.

O-14

The Frequency of Pathogenic Copy Number Variants in Children with Short Stature of Unknown Etiology

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Background: Human growth is a complex and multifactorial trait, about 80% of the variation in height is due to genetic factors. It is estimated that 3% of the general population present short stature. The short stature etiology is heterogeneous and can be caused by genetic disorders. Analysis of chromosomic copy number variants (CNVs) has been used to identify the genetic basis of several clinical settings.

Objective: To analyze the frequency and describe novel submicroscopic chromosomal CNVs in a group of patients with short stature of unknown cause.

Method: We evaluated new 49 patients with short stature associated to other physical or developmental defects (dysmorphic features and/or intellectual disability), but without criteria for the diagnosis of known syndromes. All patients had normal G-banded karyotyping. Array-based comparative genomic hybridization (aCGH) or single nucleotide polymorphism array (aSNP) were performed with DNA from all patients. Detected CNVs were compared with CNV data from healthy control individuals and common copy number polymorphisms were excluded.

Results: We found 11 CNVs and 2 uniparental disomies in 12/49 patients (24%). According to established criteria for assessment of CNV pathogenicity, at least 7 CNVs in 6 patients were considered pathogenic as well as one maternal uniparental disomy (14%). In 3 patients we found deletions affecting the IGF1R gene (including a child born appropriate for gestational age), 2 patients with deletions consistent with Miller-Dieker lissencephaly syndrome (deletion involving 17p13.3) and a maternal uniparental disomy of chromosome 14 (Temple syndrome). Another patient has an interstitial de novo duplication of 7p14.3p12.1 (31.828.208–53.625.890) involving 125 genes, including IGFBP3 and GRB10. Taking together all previously published results and the present one, the frequency of pathogenic CNVs in children with short stature of unknown etiology is 13% (95% CI: 10–16%, n = 498).

Conclusion: Pathogenic CNVs were common in the selected patients, suggesting that CNVs might contribute as a genetic cause of short stature. Genome-wide copy number analysis should be used as a diagnostic tool for evaluation of short stature and also for further therapeutic approaches.

O-15

Growth Hormone Insensitivity in a Girl with Hyper IgM-Like Syndrome Due to Mutation in PIK3R1

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Hyper-IgM (HIGM) syndrome includes a group of disorders characterized by increased susceptibility to bacterial infections, normal or elevated serum IgM levels, and reduced or absent IgG, IgA, and IgE levels. Activated PI3Kδ Syndrome 2 (APDS2) due to mutations in the PIK3R1 gene has been recently described as cause of HIGM. PIK3R1 gene encodes a regulatory p85α subunit of PI3K. Poor growth has been described in 7 of 12 patients with APDS2 but the mechanism has not been clarified.

Case: A 6 years old girl, full term baby born after an uneventful pregnancy. Birth weight, 2370 g; Z score target height, +0.17. She was referred due to short stature when she was 1 year old. She looked healthy with some physical stigmata of GH deficiency. Height: –2.04 SDS. Initial complementary studies: mild anemia, glucose 64 mg/dl with normal karyotype, thyroid function and cortisol. Malabsorption syndrome, celiac disease and fibrocystic disease of the pancreas were ruled out. Her growth was poor and at 2.5 years of age, her height Z score was –2.79. The evaluation of the somatotropic axis showed IGF1 persistently low so an arginine test was performed and showed basal and peak GH 3.2 and 39.6 ng/ml respectively. The IGF1 generation test showed insufficient response of IGF1 (27.4 and 24.9 ng/ml, 4th and 8th day) and IGFBP3 (2.0 ug/ml, 4th day). She suffered recurrent otitis, pneumonias and parotitis episodes. Immunological evaluation, at 2 years of age, showed an altered serum immunoglobulin profile with low IgG, high IgM and nor detectable IgA neither IgE. B cells were present at low percentages. Though vaccinated, no antibodies to rubella, hepatitis A, varicella and Streptococcus pneumoniae were detected. Moderate low number of CD4+ T cells for age were observed with an inversion of CD4/CD8 ratio. HIGM syndrome was diagnosed. She was treated with gammaglobulin and trimethoprim-sulfamethoxazole prophylaxis since 3 years old. She has no further infections but growth continued to be poor.

Direct sequencing of gene PIK3R1 was performed. A heterozygous splice site mutation in PIK3R1 was detected: c. [1425+1 G>A; wt].

PIK3R1 mutations should be considered in patients with immunodeficiency and insensitivity to GH.

O-16

Peripheral Blood Whole Transcriptome Analysis and Machine Learning Methods Accurately Predicts Diagnosis and Severity of Childhood Growth Hormone Deficiency

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Background: The diagnosis of Growth Hormone Deficiency (GHD) involves the use of GH stimulation tests that require day case admission and multiple blood sampling. The tests are associated with adverse effects and concerns about their diagnostic reliability.

Aim: To assess the utility of gene expression (GE) profiling and candidate SNP analysis for the diagnosis and classification of GHD.

Method: Pre-pubertal treatment-naïve children with GHD (n = 98) were enrolled from the PREDICT study and controls (n = 26) acquired from online datasets. Whole blood gene expression (GE), determined with Affymetrix HU133v2.0 microarrays, was correlated with peak GH using rank regression and then a Random Forest algorithm tested for prediction of the presence of GHD and classification into severe (peak GH <4 μg/L) and non-severe (peak >4 μg/L). For GHD severity classification data on age, gender, baseline IGF-I and IGFBP-3 levels was added to the Random Forest model along with SNP genotype for 97 growth-related candidate genes. Performance was assessed using Area under the Receiver Operating Characteristic Curve (AUC-ROC). Association of SNP genotype with peak GH concentration was assessed with Kruskal-Wallis and Fisher's exact tests. A biological network of the GE related to peak GH levels was generated and cluster hierarchy assessed.

Results: Rank regression identified 347 probesets representing 271 genes where expression (both overexpressed and supressed) correlated with peak GH concentrations: (r + 0.28). At the DNA level, 18 SNPs in 12 genes were associated with peak GH concentrations; 16/18 were intronic and none were rare (defined as Minor Allele Frequency <1%). The 347 GE probesets gave an AUC-ROC of 0.98 (sensitivity 100%, specificity 96%) for predicting GHD status versus controls, while using only the top 10 probesets ranked by network centrality gave an AUC-ROC of 0.94.

Random Forest analysis predicted GHD severity (severe vs. non-severe) with an AUC-ROC of 0.93 using transcriptomic data, not improved with addition of demographic, biochemical or SNP genotype data.

Conclusion: GE profiling differentiated control children from GHD children as well as severe from non-severe GHD patients. It may therefore have a role in the diagnosis and classification of GHD, replacing two GH stimulation tests with a single blood sample.

O-17

Cardiometabolic Health Is Associated with the Chances of High School Completion in a Chilean Birth Cohort

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Background: The Metabolic Syndrome (MetS), a clustering of risk factors for type-2 diabetes mellitus and cardiovascular disease, is known to affect cognition and raise the risk for dementia in adults. Positive cognitive changes have been seen with some interventions targeting individual MetS components. Very few studies have explored these relationships in younger age populations and even few have investigated the impact on educational outcomes.

Aim: We explored the association between a number of cardiometabolic markers and the rates of high school (HS) completion in adolescents from a Chilean birth cohort.

Methods: Of 678 16 years-old participants, 633 (93%; 52% males) entered HS and, thus, met criteria for the study. At 16 years-old, waist circumference (WC), systolic and diastolic blood pressure (SBP&DBP), triglycerides (TG), HDL-cholesterol and glucose. HOMA-IR was estimated. A continuous score (zMetS) representing a composite metabolic risk factor profile was computed with gender-specific z-scores of WC, SBP, Gli, TG and HDL; lower values denotes a healthier cardiometabolic profile. MetS was diagnosed with the NHBLI/AHA/IDF criteria. HS graduation data were collected from administrative records. Data were analyzed with multiple linear and logistic regressions, controlling for sociodemographic, lifestyle and educational confounders.

Results: In the sample, 90% completed the HS diploma. Seventy-nine percent had at least one CDV risk factor and 8.1% had MetS. The association of zMetS, WC, and TG at 16 y with the odds of completing HS was negative and significant, even after controlling other influences. Notably, for a one-unit increase in the zMetS, we found 43% reduction in the odds of getting the HS diploma (OR: 0.57, 95% CI: 0.41–0.79). Conversely, HDL levels were positive and significantly related with the odds of HS completion. Finally, the chances of HS completion in participants diagnosed with MetS were 10% (95% CI: 0.02–0.36) that of participants with no cardiometabolic risk factors.

Conclusions: In adolescents, cardiometabolic health appears to be associated with the chances of high school completion. Funding: NHLBI/NIH (grant R01HL088530).

O-18

Pediatric Visceral Adiposity Index Correlates with Visceral Adiposity, Cardiovascular and Metabolic Distress in children

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Introduction: Visceral Adiposity Index (VAI) is a mathematical model associated with cardiometabolic diseases in adults. Previous studies on children failed to demonstrate any association of VAI with metabolic and cardiovascular risk. We adapted VAI components to pediatric population (VAI^P), but its association with cardiometabolic risk, has not been yet evaluated. The aim of this study was to adjust VAI^P by age and analyze correlation with insulin resistance indexes and surrogate markers for cardiovascular risk.

Methods: To adjust VAI^P, a cross-sectional study was performed. Data from 396 children (211♂, 185♀; 5–17 years) with BMI, WC, TG and HDL were used. Correlation analysis against intima media thickness (IMT), flow mediated dilatation (FMD), HOMA-IR, Matsuda-ISI, and QUICKI indexes, Visceral Fat Adiposity (VFA), Body Fat, and preperitoneal fat thickness (PP), from 85 other children, was performed. Pearson and Spearman correlations were done. Cut points were calculated by ROC curve.

Results: VAI^P was adjusted considering children <10 and ≥10 years of age, to avoid bias of puberty metabolic changes. BMI was adjusted by age. Significant moderate correlation was found between VAI^P and HOMA-IR ($r = 0.404$, $p = 0.001$), Matsuda ($r = -0.470$, $p = 0.001$), QUICKI ($r = -0.406$, $p = 0.001$), IMT ($r = 0.571$, $p = 0.001$), FMD ($r = -0.381$, $p = 0.001$), and a strong correlation was found between VAI^P and VFA ($r = 0.616$, $p = 0.001$), Body Fat ($r = 0.735$, $p = 0.001$), and PP ($r = 0.571$, $p = 0.001$). A cut of point of 2 was considered at risk.

Conclusions: Adjusted VAI^P has a strong correlation with adiposity and correlates with cardiovascular and metabolic distress. It could be a helpful tool for identifying children at risk for cardiometabolic diseases, and for the assessment of these children during treatment.

O-19

Comparison of HOMA-IR Ratio and TG/HDL-C Ratio for the Diagnosis of Metabolic Syndrome in Obese 3–5 Years Old Children

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Background: The insulin resistance is the pathophysiological basis of metabolic syndrome (MS) and cardiovascular risk (CVR); traditionally assessed by the HOMA-IR ratio. Whereas early changes in the lipid profile are increased triglycerides (TG) and decreased HDL-C, TG/HDL-C ratio is reported as a useful and practical index. In this study we compared the HOMA-IR and TG/HDL-C ratios for the diagnosis of MS in obese 3–5 years old children.

Material and Methods: 43 obese children (3–5 years old, 18 F/25 M) were included. It was assessed BMI z-score, waist circumference (WC), blood pressure (BP), lipid profile and fasting glucose. MS was defined with three or more criteria, according to the American Academy of Pediatrics: TG ≥75 mg%, HDL-C ≤45 mg%, glucose ≥100 mg%, BP≥p90 and WC≥p90 by age and sex. CVR was defined as HOMA-IR≥p95 for age and sex, according IDEFICS; TG/HDL-C ≥2.32. The sensitivity and specificity of HOMA-IR and TG/HDL-C ratio for the diagnosis of MS was calculated. Pearson's chi squared and logistic regression was performed considering significant <0.05.

Results: The mean age was 4.6 ± 0.8 years old and BMI z-score 3.2 ± 1. MS was found in 21 obese children (48.8%), the most frequent criteria were WC≥p90 (100%), elevated TG (95.24%) and low HDL-C (80.95%). The TG/HDL-C ratio had a sensitivity of 76.19% and specificity of 72.73% compared with 52.38% and 50% of the HOMA-IR index. Odds ratio for high TG/HDL-C ratio was 8.53 ($p = 0.002$) and 1.1 ($p = 0.16$) for high HOMA-IR ratio.

Conclusions: HOMA-IR ratio is less sensitive and specific than the TG/HDL-C ratio for the diagnosis of MS in obese 3–5 years old children. We recommend evaluation of TG/HDL-C ratio in all obese 3–5 years old children.

O-20

Circulating β-Klotho Levels in Children with Type 1 Diabetes Are Influenced by the Time of Onset Diabetes

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Introduction: β-Klotho has been identified as a putative aging-suppressor gene and co-receptor for FGF 21. The deficiency of β-Klotho is associated with human diseases associated with aging, such as type 2 diabetes (T2D). β-Klotho gene is expressed in the kidneys, placenta, and pancreatic islets. Recent studies showed that

Table 1. (for Abstract O-20)

	T1D	Control
Age (years)	13.4±0.5	13.8±0.7
Height SDS	–0.25±0.22	–0.68±0.37
BMI SDS	0.68±0.13 *	1.48±0.25
B-Klotho (ng/ml)	252.4±28.8 *	169.0±39.0

* $p < 0.05$.

β-Klotho ameliorates b-cell damage in T2D. No previous studies have determined β-Klotho levels in type 1 diabetes (T1D).

Aim: To assess the serum concentration of b-Klotho in children patients with T1D and determine the correlation of this hormone with duration of diabetes, metabolic control or insulin dose.

Methods: Children with T1D (n:32, girls: 17) and healthy children (n:18, girls; 12) were studied. β-Klotho levels were determined by ELISA (Cusabio, Japan). Mann-Whitney's U test and Spearman's correlation was used. Results are expressed as mean ± SEM.

Results: Both groups had similar age and height. Higher β-Klotho levels were observed in T1D compared to control group. A negative correlation between Klotho levels and T1D duration was observed ($r = -0.391$, $p = 0.027$) (table 1).

Conclusions: We report the first study that has evaluated β-Klotho levels in T1D patients. Future studies should evaluate the mechanism why patients with T1D exhibit elevated β-Klotho levels and why the levels of this hormone negatively correlate with increasing duration of this condition. (Fondecyt 111 0240).

O-21

In vitro Characterization of Two STAT3 Gain of Function Mutations Associated with IGF-1 Deficiency and Immune Dysregulation

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We have recently reported two heterozygous de novo mutations, c.1847_1849delAAG (p.E616del) and c.1276T>C (p.C426R), in the STAT3 gene in children with severe growth failure associated with a spectrum of early-onset autoimmune disease. The aim of the present study was to characterize in vitro the effects of interleukin (IL)-6 (20 ng/mL) and growth hormone (GH) (200 ng/mL) on the expression, phosphorylation and transcriptional activity of WT-STAT3 and these two variants. STAT3 gene variants were generated by site-directed mutagenesis and transfected into HEK293T cells. The activity of each mutant was evaluated using a STAT3-responsive dual-luciferase reporter assay. Expression of both newly identified mutants resulted in a significant increase in reporter activity ($p < 0.01$) in comparison to WT-STAT3 under non-stimulated conditions. GH stimulation of STAT3 variants induced the luciferase reporter gene 2- and 4-fold for p.E616del and p.C426R, respectively ($p < 0.01$). However, activation of the luciferase reporter plasmid under IL-6 stimulation was increased only by p.C426R ($p < 0.05$), but not by p.E616del STAT3. To further investigate the differences in IL-6 and GH activation of p.E616del and p.C426R STAT3 variants, we evaluated Y705-STAT3 phosphorylation by Western blot. Under basal conditions (unstimulated), Y705 phosphorylation was not detected neither in WT-STAT3 nor mutants-STAT3. In response to GH and IL-6, WT-STAT3 and the two variants were phosphorylated, but phosphorylation kinetics was different for each mutant: p.C426R exhibited delayed dephosphorylation only under GH treatment, while p.E616del, only under IL-6-stimulation. We can conclude that p.E616del and p.C426R STAT3 variants are gain-of-function mutations since they both presented increased basal transcriptional activity. While GH was able to induce the STAT3 responsive reporter vectors for both variants studied, IL-6 does not lead to enhanced transcriptional activity for p.E616del mutant compared to WT. STAT3 mutants were not constitutively phosphorylated and neither GH nor IL-6 affected abundance of the STAT3 proteins. Further studies are necessary to disclose the underlying molecular mechanisms of gain-of-function STAT3 mutations.

O-22

Isolated Growth Hormone Deficiency with Advanced Bone Age: Phenotypic Interaction between GHRH Receptor and CYP21A2 Mutations Diagnosed by Sanger and Whole Exome Sequencing

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Context: Isolated Growth Hormone Deficiency is the most common pituitary hormone deficiency and, clinically, children have delayed bone age. We report the unusual phenotype of a boy

with GH deficiency and advanced bone age due to non-classic congenital adrenal hyperplasia. High sequence similarity between CYP21A2 gene and CYP21A1P pseudogene poses difficulties for exome sequencing interpretation.

Case Description: A 7.5 year-old boy born to second-degree cousins presented with severe short stature (height SDS-3.7) and bone age of 6 years. Clonidine and combined pituitary stimulation tests revealed GH deficiency. Pituitary MRI was normal. The patient was successfully treated with rGH. Surprisingly, at 10.8 years, his bone age had advanced to 13 years, but physical exam, LH and testosterone levels remained prepubertal. An ACTH stimulation test disclosed a non-classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency explaining the bone age advancement and, therefore, treatment with cortisone acetate was added. The genetic diagnosis of a homozygous mutation in GHRHR (p.Leu144His), a homozygous CYP21A2 mutation (p.Val282Leu) and CYP21A1P pseudogene duplication was established by Sanger sequencing, MLPA and whole exome sequencing. We proposed a method of paired read mapping aided by neighbouring mismatches to sort out the real genotype for the variant of interest at CYP21A2 by exome sequencing.

Conclusion: We report the unusual clinical presentation of a patient born to consanguineous parents with two recessive endocrine diseases: non-classic congenital adrenal hyperplasia modifying the classical GH deficiency phenotype. Our experience reveals the strengths and challenges of each sequencing technology and its applications.

O-23

Clinical and Biochemical Response to rhGH Treatment in Children with Idiopathic Short Stature (ISS): Impact of Heterozygous Variants in the IGFALS Gene

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Background: Acid-labile subunit (ALS) is crucial to stabilize IGF-I in circulating ternary complexes. Complete ALS deficiency is characterized by short stature, severe reduction of serum IGF-I and IGFBP-3 levels and poor response to rhGH treatment. Less information is available on the response to rhGH treatment in children heterozygous carriers for IGFALS gene variants.

Aim: Evaluate auxological and biochemical responses to one year of rhGH treatment in short children either homozygous wild-type (WT) or heterozygous carriers (HC) for non-synonymous IGFALS variants.

Patients: Short children (height ≤ –2.5 SDS) presenting normal stimulated GH levels (GH max ≥4.7 ng/ml) were recruited. Six patients (5 boys, aged 6.7 ± 2.2) had heterozygous IGFALS gene variants: 4 probably pathogenic by in silico or in vitro assessment: p.E35Gfs*17 (n = 2), p.G506R (n = 1), p.H128R (n = 1), and 2 probably benign: p.R548W (n = 1) and p.P22L (n = 1). Other 6 ISS children (4 boys, aged 6.5 ± 2.0) were homozygous WT. Height and IGF-I, IGFBP-3 levels were evaluated before and after one-year of rhGH treatment (dose of 0.33 mg/kg/week). ALS levels were evaluated only before treatment [HC: –1.95±-0.15 (n = 6); WT: 1.57 ± 2.00 (n = 4); NS).

Table 1. Auxological and biochemical data (for Abstract O-23)

	HC (mean ± SDS)	WT (mean ± SDS)	T-test
Height SDS	–2.90±0.15	–2.82±0.53	NS
IGF-I SDS	–2.25±0.44	–0.44±0.95	p = 0.0018
IGFBP-3 SDS	–2.05±0.98	0.00±0.55	p = 0.0012
IGF-I SDS on rhGH	0.32±1.48	2.21±0.94	p = 0.025
IGFBP-3 SDS on rhGH	0.16±0.92	1.14±0.82	NS
HV (cm/year)	9.93±1.49	10.72±1.53	NS
Delta height SDS	1.21±0.43	1.15±0.26	NS

Results: Auxological and biochemical data are shown in the table 1.

Conclusions: Short children HC for IGFALS variants showed a satisfactory and similar response to one year rhGH treatment compared to WT-ISS children, although with a lower increase in IGF-I levels. This suggests that short children, carriers for IGFALS variants, could be more sensitive to IGF-I, that paracrine action of locally produced IGF-I has a more important effect on linear growth, or a combination of both. The impact of rhGH treatment on adult height in carriers for IGFALS variants remains to be determined.

O-24

Low Concentrations of Estradiol and High Concentrations of Testosterone Increase JAK2 Phosphorylation in a Human Hepatic Cell Line (HEPG2): Preliminary Results

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Background: Growth hormone and sex hormones are critical regulators of body growth and composition. Effects of sex hormones may be direct, through their receptors, or indirect by modulating the GH/JAK2/STAT5 signaling pathway. However, it is unknown whether sex hormones modulate the GH signaling pathway.

Objective: To study the effect of sex hormones on the GH signaling pathway in vitro in a human hepatic cell line.

Methods: HEPG2 cells were grown in a steroids free medium. At 80% confluence, cells were treated for 24 h with or without estradiol (0, 20, 75 and 200 pg/mL) or testosterone (0, 1, 5 and 10 ng/mL), and were subsequently stimulated with rhGH (40 ng/mL) for 15 min. The activation of JAK2 was analyzed by western inmunob-

lotting. The data were compared to their respective basal levels (Mann-Whitney test) and expressed as mean ± SEM.

Results: GH stimulation in HEPG2 cells increased phosphorylation of JAK2 (0.55 ± 0.12 vs. 0.95 ± 0.09) and STAT5 (0.40 ± 0.04 vs. 0.80 ± 0.08) compared to basal levels. Preincubation with the lowest concentrations of estradiol (20 pg/mL) for 24 h and GH for 15 min increased JAK2 (0.95 ± 0.09 vs. 1.84 ± 0.15) phosphorylation, compared with GH stimulation alone. In addition, an increase in JAK2 (0.87 ± 0.04 vs. 1.85 ± 0.22) was observed only during preincubation with the highest concentrations of testosterone tested (10 ng/mL) and GH for 15 min.

Conclusion: These preliminary results show that incubation with low concentrations of estradiol and high concentrations of testosterone during GH stimulation, increases the phosphorylation of JAK2, suggesting that sex steroids may modulate GH signal transduction.

O-25

Genotype-Phenotype Correlation in Severe Insulin Resistance Syndromes: 5 Cases with Recessive Mutations in INSR

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Introduction: Donohue (DS) and Rabson-Mendenhall syndromes (RMS) are recessive autosomal disorders associated with severe insulin resistance, caused by biallelic mutations in the insulin receptor gene (INSR). The syndromes are characterized by hyperinsulinemia and loss of glucose homeostasis. Phenotypically, elfin facies, dental abnormalities, delayed intra and extrauterine growth, acanthosis nigricans, lipodystrophy, hypertrichosis, abdominal distension and macrogenitalism are observed. DS is more aggressive while RMS represents an intermediate condition.

Methods: Descriptive study of 3 infants diagnosed of DS and 2 with RMS. The 22 exons and flanking intron regions of the INSR gene were analyzed by PCR and direct sequencing.

Results: Patients presented typical clinical and biochemical features of the syndromes. The genetic study of INSR confirmed the diagnosis. Seven of the mutations found were novels. 1) 3 year old girl diagnosed of DS with a compound heterozygous (CH) mutation in exon 2&3: p.[Gly142Asp];[Cys293Arg]. 2) Boy affected of DS who died at month 9, with homozygous mutation in exon 2: p.[(Tyr134*; Lys148*)]; [(Tyr134*; Lys148*)]. 3) Boy suffering from DS who died at month 19, with CH mutation: p.Arg1027* in exon 17 and c.3529+5G>A affecting the splicing. 4) 11 year old RMS boy showed a CH mutation in exon 14: p.[Arg926Trp]; [Arg914Cys]. 5) 15 year old girl with RMS with CH mutation in exons 4&19: p.[Arg372Gln]; [Asp1177Asn]. In all cases both parents carried one of the two alterations observed in the children. All parents were healthy, with normal fasting glucose and glucose tolerance test. Patients 1&2 with SD, presented mutations in the extracellular domain of the INSR (α subunits, encoded by exons 1–11) that normally affect the number of mature receptors or their affinity for binding insulin. Otherwise, missense mutations in the tyrosine kinase domain (β subunit, encoded by exons 12–22), are commonly associated with a milder impairment of insulin binding, as in our RMS patients 4&5. Although patient 3, presented a nonsense and splice site mutations, both located in β subunit, these alterations totally disrupt INSR function.

Conclusions: There is considerable clinical heterogeneity in cases presenting severe insulin resistance. However, phenotype can be correlated with the severity of the observed mutations in the INSR gene.

O-26

Sarcopenia Is Associated with Increased Cardiometabolic Risk Regardless of Nutritional Status in Adolescents from a Chilean Birth Cohort

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Background: Increased cardiovascular and metabolic risk has been documented in obese and non-obese adolescents with low muscular fitness. However, the association of sarcopenia with cardiovascular risk, independent of weight status, has not been examined in the youths. We aimed to examine the role of sarcopenia as a predictor of cardiometabolic risk (CMR) in apparently healthy adolescents, regardless of their weight status.

Methods: Observational, cross sectional study in 660 adolescents from a birth cohort. BMI, waist circumference (WC), and systolic and diastolic blood pressure (SBP and DBP) were measured. Total fat mass (TFM) and total lean mass (TLM) were estimated with DXA. Total cholesterol (TC), Triglycerides (TG) and HDL cholesterol, glucose (Gli) and insulin were measured. HOMA-IR and Castelli's atherogenic index (TC/HDL) were estimated. A continuous score representing a composite metabolic risk factor profile (zMetS) was computed with sex-specific z-scores of WC, SBP, Gli, TG and HDL; lower values denotes a healthier cardiometabolic profile. Metabolic Syndrome (MetS) was diagnosed using the AHA/NHLBI/IDF criteria. ROC analysis was performed to find the optimal cutoff values of muscle mass percentage for MetS diagnosis. Values below this cutoff defined sarcopenia. Then, ANCOVA was used to examine the association of sarcopenia with selected cardiometabolic biomarkers.

Results: In males and females, TLM values of 66.1% and 56.3%, respectively, were the optimal cutoff for MetS diagnosis. In the sample, 17.3% of males and 23.7% of females had sarcopenia. In both sexes, sarcopenic adolescents had significantly higher values of WC, SBP, TG, TC/HDL, HOMA-IR and z-MetS than non-sarcopenic participants. A comparison of the cardiometabolic profile between nutritional categories showed that sarcopenic adolescents, regardless nutritional status (obese and non-obese), had significantly increased values of z-MetS, SBP, TG, TC/HDL-chol and HOMA-IR than non-obese non-sarcopenic adolescents. Obese sarcopenic adolescents were the group with the unhealthiest cardiometabolic profile.

Conclusion: In adolescents, sarcopenia was associated with higher cardiometabolic risk, regardless of nutritional status. In obese adolescents, sarcopenia increased obesity-associated cardiometabolic risk.

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O-27

Laparoscopic Vertical Gastrectomy in Obese Adolescent with Pseudotumor Cerebri

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■■■

Introduction: The pseudotumor cerebri (PTC) is a syndrome characterized by headache (70%), papilledema (95%), transient visual obscuration (70%), visual loss (30%), nausea and vomit. The lumbar puncture shows hypertension and the cerebrospinal fluid constitution is normal. There are no radiological alterations. It is frequently associated with obesity and, in this case, the weight loss is urgent and maybe curative.

Case Report: C.G., 16-year-old male, has been followed in the Pediatric Endocrinology Department since 8 years old due to a severe exogenous obesity associated with insulin resistance, non alcoholic fatty liver disease, severe obstructive sleep apnea, mild asthma and systemic hypertension with target-organ damage. The pharmacological treatment of the obesity and the comorbidities was unsuccessful. He reported a severe biparietal pulsatile headache, 5 times a week, with nocturnal awakening and partial improvement with analgesic. The headache was worsening in the last 3 months.

Physical Examination: IMC 44.5 Kg (P > 99), BP – 120x70 mm Hg (p > 90). The ophthalmic evaluation showed bilateral papilledema, normal visual acuity and no alterations in the cranial nerves. The cranial CT was normal. The lumbar manometry was 40 cmH_2O (normal <20 cm H_2O). The diagnostic hypothesis was Pseudotumor Cerebri due to severe obesity and acetazolamide was started, with partial remission of the headache. Vertical laparoscopic gastrectomy (VLG) was indicated and the patient evolved with significant weight loss (37.4% of the excess weight in the 75th post op day) as well as total PTC 's remission.

Discussion: PTC is a rare condition in childhood and it is uncommom in males. This diagnosis has to be considered in patients with severe obesity and a history of headache with warning signs such as blurred vision and nausea. They need a complete lab workup and a cautious ophthalmic evaluation. The severe obesity is a true challenge to the Pediatrician and the VLG is an alternative with good results and low risk, even in adolescents. Conclusion: THE VLG is a safe and effective treatment for patients with severe obesity and pseudotumor cerebri.

O-28

Adiposity Makers Are Associated with School Performance in Adolescents from a Chilean Birth Cohort

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Background: While the cardiometabolic complications of adolescent overweight and obesity have been widely explored, its impact on cognition and educational outcomes attracted scientific attention much later.

Aim: We explored the association between a number of adiposity biomarkers and academic performance in high school students from Santiago, Chile, who were part of a follow-up study beginning in infancy.

Methods: Of 678 participants, 571 (84%) completed high school and, thus, met criteria for the study. At 16 years-old, height, weight and waist circumference (WC) were measured using standardizes procedures. BMI (kg/m^2) was calculated and BMI z-score (zBMI) for age and sex was estimated. Weight status was evaluated with WHO references. Abdominal obesity was diagnosed with IDF references. Fat mass was measured using dual X-ray absorptiometry, and Fat Mass Index (FMI) was estimated. A FMI ≥75th p by sex was considered high FMI. School grades (9th-12th) and final grade-point average (GPA) were collected from administrative records and transformed into score. Multiple linear regressions estimated the correlation of adiposity biomarkers and school grades, controlling for sociodemographic, lifestyle and educational confounding variables. Also, logistic regressions model the relation of excess weight, abdominal obesity and high FMI with having a GPA in the top 25% and top 10%.

Results: Thirty-eight percent of participants in our sample had either overweight or obesity. BMIz, FMI and WC were negatively correlated with school grades in 9th, 10th and 12th grades. Having excess weight and abdominal obesity also led to significant reductions in the odds of performing top 25% and top 10%.

Conclusions: In adolescents, we found a negative and significant association of adiposity markers such as BMI, WC and FMI with school performance, as measured by high school grades. The associations remained significant after controlling other influences. Funding: NHLBI/NIH (grant R01HL088530).

O-29

Fertility and Pregnancy Outcomes after Ovarian Stimulation in Five Patients with Congenital Hypopituitarism Treated with GH Since Childhood

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Hypopituitarism yields low pregnancy rates after ovulation induction and associated pituitary hormone deficiencies might play a role in this poorer outcome.

Objective: To evaluate fertility treatment and pregnancy outcomes in women with congenital combined pituitary hormone deficiencies (CPHD) with adequate hormone replacement including GH since childhood.

Patients and Methods: Five women with congenital CPHD treated since childhood for all deficiencies including GH were referred to fertility treatment as soon as they manifested their wish for pregnancy. Patients were submitted to controlled ovarian stimulation (COS) for timed intercourse (TI), intra uterine insemination (IUI) or in vitro fertilization (IVF), according to the presence or not of other infertility factors (male or tubal) rather than anovulation.

Results: All women succeeded in becoming pregnant. Prior to ovarian stimulation we performed an adequacy of hormonal replacement therapy including GH. All patients achieved normal IGF1 prior to fertility treatment. The number of COS attempts until pregnancy was achieved varied between 1 and 5. The duration of COS resulting in at least one dominant follicle varied between 9 and 28 days, and total gonadotropin consumed to achieve successful follicular development varied between 1200 and 3450 IU. Only 2 patients had a cancelled COS cycle; interestingly, these patients had also severely suppressed basal gonadotropin levels and reduced ovarian reserve tests results. One patient had a monochorionic twin gestation. The gestational age at birth ranged from 35 to 39 weeks and 4 days, there were 3 cesarean and 2 vaginal deliveries. Only one patient had a newborn small for gestational age at 35 weeks of pregnancy.

Conclusion: Adequate hormonal replacement therapy, including GH, may be an important step prior to fertility treatments in women with congenital hypopituitarism.

O-30

FGFR1 Pathway (FGFP) in Women with GNRH Deficiency (GNRHD): Mild Reproductive Phenotype?

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Background: Congenital hypogonadotropic hypogonadism (CHH) has been associated with a broad spectrum of smell abnormalities and reproductive phenotypes. FGFR1 mutations and in its ligands (KAL, FGF8) have been identified in individuals with severe anosmic hypogonadism. Most cases have been reported in males, but scarce data exists in females with GNRHD.

Aim: To describe the reproductive phenotype in hypogonadic women (HW) with mutations in FGFP (FGFR1, KAL, FGF8) and to compare them with HW with other mutations in genes that determine GNRHD.

Methods: 170 probands with GNRHD were recruited: 92 women and 78 males. A complete health evaluation and smell test (University of Pennsylvania Smell Identification Test) was performed.

Results: 22/92 WH were positive for mutations in genes determining GNRHD: 8 in the FGFP (FGFP+) and 14 in genes of GNRHD (TAC3R, PROK2, CHD7, GNRHR, NSMF, KISS1R: FGFP-). Spontaneous telarche and menarche were presented similarly in FGFP+ and FGFP– (X^2, p = 0.39), see Table. Regarding smell phenotype: 50% of FGFP+ and 57% of FGFP– have normal smell with a 12% of anosmia in each group (p=ns).

Conclusions: Reproductive phenotype in HW with mutations in FGFP is less severe than previously described. These results suggests other genetic or environmental factors could modify the severity of the phenotype in women. It is also important to suspect alterations at these levels in adolescents without anosmia or spontaneous puberty that is arrested thereafter.

Table 1. Pubertal development in women with mutation in FGFP (for Abstract O-30)

		No mutations (n = 70)	FGFP+ (n = 8)	FGFP– (n = 14)
Telarche	NO	4	2	1
	Spontaneous	49	5	12
	Induced	17	1	1
Menarche	NO	14	3	3
	Spontaneous	35	3	8
	Induced	21	2	3

O-31

A New GNRH1 Mutation in a Boy with Congenital Isolated Hypogonadotropic Hypogonadism

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Background: Gonadotropin-releasing hormone (GnRH) is the master hormone of the reproductive endocrine system. Congenital isolated hypogonadotropic hypogonadism is characterized by partial or complete lack of pubertal development due to defects in the synthesis, secretion or action of GnRH. Several genes have been associated with GnRH deficiency, but the most obvious candidate gene, GNRH1, remains a very rare cause of IHH.

Design and Methods: We evaluated the clinical, hormonal and molecular features of a Brazilian boy with congenital normosmic IHH born to consanguineous parents. Genomic DNA was analyzed by targeted Next Generation Sequencing, within a panel of 34 candidate genes, using the Illumina MiSeq platform. Variants were compared to available databases. Confirmation and familiar segregation analysis were performed by Sanger sequencing. The softwares Human Splicing Finder and NetGene2 were used for in silico analysis.

Results: A homozygous variant affecting the consensus acceptor splicing site in the intron1-exon2 boundary (c.142-2A>C) was identified in the GNRH1 gene. The proband was 18 yr old boy who presented with lack of puberal development, micropenis and history of bilateral cryptorchidism. He had eununcoid proportions and BMI 30.2 kg/m^2. Olfactory test was normal and he had no other clinical abnormalities. Hormonal evaluation revealed prepubertal levels of serum testosterone, <11 ng/dL (271 to 965 ng/dL), and undetectable levels of basal LH, 0.1 IU/L (1.0 to 8.4 IU/L), FSH <1 IU/L (1.1 to 10.5 IU/L) and inhibin B <10 pg/mL (25 to 325 pg/mL). MRI scan of central nervous system was normal. His unaffected parents were heterozygous for the c.142-2A>C variant. This variant showed high probability of being deleterious by in silico analysis and was predicted to lead to an abnormal transcription product. The c.142-2A>C variant was located in the GnRH precursor protein, in the region that encodes for the GnRH-associated peptide (GAP). Interestingly, this corresponds to the same region that is deleted in the hypognadal (hpg) mouse, a natural occurring model of GnRH deficiency.

Conclusion: We described a novel homozygous mutation in the GNRH1 gene in a male with complete normosmic congenital IHH.

O-32

Hypogonadotropic Hypogonadism and Short Stature in Patients with Diabetes Due to NEUROG3 Deficiency

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Introduction: Biallelic mutations in NEUROG3 are known to cause early-onset malabsorptive diarrhea due to congenital anendocrinosis and diabetes mellitus at a variable age. No other endocrine disorders have been described so far. We report four patients with homozygous NEUROG3 mutations who presented with short stature and failed to show any signs of pubertal development.

Aim: Report the association of NEUROG3 deficiency and hypogonadism and short stature.

Case Description: Four patients were diagnosed with homozygous mutations in NEUROG3 due to the association of congenital malabsorptive diarrhea and diabetes. All of them had severe short stature and failed to develop secondary sexual characteristics at an appropriate age, despite some having normal weight and irrespective of their gender. Absence of gonadal function persisted into the third decade in one patient. Upon testing, both basal and stimulated LH and FSH levels were low with the remaining pituitary hormones within the normal range. MRI scans of the hypothalamic-pituitary axis did not reveal structural abnormalities. A diagnosis of hypogonadotropic hypogonadism was made and replacement therapy with sexual hormones was started.

Conclusion: NEUROG3 mutations expand on the growing number of genetic causes of acquired hypogonadotropic hypogonadism. The high reproducibility of this novel phenotype suggests that central hypogonadism and short stature are common findings in patients with mutations in NEUROG3. Growth rate needs to be carefully monitored in these patients, who also should be routinely screened for hypogonadism when they reach the appropriate age.

O-33

The Anthropometric and Cardiometabolic Profile of Adolescence Is Associated with Increased Risk of Metabolic Syndrome in Early Adulthood

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Background: The Metabolic Syndrome (MetS) is a clustering of cardiometabolic and vascular disorders and allows early identification of individuals with future risk of type-2 diabetes and cardiovascular disorders. We explored how adolescent anthropometric and cardiometabolic profile related to the risk of MetS in emerging adulthood.

Methods: Observational, prospective study in 248 youths of low-to-middle SES (48% males), participants in a birth cohort. BMI, waist circumference, systolic and diastolic blood pressure, fat and lean mass (by dual-energy X-ray absorptiometry), triglycerides (TG), HDL-cholesterol, glucose, insulin, and HOMA-IR, were measured at 16 and 22 years-old. MetS was diagnosed using the AHA/NHBLI/IDF criteria whereas insulin resistance (IR) was diagnosed using HOMA-IR ≥2·6, according to previous studies. Physical activity (PA) was self-reported using a validated questionnaire. Multivariate regression models examined the associations of selected cardiometabolic biomarkers in adolescence with the risk of having MetS in emerging adulthood. Models were adjusted for sex, PA and having MetS at 16 y.

Results: In our sample, BMI significantly increased from adolescence to early adulthood (23.5 to 26.6; P < 0.001). We also found a significantly higher prevalence of obesity (12.1% to 24.2%; P < 0.001), IR (20.2% to 48.2%; P < 0.001) and MetS (8.9% to 15.2%; P < 0.01). The association of BMI, WC, PAS and PAD, TG, Gli, HOMA-IR at 16 y with the risk of having MetS at 22 y was positive and significant, even after controlling other influences. Notably, for each one-unit increase in BMI at 16 y, the risk of MetS at 22 y increased by 2.7 (95% CI: 1.78–4.20) times. Likewise, for each one-unit increase in HOMA-IR at 16 y, we observed 44% (OR: 1.44; 95% CI: 1.10–1.89) increase in the odds of having MetS at 22 y. Conversely, HDL levels and lean mass at 16 y were negative and significantly related with the risk of MetS at 22 y (OR: 0.94; 95% CI: 0.91–0.98 and OR: 0.91; 95% CI 0.86–0.96, respectively).

Conclusions: In youths of mid-to-low SES, the anthropometric and cardiovascular profile of adolescence was related to the risk of having MetS in early adulthood. Funding: NHLBI/NIH (grant 2R01HL088530).

O-34

Clinical Experience with Intragastric Balloon for Obesity Treatment in Adolescents

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Pediatric obesity and associated comorbidities are increasing around the world. Medical management has featured variable and modest efficacy for weight control. Intragastric balloon (IB) is an endoscopic non-surgical alternative for patients who fail medical treatment and that bariatric surgery is not suitable.

Aim: The aim of this study was to describe the baseline comorbidities and anthropometric outcomes of obese adolescents treated with IB, in one single center.

Methods: We reviewed the medical records of all patients undergoing ORBERA IB System in our center from June 2010 to June 2016. Inclusion criteria: Adolescents (age under 20 years), with BMI >2 SDS and metabolic associated comorbidities.

Results: 12.4% out of a cohort of 105 patients were adolescents (n = 13), 84.6% female, age 16.3 + 2.13 years (13–19), initial BMI was 31.7 + 2.5 (28.7–35.9) and final BMI was 29.51 + 5.06 (22.2–36.1) p < 0.005; initial BMI SDS was 2.5 + 0.45, and final BMI SDS was 2.05 + 0.80 p < 0.005. Weight loss was achieved in 84% of the patients, with an average of 59.8% of excess weight loss (%EWL) in this group. Anthropometric outcomes by EWL group are shown in the table 1. Comorbidities: insulin resistance 77%, fat liver 46%, dyslipidemia 77%, cholelithiasis 15%, 15% high blood pressure and 7.5% asthma. One male patient had poor tolerance and requested an early removal. No serious adverse events were reported.

Conclusions: Intragastric balloon seems to be an effective and safe non-surgical alternative for the treatment of obesity in adolescents. With a multidisciplinary approach could be advantageous for selected individuals in this age group. Patients that gain weight were more obese and less adherent to medical controls. Further studies and follow up are required to establish the long-term outcomes.

Table 1. Baseline characteristics and anthropometric outcomes by group of subjects who lose and did not lose weight after intragastric balloon therapy (for Abstract O-34)

Lose weight group	I BMI SDS	F BMI SDS	%EWL	Post IB controls
Yes 11 (mean + SD)	2.35+0.35	1.56+0.45	59.85+24.56	3.78+2.86
No 2 (mean + SD)	3.18+0.11*	3.15+0.15*	−15.0+7.07*	2.00+1.4*

I = Initial; F = final. * p < 0.05.

O-35

Neck Circumference Cutoff Values in Mexican Overweight and Obese Children by Gender and Tanner Stage

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Background: At present, appropriate anthropometric measures and cut-off points to identify children with elevated cardiometabolic risk factors are not well established. The most widely used to predict cardiovascular and metabolic risk is the body mass index (BMI) and waist to height ratio (WHtR), and both have its limitations. Upper body subcutaneous fat (USBF) is suggested that plays a role in cardio-metabolic risk, and is estimated by neck circumference (NC).

Aim of the Study: The aim of this study is to determine cutoff values for NC in children with overweight and obesity to behave as diagnostic tool for predicting cardio-metabolic risk in Mexican children compared with other anthropometric measures.

Methods: Anthropometric measurements were performed and biochemical profiles determined in a cross-sectional study that included 499 children and adolescents, aged 6–16 years. Demographic, clinical, anthropometric and biochemical data were collected from all patients. The International Diabetes Federation criteria were used to determinate metabolic syndrome (MetS). Multiple linear regression analysis was applied and determined by receiver operating characteristic (ROC) analyses the optimal cutoff for NC compared with other anthropometric measurements.

Results: We found a NC cutoff of 30.65 cm (p = 0.006) in prepubertal, 33.75 cm (p = 0.0001) in pubertal stage 2–3 and 37.84 cm (p = 0.001) pubertal stage 4–5 boys. In Girls the NC cutoff was 29.95 cm (p = 0.006) in prepubertal girls, 31.60 cm (p = 0.066) in pubertal stage 2–3 and 34.95 cm (p = 0.0001).

Conclusions: We determine that NC sensibility is similar to waist circumference and WHtR in prepubertal girls and boys. NC is similar to determinate MetS compared with other anthropometric measurements.

O-36

Leptin Is Associated with Serum Aldosterone in Paediatric Subjects, Independently of Body Mass Index, Blood Pressure and Plasma Renin Activity

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Background: Leptin is considered to play an important role in the development of hypertension in obesity. The excessive synthesis of aldosterone contributes to the development and progression of metabolic and cardiovascular dysfunctions. Leptin is a newly described regulator of aldosterone synthesis that acts directly on adrenal glomerulosa cells to increase CYP11B2 expression and enhance aldosterone production in human adrenal cells lines and in animal models.

Objective: To analyze if there is association between leptin with serum aldosterone (SA), as well as with blood pressure (BP), plasma renin activity (PRA), trans-tubular potassium gradient (TTKG), fractional excretion of sodium (FENa) and 24 h-Na/K urine ratio.

Design: Cross sectional study.

Subject and Methods: We studied 79 subjects between 6.1 and 18 years old (mean, 13.2 years; 42 females); 37 were normal weight, 18 were overweight, and 24 were obese. After overnight fasting: anthropometric parameters, SA, PRA, plasma and 24-h-urine electrolytes were measured and TTKG, FENa and 24 h-Na/K urine ratio were calculated. For variables without normal distribution, Spearman correlation was used, and log transformation was calculated previously to partial correlation analyses.

Results: Leptin was directly associated with SA (Rho = 0.275; P = 0.016). None association was found between leptin with systolic and diastolic blood pressure (P = 0.657 and P = 0.869, respectively) and PRA (P = 0.197). Moreover, after controlling by age, body mass index z-score (BMI-z), $\log_{10}$ PRA and $\log_{10}$ 24 h-Na/K urine ratio, the association between $\log_{10}$ leptin and $\log_{10}$ SA increase (Partial correlation = 0.367; P = 0.002). In other hand, SA was associated with PRA (Rho = 0.400; P < 0.001) and TTKG (Rho = 0.330; P = 0.037); and negative associated with FENa (Rho= –0.246; P = 0.035) and 24 h-Na/K urine ratio (Rho= –0.276; P = 0.014).

Conclusion: In paediatric subjects, leptin was associated with serum aldosterone. This association was independently of the effect of age, BMI-z, PRA and blood pressure. Our clinical results agree with the recently described effect between of leptin upon aldosterone secretion in human adrenal cells lines and in animal models.

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O-37

Bone Mass Gain from Adolescence to Emerging Adulthood in Chilean Birth Cohort: Association with Nutritional, Biological and Environmental Factors

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Background: The risk of osteoporotic fracture relates to the peak bone mass achieved in emerging adulthood. Adolescence is a critical period for bone mass gain (BMg). Despite genetics play a major role in bone density variance, environmental factors (e.g. dietary calcium and physical activity (PA)) and weight status also contribute to the variance in bone density. We analyzed (BMg) from adolescence to emerging adulthood and its association with a number of biological, nutritional and environmental factors.

Methods: Observational, prospective study in 248 youths of low-to-middle SES (48% males), participants in a birth cohort. BMI, fat and lean mass (FM% and LM%) and bone mineral density (BMD gr/m^2 assessed with DXA), glucose, insulin and HOMA-IR were assessed at 16 y. Diet and PA were self-reported using validated questionnaires. BMD was reassessed at 22 y. BMD z-score (zBMD) was calculated. BMg was estimated as the percentage difference between BMD at 22 y and 16 y. To assess quality of gain, BMg distribution was divided into terciles: low, intermediate and high. Multivariate regression models examined the associations BMg quality with weight status, IR, sex, and PA at 16 y.

Results: A significant increase ($P < 0.001$) in zBMD from adolescence to emerging adulthood was found in both males (0.18 ± 1.0 to 0.73 ± 1.0) and females (–0.41 ± 1.1 to 0.54 ± 1.0). Obese subjects did not show a significant change in zBMD from 16 y to 22 y. There was a significant association of BMg with anthropometric and bone mass profile at 16 y. Participants with low BMg (≤3.4%) had significantly higher BMI and FM% and lower LM% and zBMD at 16 y than participants in the highest BMg tercile (≥9.2%). Low BMg was significantly associated with being female, having obesity and IR, and being physically inactive. Conversely, highest BMG was significantly associated with being male, having normal weight and insulin sensitivity.

Conclusion: BMg from adolescence to early adulthood was associated with nutritional, biological and environmental factors. Obesity, IR, female sex and physical inactivity were associated with lower bone mass variance. Funding: NHLBI/NIH (grant 2R01HL088530).

O-38

Effect of KRN23, a Fully Human Anti-FGF23 Monoclonal Antibody, on Rickets in Children with X-Linked Hypophosphatemia (XLH): 40-Week Interim Results from a Randomized, Open-Label Phase 2 Study

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In XLH, high circulating FGF23 causes hypophosphatemia, rickets, and short stature. KRN23, an investigational product, binds and inhibits FGF23 activity. In our Phase 2 study, 52 XLH

Table 1. Rickets severity before and after a 40-week course of KRN23 in children with XLH (for Abstract O-38)

All patients		All (n = 36)	Q2W (n = 18)	Q4W (n = 18)
	mean total RSS BL	1.4	1.5	1.3
	mean total RSS Week 40	1.0*	0.9*	1.1
	mean RGI-C Week 40	+1.4#	+1.6#	+1.2#
Pts: BL total RSS ≥1.5		All (n = 18)	Q2W (n = 9)	Q4W (n = 9)
	mean total RSS BL	2.3	2.4	2.2
	mean total RSS Week 40	1.2#	1.0#	1.4*
	mean RGI-C Week 40	+1.9#	+2.0#	+1.7#

* $p < 0.05$, comparing Week 40 to baseline. # $p < 0.001$, comparing Week 40 to baseline.

children (ages 5–12 years, ≤Tanner 2) were randomized to receive KRN23 subcutaneously biweekly (Q2W) or monthly (Q4W). Serum phosphate (Pi) was measured biweekly. KRN23 dose was adjusted (maximum 2 mg/kg) to achieve age-appropriate serum Pi concentrations.

The first 36 patients had received standard-of-care treatment for a mean of 6.6 years before enrolment. Serum Pi increased from baseline in all patients to near normal levels (mean increase, 0.94 mg/dL at 38 weeks; $p < 0.0001$). Levels were more stable with Q2W dosing; hyperphosphatemia did not occur. KRN23 significantly improved rickets, assessed by the total Thacher Rickets Severity Score (RSS), with greater improvements occurring with Q2W dosing (44% reduction; $p = 0.0126$) and in patients with more severe rickets at baseline (baseline total RSS ≥1.5) (59% reduction; $p < 0.0001$). The Radiographic Global Impression of Change (RGI-C; –3 = worsening; +3 = complete healing) showed that Q2W dosing improved rickets by +1.6 ($p < 0.0001$), with the higher-severity rickets subset showing substantial healing (+2.0; $p < 0.0001$). Serum alkaline phosphatase, a marker of rickets severity, decreased. Most treatment-related adverse events (AE) were mild, most commonly a transient injection site reaction (39%). One child experienced a serious AE and was hospitalized for fever/muscle pain that resolved and the patient continues to participate in the trial. No clinically meaningful changes occurred in serum or urine calcium, serum iPTH, or renal ultrasound. In summary, KRN23 improved phosphorus homeostasis and rickets in children with XLH, with an acceptable benefit-risk profile.

O-39

Surgical Treatment of Hyperparathyroidism in Children with Chronic Kidney Disease. Experience in 15 Patients

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Secondary hyperparathyroidism (HPTs) is an important contributor to bone disease and cardiovascular calcifications in children with Chronic Kidney Disease (CKD). When conservative measures (pharmacological and dietary interventions) are ineffective, parathyroidectomy is indicated. However, the results of this treatment have not yet been well evaluated in children.

We retrospectively analyzed the course of 15 pediatric CKD patients on dialysis with refractory HPTs (Parathormone (PTH) >800 pg/ml for more than 6 months) who underwent subtotal parathyroidectomy (PTXs) in our institution between 2010 and 2015. Nine males and 6 females were included; mean age (± SD): 14.5 ± 1.4 years (range 11.9–17), weight: –2.5 ± 1, height: –3.3 ± 1.2 (n = 11).

All patients had clinical, radiological and biochemical signs of renal osteodystrophy. Preoperative PTH levels had a significative positive correlation with serum alkaline phosphatase (ALP) (p 0.04).

PTXs was successful in all patients except in one, who required percutaneous ethanol injection 2 years later.

Mean serum PTH value (± SD) dropped within 1 year after PTXs from 2072 ± 1072 to 183 ± 204 pg/ml (p 0.0001), mean serum ALP level (± SD) from 1513 ± 969 to 321 ± 211 IU/l (p 0.002), mean Ca x P product (± SD) from 48.9 ± 11.6 to 44.3 ± 11.5 mg^2/dl^2 (p 0.07).

Due to severe hungry bone, oral calcium supply after surgery was 256 ± 121 mg/kg/day and calcitriol was 115 ± 70 ng/kg/day. None patients had postoperative complications.

Histological findings had good correlation with pre-operative parathyroid ultrasound imaging (n = 11) in 100% and with ^{99}Tc Sestamibi scintigraphy (n = 12) in 83.3%.

All patients improved clinical and radiological signs of bone disease. Four of them, who previously were wheelchair-bounded, started walking after PTXs.

Pediatric PTXs is an effective and safe treatment to control HPTs and calcium-phosphate metabolism in children with CKD on dialysis and may mitigate unreversible bone deformities and progression of cardiovascular disease.

O-40

Pseudohypoparathyroidism Type IB Associated to Assisted Reproductive Technologies

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Introduction: Pseudohypoparathyroidism type Ib (PHP-Ib) is due to a maternal loss of GNAS exon A/B methylation and leads to decreased expression of the stimulatory G protein (Gsα) in specific tissues. Evidence suggests an increased incidence of imprinting disorders in children conceived by Assisted Reproductive Technologies (ART). Nevertheless, no associations between ART and PHP – Ib have been found to date.

Clinical Case: 7.4-years-old male with history of mild impaired neurological development noticed in motor milestones delay. Conceived by ART, born small for gestational age. Presented at 4 yrs of age with a persistently increased creatine kinase (CK) (200–278 IU/L, NV <140). At 6 yrs an elevated PTH was detected (199 pg/mL NV <60) with normal calcium, phosphorus, alkaline phosphatases, and a low 25(OH) Vitamin D (18.3 ng/ml). He was asymptomatic and diagnostic work-up excluded systemic diseases, thyroid and adrenal compromise, inborn errors of metabolism, skeletal and chromosomal abnormalities. Physical exam was unremarkable except for a narrow forehead, nasal bridge hypoplasia and micropenis (penile length 3.2 cm, <-2 SDS). His height was at 0.63 SDS, and BMI 1.48 SDS. Vitamin D supplementation increased 25(OH)D to 25.9 ng/ml, but PTH remained elevated.

PHP-Ib was considered but analysis of microsatellites for the GNAS region on Chr. 20q did not reveal paternal uniparental disomy (patUPD20q). Instead, an almost complete loss of methylation at GNAS exons A/B and AS, and a gain of methylation at exon NESP were found. There were no changes at exon XL and no evidence of a micro deletion within the GNAS/STX16 region.

After 1 year of calcitriol treatment he remains asymptomatic and presents biochemical improvement normalizing his 25(OH)D 25.9 ng/ml, and CK, maintains normal calcium and phosphorus 4.8 mg/dl, and decreased his PTH (105 pg/ml). Spine and femoral neck bone densitometry is within normal levels.

Conclusion: We present a patient with PHP – Ib due to impaired methylation at GNAS exons A/B, AS and NESP most likely associated to ART.

O-41

Molecular Basis of 47 Patients with FGF23-Mediated Hypophosphatemic Rickets in a Single-Center Study

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Background: FGF-23-mediated hypophophatemic rickets (FGF23-HR) are defective mineralization of bones associated with a pathological increase in FGF23 serum levels, hyperphosphaturia and hypophosphatemia. The most common form of heritable rickets is X-linked dominant hypophosphatemic rickets (XLH) characterized by inactivating mutations in PHEX gene.

Aim: Identify the molecular basis of 47 patients with FGF23-HR (16 children and 31 adults).

Methods: Mutation analysis of PHEX and FGF23 hotspot were performed by Sanger sequencing. In absence of mutations found by this method, MLPA was used to detect abnormal copy numbers of PHEX or FGF23.

Results: Sanger sequencing determined the molecular basis in 35 of the 47 patients (18 patients from 7 families and 17 sporadic patients). Twenty-four mutations were identified and 14 were novel: 3 nonsense; 5 deletions and 1 microinsertion resulting in frameshifts; 1 missense and 4 splice site mutations. MLPA determined 4 novel deletions in 3 sporadic cases and 1 familial patient, besides 1 novel duplication in 2 patients from the same family. In 6 remains, no alterations in FGF23 were determined by Sanger sequencing or MLPA.

Conclusions: In agreement with previous reports, the most common inheritable form of FGF23-HR was XLH due to PHEX mutations and this gene must be the first one to be investigated in this group of patients. In this study, MLPA determined 14.6% of PHEX mutations that were not identified by Sanger sequencing and we recommend this method as an important tool in the molecular analysis.

O-42

Two Cases of Unusual Clinical Presentation of Pediatric Pseudohypoparathyroidism Type 1b

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Pseudohypoparathyroidism type 1b (PHP1b) refers to a condition characterized by renal resistance to parathormone (PTH) in the absence of other endocrine or physical abnormalities. This resistance occurs in the proximal renal tubule, and it is not present in the distal renal tubule or the bone. Consequently, hypocalcemia, hyperphosphatemia and hyperparathyroidism are usually found. Typically, the first clinical signs are those due to hypocalcemia as tetany, seizures or muscle cramps. Features compatible with hyperparathyroidism bone disease, osteomalacia and rickets are extremely rare as the initial manifestation.

We report two unrelated cases of presumptive PHP1b referred to our institution with bilateral genu valgum and bone pain.

Patient (P) 1, a 14-year-old male, had a history of bilateral slipped capital femoral epiphysis at 10 years old that required corrective surgery. Three years later he underwent bilateral hemiepiphysiodesis for progressive genu valgum, without clinical improvement. P2, a 12.5-year-old boy, was also referred due to progressive bilateral genu valgum during the last year.

Both patients had normal weight, height and cognitive development. None of them had family history of bone or mineral disorders. Laboratory tests of the two patients showed hypocalcemia, hyperphosphatemia, hyperparathyroidism, increased alkaline phosphatase and normal serum 25-hydroxyvitamin D level and renal function. Skull X-rays showed absent lamina dura, calvarium thickening and 'salt and pepper' appearance in both patients. P1 also had multiple well-defined calcic-density round lesions in the diploe compatible with osteosclerosis. Computer Tomography ruled out intracranial calcifications. Radiolucent lesions in the phalanges and generalized osteomalacia were observed. P2 showed rickets in both ankles. The patients were started on calcitriol and calcium carbonate, with clinical and biochemical good response. Normalization of calcemia and phosphatemia occured within the first month of treatment.

We report two cases of unusual clinical presentation of presumptive PHP1b. Slipped capital femoral epiphysis and genu valgum might be the first manifestations of a metabolic bone disease. Therefore, despite of the absence of typical symptoms of hypocalcemia, high level of suspicion is mandatory. Early treatment may prevent severe complications as bone deformities and tertiary hyperparathyroidism.

O-43

Histological Features in Partial and Mixed Gonadal Dysgenesis Biopsy and Gonadectomy Material: Review of 43 Cases

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Introduction: Diagnosis and classification of Gonadal Dysgenesis were classically established by histological evaluation; in testicular dysgenesis partial and mixed gonadal dysgenesis are distinguished on the basis of karyotype with 46,XY or mosaicism of 45X,46XY and variants. However, the histological features may have commonalities. Also, another difficulty is the differential diagnosis between mild cases of testicular dysgenesis and normal prepubertal testis.

Objective: The aim of this work was to review histopathological aspects of 43 cases of biopsy and gonadectomy material of clinically established PGD and MGD and obtain photographic material for further revision.

Methods: All patients with a diagnosis of testicular dysgenesis who were seen in our service between 1989 and 2013 were selected. Those in whom gonadal biopsy or gonadectomy were performed in our service were selected for review. Slides were retrained and reviewed together with an expert in Germany and in Belgium and rather documented.

Results: Our sample consisted of 25 cases of PGD (from 0.6 to 19.2 years) and 18 cases of MGD (from 0.2 to 43 years); after deeper histopathological review, diagnosis was changed in 1 PGD patient (an ovotesticular aspect was observed). The following aspects of the gonadal dysgenesis spectrum were described: fibrosis, ovarian-type stroma, undifferentiated gonadal tissue and also, absence of gonadal tissue with wolffian and mullerian derivatives only; small, irregular and branched tubules; intracapsular growth; sertoli-cell-only syndrome; germ cell aberration and clonal expansion; leydig cell hyperplasia; gonadoblastoma and burned out gonadoblastomas. These different features were seen isolated but also combined in the same gonad.

Conclusion: Gonadal histology remains as an important tool for differential diagnosis of patients with genital ambiguity, for early diagnosis of gonadal tumor formation and to support decision of gonadectomy. However, histological aspects of a mild dysgenesis can be difficult to distinguish from a normal prepubertal testis and sometimes biopsy findings cannot correspond to what we see in the whole gonad. Also, histological features cannot distinguish the Partial and Mixed Gonadal Dysgenesis. Thus, evaluation should be performed by an experienced pathologist and deeper histological studies like immuhohistochemistry for tumor markers sometimes are requested.

O-44

Disruption in SF1-Mediated AMH Promoter Regulation Leading to Persistent Müllerian Duct Syndrome (PMDS)

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In early fetal life, AMH secreted by the testes provokes the regression of Müllerian ducts. AMH expression in fetal Sertoli cells is triggered by SOX9, and further up regulated by SF1, GATA4 and WT1, all binding to specific sites on the proximal AMH gene promoter. The absence of AMH signalling in the XY fetus results in the Persistent Müllerian duct syndrome (PMDS).

We report the case of a non-dysmorphic newborn who presented with a normal sized penis and non-palpable gonads. Lab work-up showed normal serum testosterone (358 ng/dl), very low serum AMH (7.8 pmol/l) and a 46,XY karyotype. A sonogram and MRI showed a uterus measuring 5 x 1.4 x 1.9 cm; VCUG showed a normal male urethra without a urogenital sinus.

DNA sequencing detected no mutations in the AMH gene coding sequences, but a homozygous single-base deletion (c.-225delA) was identified at a putative SF1 response element of the AMH promoter. The AMH promoter activity of the c.-225delA variant, analysed in luciferase assays, was decreased by 58 ± 14%, to a similar extent (66 ± 5%) of what was observed when the SF1 site was completely disrupted by in vitro directed mutagenesis. The interaction between SF1 and its binding site was lost when the oligonucleotide carried c.-225delA or the fully disrupted SF1 site, when studied by EMSA.

In conclusion, the single base deletion c.-225delA within the SF1 site of the AMH gene promoter impaired SF1 binding to and transactivation of the AMH promoter, resulting in extremely decreased AMH production, leading to PMDS in this patient. This is the first description of an AMH promoter mutation leading to PMDS.

O-45

SF1 Recognition Sequences in the Anti-Müllerian Hormone (AMH) Gene Promoter Participate Together with the Androgen Receptor (AR) in the Inhibition Caused by Androgens

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In pre-pubertal Sertoli cells, AMH expression is inhibited by androgens through an unknown mechanism. Upon ligand binding, the AR interacts with specific response elements and/or other transcription factors within the regulatory regions of its target genes. We tested whether androgens exert a direct effect on the AMH promoter activity, using luciferase assays in the pre-pubertal Sertoli cell line SMAT1, after transfection with an AR expression vector and length variants or mutants of the AMH promoter. Results are expressed as percentage (mean±SEM), and compared against basal activity (theoretical value of 100%), using a one sample t-test. Endogenous levels of AMH in response to androgens were also evaluated through RT-qPCR. In AR-transfected SMAT1 cells, a decrease was observed in a [–3068 to –1] bp AMH promoter activity with a 5 min (66.0 ± 6.9%, P = 0.008) or 24 h (46.0 ± 3.0%; P < 0.0001) treatment with DHT (10^{-7} M). DHT also diminished the activity of a [–423 to –1] bp AMH promoter (56.8 ± 9.5%; P = 0.02), suggesting role for this region in the inhibition caused by androgens. By means of bioinformatics analysis, we found no androgen response elements (AREs) on the [–423 to –1] bp region. Therefore, we tested whether the AR-dependent inhibition could involve an interaction of the AR with well-known AMH transactivating factors, like GATA4, AP1 and SF1. AMH inhibition induced by DHT was conserved when the recognition sequences for GATA4 at –74, –168 and –408b (73.8 ± 7.0%; P = 0.03) and AP1 at –203b (73.0 ± 5.3%; P = 0.015), but not when those for SF1 at –92 and –218b (102.2 ± 11.1; P = 0.85), were mutated. We further analyzed the effect of DHT on the AMH promoter when the SF1 sites were mutated independently. In both cases the inhibition persisted, whether the site at –92b (49.28 ± 5.3%; P = 0.0007) or –218b (54.83 ± 6.4%; P = 0.0192) was mutated, indicating that the invalidation of both of the SF1 sequences present in the AMH promoter was necessary to abrogate the inhibitory effect of androgens. In conclusion, DHT is capable of inhibiting the AMH promoter activity through the AR in the pre-pubertal Sertoli cell line SMAT1 and involves the recognition sequences of SF1 present in the proximal region of the AMH promoter.

O-46

Evident Germ Cell Loss at an Early Age in Testis of Androgen Insensitivity Syndrome Patients

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Although androgens are essential for germ cell (GC) survival and maturation, the androgen receptor (AR) is not expressed in this cell lineage. In the human testis, AR expression is evident since before birth in interstitial and peritubular-myoid cells but it is only detected in Sertoli cells after 4–5 years of age.

Androgen insensitivity syndrome (AIS) is an X-linked hereditary disease in which ARgene loss-of-function mutations in 46, XY patients produce partial (PAIS) or complete (CAIS) defects in virilization.

The aim was to analyze the effect of lack of androgen action in GC health and survival along postnatal development, previous to Sertoli cell pubertal maturation. The histological features and quantity of GC in AIS patient testes were studied and compared to controls. Fourteen gonads of ten AIS patients (median age 9.55, range 1.8–23 years) were studied. Three prepubertal and four pubertal patients were CAIS and three prepubertal patients were PAIS. Clinical diagnosis was confirmed by hormonal and molecular studies. Control testes were collected at necropsy or biopsy from eleven prepubertal and four pubertal patients without endocrine disorders. Written consent was given by the patient or its legal guardian. The study was approved by the Ethical Committee. GCs were identified using anti MAGE-A4 antibody. Prepubertal AIS testes showed gonocytes, huge GCs, calcifications, thickened basal membranes and/or fibrous interstitium. Pubertal gonads showed signs of dysgenesis as Leydig cell hyperplasia, prepubertal-like seminiferous tubules with vacuolated Sertoli cells, scarce or none GCs and absence of meiotic spermatocytes. Prepubertal and pubertal control subjects showed normal testicular parenchyma according to age.

MAGE-A4 expression correlates with the presence or absence of GCs. AIS testes showed a drastically loss of GCs after 4.4 years (r = 0.558, p = 0.038). As the staining decreased, foci of positive cords were found. No difference between PAIS and CAIS was observed. In contrast, control subjects showed an increase of MAGE-A4 expression as a function of age (r = 0.595, p = 0.019) and the staining pattern was homogeneous.

Disturbed androgen action delayed the GC maturation rate during fetal and early postnatal life. Our results demonstrated that in an androgen deprived niche, GC number rapidly declined during childhood.

O-47

Gonadotropin-Mediated Alterations in Testis Gene Expression Associated with the First 48 Hours of Experimentally Induced Puberty in the Rhesus Monkey (Macaca mulatta)

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In primates, spermatogenesis is initiated many years after birth by re-activation of gonadotropin secretion occurring with puberty onset. To date, global changes in testis gene expression associated with initiation of primate puberty have not been characterized. To address this question, 3 juvenile rhesus monkeys (14–24 mo of age) were treated with a pulsatile iv infusion of recombinant monkey LH and FSH for 48 h and 3 with vehicle. Puberty was initiated in the hormone-treated monkeys as shown by increased testosterone production, elevated BrdU labeling of Ap spermatogonia and Sertoli cells, and appearance of differentiating B spermatogonia. To define the transcriptome of the juvenile testis, total RNA isolated from vehicle treated testes was subjected to RNA-Seq. Mapping of sequencing data to the rheMac2 genome assembly using Tuxedo suite software, identified 15,700 genes. Using a NCBI BLAST strategy nearly 400 transcripts were identified that were not present in the rheMac2 reference genome. Comparison of RNA-Seq gene expression profiles from the 3 pairs of hormone- and vehicle-treated juvenile testes identified 594 genes that were differentially expressed. As expected, LH-regulated RNAs associated with steroid production (LHCGR, STAR, CYP11a, CYP17, HSD3B2) were induced. However, FSH-inducible mRNAs (INHA, CYP19A1) were not. There was a reduction in mRNAs encoding GFRA1 and ZBTB16, proteins associated with maintaining undifferentiated spermatogonia. Also, genes encoding cytokines and regulators of cell adhesion and extracellular matrix formation were differentially regulated. Pathway analysis software identified three over-represented categories of up-regulated genes 1) mitochondrial function/energy production 2) DNA replication and 3) lipid metabolism/cholesterol biosynthesis: results consistent with increased steroid production and energy demands associated with cell biosynthetic activity and proliferation. In summary, we have provided the first description of the testicular transcriptome of a representative higher primate during juvenile development, and identified changes in gene expression that occur at the earliest stages of puberty. Further, we propose that altered expression of gonadotropin responsive genes that 1) maintain the undifferentiated state of spermatogonia (stemness) and 2) underlie cell-cell interactions resulting in initial formation of the blood testis barrier and the postpubertal stem cell niche, represent the first steps in the differentiation program that initiate spermatogenesis in the primate testis.

O-48

Copy Number Variation of RAS/MAPK Pathway Genes in Patients with Isolated Cryptorchidism

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Introduction: Copy number variation (CNV) of Ras/MAPK pathway genes is an unusual finding in patients with the classical clinical features of RASopathies. This type of molecular derangement, however, has not been studied in monosymptomatic patients with RASopathies. The aim of our study was to determine whether patients with only one feature of this condition, such as cryptorchidism, exhibit copy number variations in the Ras/MAPK pathway genes.

Methods: Seventy seven patients with cryptorchidism were recruited and classified into three study groups, according to their stature and the presence of a phenotype suggestive of RASopathy. Genomic DNA was extracted from peripheral blood. Determination of genes PTPN11, SOS1, KRAS, NRAS, HRAS, RAF1, BRAF, MAP2K1 and MAP2K2 copy number variation was performed by Comparative Genomic Hybridization array (aCGH).

Results: Fifty nine patients were classified as having isolated cryptorchidism (Group 1) [Age (years): 5.9 ± 0.4; height (SDS): 0.28 ± 0.15], 8 as having cryptorchidism, short stature and normal phenotype (Group 2) [Age (years): 5.7 ± 1.6; height (SDS): –1.69 ± 0.21] and 10 as having cryptorchidism, short stature and a phenotype suggestive of RASopathy (Group 3) [Age (years): 6 ± 1.0; height (SDS): –2.16 ± 0.21]. Molecular analysis of Group 1 showed a ~292 Kb duplication that includes the RAF1 gene, and a ~4.9 Kb deletion that involves KRAS sequences. Group 2 analyses did not show any copy number variations, but Group 3 analysis showed a ~0.9 Kb deletion that includes the KRAS intron 1. KRAS deletions have not been reported previously and may affect promoter sequences. In addition, the RAF1 gene duplication observed in our cohort has been previously reported in patients with clinical features suggestive of RASopathies.

Conclusions: We report variations in copy number in the Ras/MAPK pathway genes in a cohort of patients with isolated cryptorchidism. We found a few deletions and duplications in the KRAS and RAF1 genes in our patients with isolated cryptorchidism. This suggests that a careful clinical exam looking for subtle dysmorphic features of RASopathy should be performed in patients with cryptorchidism. (Fondecyt 1140450).

O-49

Gonadotropin Surge during the Early Postnatal Activation Period in 46,XX Testicular/Ovotesticular Disorder of Sex Development (DSD) Patients

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Background: During the normal early postnatal activation period of the hypothalamo-pituitary-gonadal axis, serum LH levels in girls are lower than in boys. The mechanism of this sex difference is not completely understood. It has been proposed that fetal or perinatal androgenic steroids have an effect on the control of LH secretion.

Aim: To analyze the possible influence of high levels of androgens on the regulation of serum gonadotropin levels in a cohort of 46,XX testicular/ovotesticular DSD patients during the early postnatal activation period.

Method: Nine 46,XX testicular/ovotesticular DSD patients between 12–142 days of age were studied. Inclusion criteria were lack of SRY gene detection in peripheral genomic DNA, basal serum testosterone levels within the normal male reference values (RV), and an adequate male testosterone response to hCG stimulation.

Results: Gonad histological studies revealed bilateral ovotestes in three patients, one ovary and one testis in two, one ovotestis and one testis in one patient, while the remaining three patients presented bilateral disgenetic testes. In all patients, serum basal LH levels (mean ± SD) were significantly higher (5.24 ± 3.13, range 1–10.98 UI/L) than in normal female (0.29 ± 0.46 UI/L, $p < 0.05$), and were even higher than male RV (2.31 ± 1.41 UI/L, $p < 0.05$). In all patients serum basal FSH levels (mean ± SD 3.73 ± 1.81 UI/l, range 1.3–6.13 UI/L) were within female RV and were significantly higher than male RV ($p < 0.05$). Serum Inhibin B levels (mean ± SD 201.7 ± 129.1 pg/ml) were within the normal male RV. Basal serum FSH/LH ratio (mean ± SD 1.05 ± 1.09, range 0.25–3.83) was within the normal male range and was significantly lower than the normal range for the female sex ($p < 0.05$).

Conclusion: In conclusion this study reinforces the concept that prenatal and early postnatal androgen exposure might be involved in programming of LH secretion independently of chromosomal sex. In our patients, the presence of high serum FSH levels along with normal male serum Inhibin B levels, suggest that the increase in FSH levels would not be related to gonadal dysgenesis.

O-50

Pubertal Onset in Chilean Children: Ethnic Disparities

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Introduction: Age at pubertal onset exhibits a remarkable inter-individual and ethnic variation. Twin studies suggest that genetic factors accounts for more than half of the phenotypic variation of pubertal onset. In Chile, 5% of the population is indigenous but ethnic disparities in pubertal development have not been studied.

Objective: To compare pubertal onset milestones in Amerindian Chilean children vs. non – indigenous children (according to parental and grand-parental surnames). Considering an appropriate correlation of last names with indigenous genetic background.

Design: Longitudinal cohort study of 1003 children (50.2% females) participating in the Chilean Growth and Obesity study (ECCO).

Methods: Annual anthropometric evaluation since birth up to 7 years of age. Thereafter, Tanner staging and anthropometry every 6 months. In females Tanner stage was assessed by breast palpation and in males by testicular volume according to Prader orchidometer. Children were stratified in 3 groups depending on Amerindian surnames number (1–2 surnames, ≥3 surnames, and no Amerindian surnames). We analyzed mean ages of pubertal milestones and the prevalence of precocious telarche (B2), pubarche (PH2), menarche and gonadarche (Testicular volume ≥4 ml – G2), using a cut off age of 8 yrs in females and 9 yrs in males. Differences were adjusted by socioeconomic status, body mass index, waist circumference, IGF-1 and DHEAS at 7 years of age.

Results: There were no significant differences in B2, PH2 and menarche mean ages in females between the groups. In males, prevalence of precocious gonadarche was higher in children with ≥3 indigenous surnames (29.2%) vs. Non-indigenous children (6.0%) and vs. Children with 1–2 indigenous surnames (10.5%) [$p = 0.001$, $p = 0.004$ respectively]. To have ≥3 indigenous surnames was associated with an increased risk of precocious gonadarche in boys, even after adjusting by confusion variables [OR 7.31; 95% IC (2.32–23.51); $p = 0.001$].

Conclusion: Indigenous origin in Chile is an independent risk factor for precocious gonadarche in males. Nonetheless, ethnicity is not a determinant factor for pubertal onset and age at menarche in females.

O-51

Long-Term Outcome of Patients with Central Precocious Puberty Due to Hypothalamic Hamartoma Treated with GnRH Analogs: Anthropometric, Bone Density, Metabolic and Reproductive Aspects

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Background: Hypothalamic hamartoma (HH) represents the main cause of organic central precocious puberty (CPP). Long-acting GnRH analogs (GnRHa) are the first-line for treatment of CPP. Reports of long-term follow-up are scarce in HH.

Aim: To describe the anthropometric, bone density, metabolic and reproductive parameters of patients after treatment with GnRHa.

Patients and Methods: 14 patients (7 boys) with CPP due to HH treated exclusively with depot GnRHa from a single tertiary center were reviewed. Final height, body mass index (BMI), bioimpedance, bone densitometry, hormonal and biochemical evaluation, pelvic ultrasound and a reproductive function questionnaire were utilized at the cross-sectional evaluation.

Results: Duration of GnRHa treatment was 7.7 ± 2.4 yr for boys and 7.9 ± 2.1 yr for girls. GnRHa treatment was interrupted at 12.1 ± 1.1 yr for boys and 10.7 ± 0.5 yr for girls. At last evaluation, the mean chronological age (CA) of male and female patients was 21.5 ± 3.2 yr and 24 ± 3.9 yr, respectively. Eleven of 14 patients reached final height within target height range (SDS –0.6 ± 0.9 for males and –0.6 ± 0.5 for females). Mean BMI and % of body fat mass was higher in females than in males (29.4 Kg/m^2 vs. 20.7 Kg/m^2; 39.3% vs. 8.5%, $p < 0.05$). Hypercholesterolemia was identified in one man and 3 women. Glucose intolerance was identified in one women. The mean CA of menarche was 12.3 ± 1.4 yr. Bone mineral density was normal in both sexes. All women informed regular menstrual cycles and no evidence of hyperandrogenism was identified. Hormonal assessment revealed basal LH, FSH, E_2, testosterone, androstenedione and DHEA-S within normal ranges for age and sex. Progesterone levels in the luteal phase were at ovulatory levels in all women. Pelvic ultrasound was normal in all women. Paternity was referred by 3 male patients. Three patients (21%) present generalized epilepsy; one of them required surgical treatment.

Conclusion: GnRHa was effective for treatment of CPP due to HH, resulting in normal final height without deleterious effect on bone mineral density at adulthood. A high prevalence of overweight/obesity and metabolic alterations occurred in the female patients. Reproductive abnormalities were absent, indicating normal function of hypothalamic-pituitary-gonadal axis in both sexes at adulthood.

O-52

Early and Accelerated Puberty in a Boy with a Homozygous R192C Mutation in CYP19 (Aromatase) Gene

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Background: Aromatase deficiency is a rare autosomal recessive disorder produced by CYP19 gene mutations. 46XX affected patients presented with ambiguous genitalia leading to early identification. Most 46XY affected patients presented normal external genitalia and the condition often remains undiagnosed until late puberty. Information on pubertal development in affected boys is scarce since to the present date only 2 patients, younger than 4 ys of age, without long term follow-up, had being reported.

Objective and Hypotheses: We report the clinical phenotype and hormonal studies of a 46,XY aromatase deficient boy.

Results: Molecular analysis revealed a previously reported homozygous mutation (R192C) in the CYP19 gene, predicted to compromise enzyme function. The patient was the oldest brother of a 46XX affected sister. Maternal virilisation was present during both pregnancies. First evaluation at 7.9 ys: 3 years delayed bone age was the only remarkable finding observed. Laboratory tests showed normal prepubertal basal serum gonadotropin (including an adequate GnRH stimulation test), inhibin B, AMH, testosterone and androstendione levels. OGTT was normal as well as bone mass, assessed by DEXA. The patient was followed in other center. Pubertal onset was observed at 9.8 ys assessed by testicular volume (right 4 cc and left 3 cc) and basal testosterone level (0.57 ng/ml). The patient was returned to our hospital at 11.3 years of age with signs of advanced puberty (Tanner stage IV, testicular volume 12/15 ml). Bone age was 2 ys delayed. Laboratory tests revealed normal pubertal basal and GnRH stimulated gonadotropin levels and increased serum testosterone (5.9 ng/ml, male reference range for Tanner IV: 1–5.4 ng/ml).

Conclusion: Normal pubertal development was referred in adult men with aromatase deficiency. Interestingly our patient presented with early and accelerated puberty and apparently normal pituitary gonadal function. Estrogen restrain on gonadotropin secretion has been demonstrated in animal and human models of estrogen deficiency operating since early phases of puberty in males. This human model of nature suggests that aromatase activity at hypothalamic level is required to define pubertal tempo and/or the time of puberty onset in boys.

O-53

Overtreatment during the First Six Months in Congenital Hypothyroidism: Impact on Neurocognition

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Background: Early diagnosis and treatment of Congenital hypothyroidism (CH) prevents mental retardation. Although initial treatment with high doses of levothyroxine (LT4) is recommended, moderate hyperthyroxinemia with suppressed TSH during the first months of some patients is difficult to avoid. Whether this is innocuous or constitutes a risk factor for neurocognitive impairment is controversial.

Objective: To evaluate the cognitive outcome at age 9–10 of early detected and treated CH in whom suppressed TSH and moderate hyperthyroxinemia were present during the first six months of treatment.

Patients and Methods: We retrospectively reviewed age, TSH, T4 levels at diagnosis a, LT4 initial doses, etiology, symptoms of hyperthyroidism and T4 levels attained at 2 and 6 months of 35 CH patients early detected and regularly followed up.

Patients were considered overtreated (OT) if TSH was persistently <0.5 uUI/ml along the first 6 months, or not-overtreated (NOT) with TSH 0.5–6.5 uUI/ml in the same period.

No differences were found in (median): age (days) (OT:23, NOT:21), LT4 dose (ug/kg/day) (OT: 12.9, NOT: 12.1) severity of hypothyroidism reflected as TSH >40 uUI/ml (OT:89.5%, NOT: 93.8%) and T4 <2 ug/dl (OT: 42.1%, NOT: 43.8%). Etiology was: OT:12 ectopic,4 eutopic and 3 athyreosis and NOT:5 ectopic,5 eutopic, 5 athyreosis and 1 hypoplastic. Symptoms of hyperthyroidism were always absent. T4 levels attained were moderately high in both groups at 2 months and within normal references at 6 months.

All children underwent evaluation with WISC III (global, verbal and performance IQ, verbal comprehension, absence of distractibility, processing speed, perceptual organization, attentional amplitude, working memory), Faces Test (selective attention), CPT II (omissions and commissions) and Trail Making Test (attention divided). Student T test with Bonferroni's adjustment were used for statistical analysis ($p < 0.05$).

Results: Scholar level achieved was the expected for age. Developmental scores were always normal without differences between groups in the neurocognitive evaluation. OT showed a statistical significant better divided attention ($p < 0.05$).

Conclusions: Early overtreatment (low TSH with hyperthyroxinemia) didn't impair neurocognitive outcome at age 9–10 in our patients and was even associated with better divided attention. These results have to be taken into account while treating HC, knowing that lowering LT4 dose might lead to an increased risk of undertreatment.

O-54

Thyroid Follicular Adenoma in Pediatrics: Prevalence, Clinical, Sonographic and Cytological Features

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Background: Thyroid follicular adenomas (FA) are encapsulated neoplastic benign thyroid nodules (TN) characterized by the absence of vascular and/or capsular invasion. Accurate preoperative diagnosis would allow an adequate surgical approach.

Objective: To report the prevalence and characterization of FA in a pediatric cohort of TN.

Material and Methods: 13/75 patients aged <19 years referred to our Division for TN between 2008 and 2013 were FA. We analysed retrospectively their preoperative clinical, biochemical and sonographic features, and US-FNAB cytology using Bethesda System (B). Findings were compared with those found in the patients with benign nodules excluding FA (BN) (n:48) and papillary carcinomas (PC) (n:14) of the same cohort.

Results: Prevalence of FA was 17%. Median age was 14.8 years (range:11.6–17.8), 77% were female and 92% pubertal. FA nodule/s were palpable in all cases, 12 solitary and 1 multiple. US features showed a median maximum diameter of 30 mm (range:9–70), a solid or mixed predominantly solid TN in 13/13 (100%), increased central vascularisation in 5/13 (38.5%), microcalcifications in 2/13 (15%) and irregular margins in 1/13 (7%). No more than 2 suspicious US features were found together. Cytology was categorized as BI: 2/13 (15%), BII: 3/13 (23%), BIII/BIV: 6/13 (46%), BV: 2/13 (15%) and BVI 0%. BN were cystic in 18/48 (37.5%) (p0.01) and their cytology had a tendency to be more frequently benign (BII) than FA (p0.06). PC presented as multinodular in 7/14 (50%) (p0.03), was always solid (p0.005), with pathological adenopathies in 5/1 (36%) (p0.04) and 7/14 (50%) were BVI on FNAB ($p < 0.01$). 5/14 (36%) of PC presented 3 or more US suspicious features (p0.04). Indeterminate FNAB rate (BIII/IV) was significantly greater in FA than BN or PC ($p < 0.03$), while suspicious/malignant FNAB rate (BV/VI) was significantly greater in PC ($p < 0.01$).

Conclusions: FA consulted as a predominantly solitary solid nodule without pathological adenopathies with a high rate of indeterminate FNAB representing 17% of our cohort. Three or more US suspicious features make an unlikely diagnosis of FA. Future availability of molecular tools for pediatric clinical practice will allow a better characterization.

O-55

Pilot Neonatal Screening Program for Congenital Central Hypothyroidism (CCH): Improving Detection

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Background: A recent pilot study from our Institution was launched for the diagnosis of congenital central hypothyroidism (CCH) in full term newborns. Based on T4 [cutoff (CO) of –2.3 SDS] and TSH (CO ≥10 mU/L) determinations in dried blood filter paper samples (DBS) at maternity discharge, patients were recalled and thoroughly evaluated clinically and biochemically to rule out CCH.

After 67,719 screened samples, 4 CCH newborns were detected (1:16930). Additionally, 27 neonates with transient hypothyroxinemia due to severe neonatal illnesses and 14 thyroid hormone transport defects were observed. Nevertheless, whether milder forms of CCH present with higher levels of T4 in the neonatal period remains uncertain.

We therefore aim to improve sensitivity, setting a higher CO level of lesser suspicion while keeping the previous one for the urgent recall. However, this would imply lower specificity increasing the recall of healthy babies. In the less suspected population, a second DBS would be required to confirm hypothyroxinemia before undergoing further evaluation. This study aimed to provide reference values of T4 in filter paper samples adapted to age during the first month of life to adequately interpret the results in the next step of our screening program for CCH. Material and methods.

T4 was measured with DELFIA FIA method in 832 DBS from full term healthy newborns, 509 in the second week, 177 in the third week, 101 in fourth week and 45 in the fifth week of life.

Results: T4 levels μg/dl are shown below.

Conclusion: These levels of T4 in DBS provide the normal references in full terms needed to set a proper CO, an essential tool for the early detection of milder forms of CCH. Further observations will clarify if this new screening strategy proposed is reliable and cost effective.

Table 1. DBS T4 reference levels μg/dl in the first weeks of life (for Abstract O-55)

Week	Median	P (05)	P (10)	P (25)
2nd	10.2	6.7	7.3	8.6
3rd	9.2	6.3	7	7.9
4th	9.5	5.9	6.6	8
5th	9.8	6.8	7.25	8

O-56

Cognitive Assessment of Early Detected and Treated Congenital Hypothyroid Children

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Introduction: Children with congenital hypothyroidism (CH) detected through neonatal screening and adequately treated might present mild cognitive deficits possibly related to the underlying disease.

Objectives: To characterize the cognitive profiles of children with CH, and to assess specific deficits and their relationship with variables of severity, duration and treatment of the disease.

Patients: 60 CH children aged between 9 and 10 years detected through neonatal screening and adequately treated within the first month of age, were selected and compared with a control group of 60 healthy children of the same age without CH. Inclusion criteria for both groups were: absence of other concurrent diseases, half day school, and parents with complete high school educational level.

Methods: WISC III, Rey-Osterrieth Complex FigureTest, Woodcock Muñoz–R, Continuous Performance Test (CPT II), ITPA (Illinois test of psycholinguistic abilities), Verbal Fluency Test, Test Knox Cubes, Trail Making Test, Faces Test, and 5 digits Test were administered.

Cognitive profile was related to: 1) LT4 initial dose (10–12 vs. 12–16 ug/kg/day), 2) Initial serum T4 level: (≤2 ug/dl vs. >2.1 ug/dl), 3) Etiology: athyreotic vs. ectopic, 4) Age at start of treatment (≤20 vs. 21–30 days) y 5) Epiphyseal Knee surface (≥5 mm^2 vs. <5 mm^2).

Student T test for independent samples, Bonferroni's adjustment ($p < 0.002$) were used for statistical analysis.

Results: CH showed normal average IQ. At this aqe CH had lower performance in processing speed, reaction time, attention, cognitive flexibility, visuoconstruction abilities and long term memory. Athyreotic children (with more severe disease) showed lower processing speed. The other evaluated variables were not statistically associated with cognitive impairments. Scholar level was always the one expected for chronological age.

Conclusion: Our findings confirm the importance of thyroid hormone during fetal development and the utility of early detection and treatment. Although CH children do not have mental impairment, they show mild cognitive disorders, more pronounced in those with severe etiology that have to be considered in their follow up.

P-1

DNA Methylation Is Not Involved in Specific Down-Regulation of HSD3B2, NR4A1 and RARB Genes in Androgen-Secreting Cells of Human Adrenal Cortex

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Background: RARB cooperates with NR4A1 to in-vitro regulate HSD3B2 transcription. NR4A1 expression parallels HSD3B2 expression, with both greatly reduced in androgen-producing adrenocortical tissues (childhood virilising adrenocortical tumours (VAT), fetal zone (FeZ) and zonareticularis, ZR). RARB is downregulated in starved, hyperandrogenic H295R cells. However, the mechanisms regulating this expression pattern and the relevance of RARB to human adrenal physiology are unknown.

Objective: To evaluate developmental changes in DNA methylation of HSD3B2, NR4A1 and RARB genes in VAT and normal human adrenal tissues (HAT).

Method: VAT (n = 11, age 0.75–4.5 yr) and HAT collected from 3 postnatal groups: Gr1:<3 mo, n = 9, FeZ involution; Gr2:3 mo to 6 yr, n = 9, pre-adrenarche; and Gr3:>6 to 20 yr, n = 8, post-adrenarche, were evaluated. Total DNA and RNA from whole tissue and from laser capture microdissected zona fasciculata (ZF) and ZR in Gr3 were isolated. Total RARB (RARBT) and RARB2 expression were studied using qRT-PCR. Promoter methylation pattern was examined by bisulfite sequencing.

Results: RARBT and RARB2 mRNAs were similar among HAT from the 3 groups. RARBT mRNA was lower in VAT compared to age-matched group HAT ($p < 0.05$). RARB2 tended to be lower in VAT compared to HAT without statistical significance. RARBT and RARB2 mRNA expression showed no significant difference between micro-dissected ZR and ZF. HSD3B2 NR4A1 mRNAs were much lower in ZR cells ($p < 0.05$). In silico screening showed that NR4A1 promoter was embedded within a CpG island but it remained completely unmethylated in HAT from the 3 groups and in VAT. No differences in adrenal zone-specific NR4A1 methylation were observed.

Conclusion: RARB was not associated with ZR-specific downregulation of HSD3B2 in postnatal human adrenocotical zonation. DNA methylation would not be involved in zone-specific and VAT downregulation of adrenal NR4A1. Lack of CpG island in HSD3B2 suggested that the known downregulation of HSD3B2 gene expression in human ZR would not be directly mediated by DNA methylation.

P-2

Inhibition of the Sonic Hedgehog Pathway Impairs Adrenal Steroidogenesis

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Background: The sonic hedgehog (SHH) pathway plays a key role in the development and maintenance of adrenal cortex cells. The potential role of the SHH pathway on the regulation of adrenal steroidogenesis in humans has been suggested by a recent work from our Laboratory.

Objectives: To analyze the role of the SHH pathway in adrenal steroidogenesis.

Methods: NCI-H295 human adrenocortical cells were treated with agents that inhibit the SHH pathway (Cyclopamine, 5–30 μM) or stimulate adrenal steroidogenesis (ACTH 10 nM and Forskolin 10 μM) from 12 to 96 h. Cell viability (MTS), gene expression (qPCR) of SHH pathway components (SHH, GLI1, GLI2, GLI3, SMO e PTCH), steroidogenic enzymes genes (CYP11B1, CYP11B2, CYP17, StAR), steroidogenic factor 1 (NR5A1), as well as steroid secretion (cortisol, DHEA-S and testosterone secretion – RIA) were evaluated.

Results: Cyclopamine reduced mRNA expression of SHH (30 μM, 48 h) and GLI1 (5 and 20 μM, 48 h), and increased the expression of SMO (5, 20 and 30 μM, 96 h). The association of Cyclopamine 20 μM and ACTH reduced by 43% the increase of GLI1 expression induced by ACTH alone (48 h; $p < 0.01$). Isolated, Cyclopamine 20 μM did not impair the expression of steroidogenic enzymes. However, after 48 h, Cyclopamine 20 μM associated with ACTH reduced the expression of CYP11B1 (67%; $p < 0.05$), CYP17A1 (60%; $p < 0.01$) and NR5A1 (52%; $p < 0.05$) induced by ACTH alone. Similarly, Cyclopamine 20 μM associated with Forskolin reduced the expression of CYP11B1 (48%; $p < 0.05$), CYP17A1 (33%; $p < 0.05$) e NR5A1 (32%; $p < 0.05$) induced by Forskolin alone. In line, Cyclopamine also impaired steroid secretion. Cyclopamine alone decreased DHEAS (50%) and Testosterone (20%). Moreover, the association of Cyclopamine with Forskolin partially prevented the increase of cortisol secretion induced by ACTH (25% and 95%, 12 h and 48 h, respectively) and by Forskolin (93% and 27%, 12 h and 48 h, respectively). Cyclopamine 20 μM slightly reduced cell viability after 48 h (14.5%), but not at 12 h and 24 h.

Conclusion: In vitro, the inhibition of the SHH pathway impairs the expression of steroidogenic enzymes genes and the secretion of adrenal steroids induced by ACTH and Forskolin. This new data indicates that the SHH pathway may also be involved in adrenal steroidogenesis.

P-3

Variations in 17-Hydroxiprogesterone According to Post-Conceptional Age in Healty Preterm Infants

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Introduction: Interpreting the values in the 17-Hydroxiprogesterone (17-OHP) test in preterm infants is difficult.

Objective: To determine variations in serum concentrations of 17-OHP between healthy preterm infants and term neonates.

Materials and Methods: Longitudinal study. 17-OHP was measured through the heel prick test by ELISA in 36 preterm infants. The first sample was taken between three (3) and five (5) days after birth and later every two weeks up to the corrected gestational age at term. Changes in measurements adjusting for gestational age, birth weight, sex or the use of corticosteroidsamong others were evaluated. Results at the end of the follow up period were compared with those of 82 healthy term newborns.

Results: 17-OHP levels under 34 weeks of gestational age descend to that age to then remain stable, but always above the values of those infants born at term with an average difference of 63.0% (IC 95% 11.8%–115.5%) for the preterm group. None of the term infants showed 17-OHP levels above 30 ng/mL, while 41 (33.6%) of the 122 samples taken from preterm infants measured above this value.

Conclusions: 17-OHP levels in preterm infants are higher than those of neonates at term. Thus, the cutoff point for Neonatal screening for congenital adrenal hyperplasia in these patients should be revised, even when they reach the corrected gestational age at term.

P-4

Pseudohypoaldosteronism Type 1: Report of a Novel Mutation

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Introduction: Pseudohypoaldosteronism (PHA) is a rare heterogeneous syndrome of mineralocorticoid resistance causing salt wasting, hyperkalemia, metabolic acidosis and elevated plasma aldosterone levels in the neonatal period.

Two different forms of PHA can be distinguished on the clinical and genetic level, showing either a systemic or a renal form of mineralocorticoid resistance. PHA type 1 is caused by mutations in the subunit genes of the epithelial sodium channel (genes SCNN1A, SCNN1B, SCNN1G) (systemic form) and the mineralocorticoid receptor coding (gene NR3C2) (renal form).

Material and Methods: We report the case of a 30-day-old male infant admitted to the pediatric intensive care unit as a result of vomiting, failure to thrive, hyponatremia (130 Meq/l) and hyperkalemia (6.8 Meq/l). Neonatal screening was normal. Physical and genital examination showed normal male characteristics. Family history of hypertension was remarkable (father and grandfather). Urinalysis and Renal US were normal. Hormonal feature: aldosterone >1000 pg/ml, plasma renin activity 105 ng/ml/h (range 0–15), cortisol 12 μg/dl and 17-OHProgesterone 0.7 ng/ml.

PHA type 1 was suspected based on clinical features, and the infant was supplemented with NaCl. He presented satisfactory response to addition of salt to the diet with substantial improvement of weight and height and normalized serum Na and K. The clinical diagnosis was confirmed by molecular genetic testing.

Results: Genomic DNA of the patients and his parents was isolated from whole blood samples (direct sequencing of exons 2–9 and exon-intron boundaries). A heterozygous de novo mutation in exon 2 in the NR3C2 gene (c.1108 C>T) was found. This mutation replaces the glutamine at position 370 with a stop codon resulting in a truncated protein completely devoid of major functional domains including the DNA binding domain and the hormone binding domain. (Dra Maria-Christina Zennaro. Assistance Hopitaux Publique de Paris, France).

Conclusion: We identified a novel NR3C2 gene mutation. Reporting additional patients with PHA and long-term follow up, in vitro studies of mutations and the identification of other genetic modifiers will likely help better understanding this potentially life-threatening disease and improve its management and genetic counseling.

P-5

Pseudohypoaldosteronism Type 1: 18 Years Follow-Up after a Challenging Diagnosis

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Clinical manifestations of pseudohypoaldosteronism type 1 (PHA1) may not be recognized in the neonate, leading to wrong diagnosis.

F.D.T. was admitted at 12 days old with vomiting, severe dehydration, and weight loss. Son of consanguineous parents and no relevant family history or perinatal intercurrence. He showed typical male genitalia, and no significant alteration at physical exam; weight = 2,950 g. He was diagnosed with salt wasting form of Congenital Adrenal Hyperplasia (CAH) after lab results: Na+= 121 mEq/L and K+= 7.2 mEq/L, elevated serum levels of 17hydroxyprogesterone (1127 ng/dL; RV <200 ng/dL) and androstenedione (0.6 ng/mL; RV 0.2 to 0.5 ng/mL). The child did not get better despite being under high doses of fludrocortisone (0.4 mcg/dia) and

hydrocortisone. A positive screening test for cystic fibrosis (IRT 488.5 ng/mL, RV <140 ng/mL) and negative for CAH were in disagreeing with the clinical diagnosis. The sweat test showed alterations on five occasions, suggesting cystic fibrosis (CF). Pancreatic enzymes were prescribed, although the patient had no pulmonary or digestive (normal fecal fat values) symptoms. Since a survey looking for mutations related to CF was negative for G542X, N13031C and R'553X, the treatment for CF was suspended. Successive serum evaluations showed progressive normalization of 17hydroxyprogesterone, excluding the diagnosis of CAH and its treatment was also interrupted. By 2 months of age, he showed high serum aldosterone concentrations (480 ng/dL; RV: 6 to 90 ng/dL) and plasma renin activity (18.4 ng/mL/hr; RV: 0.3 to 1.6 ng/mL/h), suggesting the diagnosis of PHA1. He got positive results under sodium replacement and he was discharged. During the follow-up, there was no impairment of nutrition, growth or intellectual performance, and he is in currently oral sodium replacement (1.1 mEq/kg/day) with normal electrolytes and no complaints. At his last visit, he was 18 years, 58 kg, 162.3 cm, and had serum aldosterone dosage of 31.9 ng/dL (RV: 2.5 to 39.2 ng/dL).

In conclusion, the patient showed a false-positive result for CAH and presents a systemic manifestation of insensitivity to aldosterone (no molecular diagnosis for ENaC mutation). Conflicting laboratory tests for CF in the neonatal period indicate a differential diagnosis with PHA1.

P-6

A Novel Variant p.Glu15Lys in MRAP Gene in Two Non Related Cases of Familial Glucocorticoid Deficiency from Two Different Isolated Argentinean Aboriginal Communities

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Introduction: Familial Glucocorticoid Deficiency (FGD) is a rare disorder characterized by severe glucocorticoid deficiency associated with failure of adrenal responsiveness to ACTH but without mineralcorticoid deficiency. Patients suffer from recurrent hypoglycemia and convulsions that may result in coma and death, hyperpigmentation, recurrent infections, and developmental delay.

FGD is an autosomal recessive disorder caused by defects in the receptor for ACTH gene also known as the melanocortin-2 receptor (MC2R) or its accessory protein (MRAP) which leads to ACTH resistance. Furthermore, mutations of MC2R gene account for approximately 25% of FGD cases while mutations of MRAP gene account for a further 20%.

We are reporting corticoid insufficiency in two non related pediatric patients belonging to two isolated Argentinean aboriginal communities, one from Wichi's and the other from Qom's communities. Both communities have different ethnic characteristics but in both high level of endogamy have been reported. Both patients were evaluated within the first year of life. Similar clinical records were reported such as hypertonic seizures associated with hypoglycemia, skin hyperpigmentation, muscle weakness and normal female genitalia. Hormonal determinations revealed high ACTH and low basal serum cortisol levels, along with normal blood electrolytes. In both cases history of consanguinity was referred. Alteration in ACTH receptor signaling pathway was suspected.

Methods: Direct sequencing of all exons and their flanking intronic regions of the MC2R and MRAPgenes was performed.

Results and Conclusions: Unexpectedly molecular studies revealed an homozygous novel variant p.Glu15Lys in MRAP gene in both patients. No mutation in MC2R gene was found The p.Glu15Lys variant was predicted to be deleterious to MRAP protein function by in silico analysis using SIFT, Mutation Taster, SNPs3D and PolyPhen-2 and it was not present in the 1000 genomes browser or dbSNP. However in vitro functional studies should be done to confirm pathogenicity of p.Glu15Lys variant. Finally a genetic population analysis in both communities could be useful to identify a common ancestor.

P-7

Vascular Function and Heart Rate Variability in Mothers of Children with Low Birth Weight

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Introduction: It is known that low birth weight (LBW) is associated with increased risk of cardiovascular disease (CVD) in adult life. The heart rate variability (HRV) results from a balance between sympathetic/parasympathetic systems and reflects our capacity to adapt to changing situations. It was demonstrated that HRV is decreased in many CVD. New researches show that the BPN may be result of multiple factors both of the child and the mother that could negatively impact on the fetal growth environment.

Objective: To study endothelial function (EF) and HRV by non-invasive methods and its relationship with CVD risk markers in mothers of children with a history of LBW.

Method: Mothers of children with or without LBW (control group) were studied. Waist circumference, height, weight, systolic/diastolic blood pressure (SBP/DBP), glucose, insulin and lipid profile were determined. EF was measured by pulse wave plethysmography evaluating flow-mediated vasodilatation. HRV (variation in the beat-to-beat interval) was analyzed by standard deviation of

beat-to-beat or NN intervals (SDNN); spontaneous variability of heart rate (percentage of consecutive beats that differ more than 50 ms: pNN50) and the product of the maximum HR and SBP (MHRxSBP).

Results: In mothers, we found that SDNN was significantly correlated with the weight of children at birth (Pearson r = 0.5634; IC50%: 0.1739 to 0.8004; $p < 0.01$, n = 21). Also in mothers, the percentage or number of children with LBW was negatively correlated with HRV. When comparing the group of mothers of children with LBW and control group, there were no differences in age, anthropometric parameters and laboratory variables and SBP/DBP in both groups. However mothers of children with LBW presented a decreased endothelial function (1.86 ± 6.6% HR n = 13) in contrast with mothers of control group (19.4 vs. 5.9; n = 8; $p < 0.02$).

Conclusions: We observed for the first time that the mothers of children with a history of LBW, although have similar characteristic in her anthropometric and biochemical parameters and blood pressure in relation with control group, these mothers have a decreased endothelial function as well as a minor HRV. These facts indicate that the BPN could be associated with early changes of the autonomic adaptive axis mothers.

P-8

Characterization and Confirmation of Beckwiedeman Syndrome by Metilation Changes in IC1 E IC2 in the Pat UPD from Chromosome 11p in Three Pediatrics Patients

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Introduction: Beckwith-Wiedemann síndrome, is a genetic or epigenetic disease and a pediatric overgrowth disorder with a predisposition to embrionic tumors. It is caused by mutations in genes that regulate growth in chromosome 11 region 11p15.5 or by genomic imprinting errors, specially by the loss of methylation in IC2 in the maternal chromosome, gaining of methylation in IC1 in the maternal chromosome. Mutations of the maternal allele CDKN1C, alterations or microdeletions, or duplications in the 11p15.5 region.

Materials and Methods: Described three patients with macrosomia, hypoglycemias, and clinical data consistent with Beckwith-Wiedeman síndrome, confirmed by clinical findings and genetic studies showing alteration of methylation.

Results: Three female patients premature with macrosomia, with hypoglycemia, hemihypertrophic, macroglosia, cardiomegaly, nephromegaly, onphalocele. The average to: age was 33 weeks of gestation, weight 3220 gr, height 45 cm, blood glucose 34 mg/dl. Who were found to have Beckwiedeman by abnormal hypomethylation found in the región imprinting center Centromerico (IC2) and hypermethylation in the región of imprinting center Centromerico (IC1). This probably corresponds to a pat UPD of chromosome 11p. During the follow up for 8 years, one patient had a Wilms tumor.

Analysis and Conclusion: Patients with macrosomia, hypoglycemia, hemihypertrophies should be classified using differential diagnosis to provide the right management and follow up. The differential includes SBW, Proteus, Klippel-Trenaunay-Weber, neurofibromatosis type 1, Sotos, Perlman. It is important to monitor them because they have a risk of wiliams tumors and hepatoblastomas.

P-9

Novel De Novo Mutation Detected in a Sporadic Weaver Syndrome

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Background: Weaver syndrome (WS), first described in 1974[1], is a genetic disorder characterized by overgrowth, tall stature, macrocephaly, typical facial features, advanced bone age, intellectual disability, and increased neoplasia susceptibility. Originally, it was thought to be a variation of Sotos syndrome, caused by mutations in NSD1; however, later it was shown that Weaver syndrome is caused by mutations in a different histone methyltransferase, EZH2[2–3]. Typically, Weaver syndrome occurs as a sporadic condition, though cases of parent-to-child transmission have been documented.

Case Presentation: An 8 year old boy presented to clinic with tall stature (+2.86 SDS national reference) and intellectual disability. Left hemiparesis, hypotonia and seizures were present from 3 to 8 years of age and an MRI showed operculization defect and atrophic right hemisphere. He also had hypertelorism, macrocephaly, a flat occiput, large ears, broad thumbs, prominent digital pads, an umbilical hernia and scoliosis. X-rays showed advanced bone age.

Genetics: Sanger sequencing of EZH2 was performed and a de novo c.403G>A (NM_004456.4), p.Gly135Arg mutation was identified.

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P-10

Frequency of Skeletal Dysplasia in Short Stature Children Born Small for Gestational Age

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Objective: To determine the frequency of skeletal dysplasia in short stature children born small for gestational age (SGA).

Methods: Anthropometric measurements and skeletal radiologic survey were performed in 35 SGA children with persistent short stature after the age of 2 years.

Results: Six patients out of 35 were considered disproportionate, corresponding to 17% of total number of short stature children born SGA. The skeletal survey showed alterations in 9 out of 35 patients (26%). Patients with nonespecific skeletal findings were more likely to have a higher birth weight (–1.4 ± 1.0 vs –2.2 ± 1.0, p = 0.052) and were shorter (–2.8 ± 1.8 vs. –1.7 ± 0.9, p = 0.011) than patients without any skeletal findings. There was no difference regarding birth length SDS, head circumference SDS, BMI SDS and arm span SDS between patients with or without skeletal radiological findings. Skeletal dysplasia was diagnosed in 3 patients (8.6%) and nonspecific alterations were found in 6 patients. Patients with skeletal dysplasia showed proportionate short stature regarding SH/H ratio but short arm span and/or short upper limbs.

Conclusion: SGA children are a heterogeneous group and the causes of their short stature are not always identified. In those patients, the diagnosis of skeletal dysplasia should be considered. Careful physical examination of patients and parents can identify disproportionate short stature. Skeletal X-ray as well as molecular diagnosis should be performed in all SGA children with an unknown cause of growth deficiency and alteration in anthropometric measurements to improve follow up of short stature.

P-11

Growth Hormone (GH) Response to Oral Glucose Tolerance Test in the Assessment of GH Excess Secretion in Paediatric Patients

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Introduction: GH excess secretion is a rare disorder in children. In adults, the failure to suppress GH levels to ≤0.40 ng/mL after oral glucose tolerance test (OGTT) together with normal IGF-I concentration exclude this diagnosis. To our knowledge, the suppression of GH in response to OGTT using sensitive GH assays is not clearly stated for paediatric patients.

Objective: To evaluate GH response to OGTT in a cohort of children with clinical suspicious of GH hypersecretion.

Design and Methods: Cross-sectional analytical study. OGTT (1.75 g glucose/kg body weight to a maximum: 75 g) was performed in 10 patients [age: 13.8 (5.3–17.0) yrs] referred to our outpatient Endocrinology Department for assessment of tall stature (height ≥ +2.0 SDS) and/or the presence of pituitary adenoma without other pituitary secretory disorder. Blood samples were taken for GH (CLIA-Siemmens), insulin and glucose measurements (30 minutes intervals during 2 hours). GH dynamics [GH nadir concentration and area under the curve (AUC)] were compared with a control group of non-insulin resistant children without GH-axis disorders (n = 10). Basal IGF-I and IGFBP-3 were measured. Data were expressed as median (range).

Results: In the control group, GH decreased at 30 minutes, maximal GH suppression was reached within 60–90 minutes [97thpercentile GH nadir concentration: 0.30 ng/mL] and AUC was 23 (6–133) ng/mL.120 min. In 8/10 patients, GH dynamic profile was similar to control group [GH nadir: 0.12 (0.07–0.20) ng/mL; AUC: 25 (10–105) ng/mL.120 min; p=NS]. Two patients did not reach GH nadir obtained for controls (0.60 and 0.80 ng/mL). Moreover, they presented a paradoxical rise at 30 minutes and elevated AUC: 286 and 294 ng/mL.120 min. IGF-I and IGFBP-3 were above +2.0 SDS in 4/8 and 6/8 patients, respectively, with normal GH response to OGTT and in 1 out of 2 patients with paradoxical response.

Conclusion: Our finding of a GH nadir concentration of 0.30 ng/mL in OGTT in children using ultrasensitive assays was similar to the one suggested for adults. A paradoxical response, an elevated GH nadir and an increased AUC in patients with clinical suspicious of GH excess secretion alert to a close follow-up to further confirm diagnosis.

P-12

Self-Esteem Level in Teenagers with Short Stature

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Background: The psychosocial impact of short stature in teenagers is controversial due to the variability of criteria for its definition and the existence of a broad psychosocial context that can be understood as lack of confidence, low self-esteem, lack of social integration or depression. In the present study we determined the association of self-esteem and short stature in teenagers.

Materials and Methods: A case-control study was performed in public and private schools of an urban district in Lima. We included teenagers aged 15–17 years old through a stratified cluster sampling. The sample was estimated considering an OR = 2, 80% power and 95% significance level. Case was defined as a teenager with low self-esteem measured with Rosemberg scale and control was defined as a teenager with normal self-esteem. Three controls per case were chosen, matched by age, sex and type of school. Anthropometric measurements were assessed: weight, height and BMI, under standardized protocol. Short stature was considered as a teenager's z-score height <-2 SD according to the Center of Disease Control and Prevention. We excluded teenagers with overweight, obesity and malnutrition. The level of self-esteem was estimated by an auto filled questionnaire, considering low self-esteem level <30 points and normal with ≥30. Student's t test and Pearson's chi squared were used, considering significant $p < 0.05$.

Results: 122 adolescents (95 F/57 M) were evaluated with a mean age of 16.2 ± 0.6 years old. The mean height z-score of the 38 cases was –2.24 ± 0.24 and of the 114 controls was 0.63 ± 0.84 ($p = 0.00$). Short stature was found in 21.01% of adolescents with a normal self-esteem and 39.39% in adolescents with low self-esteem. We found significant association ($p = 0.03$) between the presence of short stature and low self-esteem with an OR 2.44 (95% CI 1.07–5.58).

Conclusion: Adolescents with short stature have twice the risk of having low self-esteem.

P-13

Pituitary Stalk Interruption Síndrome. Clinical, Biochemical and Neuroradiological Relationships

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Pituitary stalk interruption syndrome (PSIS) is characterized by the association of an interrupted or thin pituitary stalk, absent or ectopic posterior pituitary and anterior pituitary hypoplasia. It is manifested as isolated (IGHD) or combined pituitary hormone deficiencies (CPHD) of variable degree and timing of onset with a wide spectrum of clinical phenotypes. PSIS may constitute an isolated morphological abnormality or be part of a syndrome.

To evaluate retrospectively clinical signs and symptoms present at early life stages and analyze their relationship with hormone laboratory tests and diagnostic imaging in children with Congenital Hypopituitarism (CHP) and PSIS.

This retrospective, single-center, case-cohort study was performed in 42 children (22 females) out of a total of 80 patients with CHP in a pediatric hospital over 26 years. The CA range where: 5 d – 9.5 years.

The study included, 26/42 (62%) with CPHD and 16/42 (38%) with IGHD. The perinatal histories showed hypoglycemia (19% IGHD vs. 61% CPHD, P,0.0001), jaundice (25% IGHD vs. 38% CPHD), micropenis (75% CPHD), hypoglycemic seizures (75% CPHD) and cholestasis (19% CPHD). The mean CA of consult for CPHD patient's was 2.1 years (5 d-9 y), 30% in neonatal period, 70% before 2 years. For IGHD patient's the mean CA was 3.6 years (1–9.5 y), 44% of them before 2 years.

The prevalence of deficiencies in growth hormone, thyrotropin, corticotropin, and gonadotropins, were 100%, 92%, 54%, 50%, respectively.

The MRI findings showed, absent (81% CPHD vs. 56% IGHD) or thin pituitary stalk (19% CPHD vs. 44% IGHD), ectopic (80% CPHD vs. 73% IGHD) or absent posterior pituitary lobe (16% CPHD vs. 20% IGHD) and hypoplastic anterior pituitary lobe in all the patients.

Our results demonstrate that early diagnosis of CHP can be performed with high accuracy based on a high index of clinical suspicion. One late recognition lead to increased morbidity and mortality, with potential permanent deleterious effects.

Characterization of GH deficient patients by presence and PSIS provides valuable information for physicians and families, regarding the likely severity of phenotype, potential to develop additional hormonal deficiencies and to contribute toetiologic diagnosis.

P-14

Establishment of the Southern Hemisphere's First Clinically Accredited Whole Genome Sequencing Facility, and the Development of a Gene Sequencing Panel for Application to Disparate Cancer Types Including Pituitary

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Diagnostic rates for patients with rare monogenic disorders have risen significantly due to advances in whole genome/exome sequencing (WGS/WES). However, WGS markedly outperforms WES with 40–73% of patients receiving diagnoses versus 25–40%. The Kinghorn Centre for Clinical Genomics (KCCG) was among the first three entities worldwide to acquire the Illumina HiSeq X Ten platform, which enables economical population-scale access to WGS. Recently, our service became the first in the Southern Hemisphere to achieve clinical accreditation to allow delivery of WGS-based diagnostic testing. WGS remains cost-prohibitive for analysis of tumour DNA, where much deeper sequencing is necessary to take account of tumour heterogeneity and cellularity. Therefore, target sequencing approaches remain a more practical platform for cancer diagnosis. Although targeted sequencing methods are already entering mainstream clinical care for better-studied cases such as those of the breast and lung, poorly studied/understood cancers, such as those of the pituitary, have not yet benefited from such advances. To meet this unmet need, we have developed a pan-cancer gene screening panel to apply to disparate cancer types to improve diagnoses and prognoses, and identify novel or repurpose existing therapeutic options.

Our custom panel (Roche/Nimblegen) containing 325 genes implicated in cancer and pituitary organogenesis or familial pituitary tumour syndromes (~1.0 Mb target sequence), was applied against patients with sporadic pituitary tumours or with familial history thereof (n = 28). We further validated our panel against control samples (n = 46) with known cancer-associated SNVs, small insertions/deletions and copy number variants (CNVs). Sequencing was performed on Illumina HiSeq 2500, with analysis conducted via a customised bioinformatic pipeline.

Our panel detected variants to an average depth-of-coverage of ~600x. Pathogenic mutations were detected in cancer associated-genes including AIP and we identified a novel therapeutic option for a patient with an aggressive pituitary tumour. Further, we successfully validated our panel against mutations of various types including CNVs.

Our world-first, clinically-accredited laboratory has developed an economical pan-cancer panel, applicable across disparate cancers which is validated to detect mutations of various kinds. We have the potential to improve diagnoses, prognoses and therapeutics in patients including children.

P-15

Spontaneous Remission of Pituitary Dysfunction in an Adolescent with Fluctuating Neurologic Symptoms

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Introduction: Pituitary dysfunction due to malignant cell infiltration is an infrequent pathology in children and its spontaneous complete remission has not been yet described in pediatric patients.

Case Report: We report a case of a 16-year-old boy with no remarkable past medical history who was admitted to our hospital after complaining for two months of headaches and acute left hand incoordination. An MRI showed two hyperintense lesions in the periventricular regions, one in the left talamus and parietooccipital lobe and the other in corpus callosum. In addition, a marked thickened pituitary stalk was observed. Routine laboratory workout was normal, tumor markers and serological test for human immunodeficiency virus were negative. He referred polyuria and polydipsia and clinical examination showedright hemiparesis, short stature (height – 2.6 SDS, target height –1.8 SDS) and Tanner stage 5. Hormonal studies showed low testosterone with low gonadotropins, a water deprivation test ruled out diabetes insipidus. A new MRI, one week after, showed a normal pituitary stalk. Symptoms disappeared spontaneously. Six months later without clinical symptoms, laboratory studies confirmed spontaneous partial recovery of testicular function. A new MRI revealed only a small residual lesion. He never receivedsteroids or any other treatment. Two years later he suffered an acute aphasia. A MRI showed hyperintense lesions with well-defined borders located at the left frontal lobe in the cortical and subcortical region. The patient presented seizures and sudden neurological deterioration. Stereotactic biopsy showed a B-primary central nervous system lymphoma (B-PCNSL).

Conclusions: PCNSL is extremely rare in the pediatric population. However, the incidence of this tumor has increased ten-fold over the last three decades in both immunocompetent and immunocompromised individuals. Pituitary infiltration has been described as a rare presentation in adult patients. PCNSL spontaneous remission is exceedingly rare and is referred in the literature as a type of brain vanishing tumor. We believe it is important to report this case to pediatric endocrinologists to alert for patients with neurological and endocrinological symptoms that wax and wane, in whom the diagnosis can be elusive.

P-16

Characterization of Insulin Like Growth Factor (IGF) System Components in Pediatric Tumors of Central Nervous System (CNS)

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Background: CNS tumors are the most frequent solid tumors in pediatric population. The IGF system of ligands and receptors are known to play an important role in both normal and neoplastic growth. Recently, quantitation of components of this system have been reported in CNS tumors from adult population, but information from pediatric patients is scarce.

Objective: To characterize the expression of IGF-1, IGF-1R, IGF-2 and IR in CNS tumors from pediatric patients.

Patients and Methods: We performed a prospective study (6/2012–6/2016) of pediatric patients with CNS tumors without previous medical treatment that underwent surgery in our Hospital. Tissues were collected at the time of surgery. IGF-1, IGF-1R, IGF-2 and IR expression was measured by qRTPCR using extracted RNA. Specimens were classified according to localization or histology type and grade based on WHO2007 classification. Mann-Whitney, Kruskal-Wallis followed by Dunn's Testwere used for comparisons.

Results: We included 89 patients (50 males/39 females), median aged 8.9 yrs, (range 0.9–18.6). The most common subgroups of CNS tumors were gliomas (n:36); ependymomas (n:16); medulloblastomas (n:11). Levels of IGF-1, IGF-1R, IGF-2 and IR mRNA were detectable in all specimens. Changes in IGF-2 mRNA levels among tumors were significantly different compared to the changes observed in the other genes analyzed (IGF-2:47 (12–82) vs. IGF-1:1 (0.7–1.4); IGF-1R:0.8 (0.5–1.0); IR: 0.9 (0.7–1.1), mean (CI) fold change, $p < 0.0001$). In gliomas IGF-2 mRNA was lower while IGF-1 expression was higher in high grade compared to low grade tumors ($p < 0.05$). IGF-IR and IR mRNAs were similar. Expression of IGF-2 and IR were lower in grade 2 and 3 ependymomas compared to grade 1, while IGF-1 and IGF-1R were similar among grades. When analyzed according to localization (supra/infratentorial, spinal cord) we found that IGF-1R expression was low in supratentorial ependymomas ($p < 0.001$). Finally, we found no differences in IGF-1, IGF-1R, IGF-2 and IR expression levels between classic and anaplastic medulloblastomas.

Conclusions: IGF-2 is highly variable in pediatric CNS tumors compared to other components of the IGF system. In gliomas and ependymomas IGF-2 was higher in lower grade tumors suggesting a role for IGF-2 in their biological behaviour. Further studies including patients' follow up are necessary to confirm these results.

P-17

Central Diabetes Insipidus in Infants – Treatment with Hydrochlorothiazide

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Introduction: Central diabetes insipidus (CDI) is a rare disease with high morbidity and mortality. It comes from changes to the hypothalamic-neurohypophysis system, leading to deficiency of the hormone arginine vasopressin (AVP). The treatment of infants and preschool children with desmopressin (dDAVP) is challenge, and excess water from the milk liquid diet implies greater risk of water intoxication. Thus, the use of hydrochlorothiazide and diets with low renal solute load has also been used in patients in this age group.

Study Design and Methods: A retrospective study of a series of cases. It describes: age at diagnosis, previous or associated pathologies, hydrochlorothiazide therapy, median and range of serum sodium values, the presence of other pituitary hormone deficiencies.

Results: The medical records of five patients with DIC treated with hydrochlorothiazide were reviewed from 2006 to 2016. The average age at diagnosis was 0.23 ± 0.3 years. Four were diagnosed with Septo-optic dysplasia and one developed post-meningitis pneumococcal CDI. After the diagnosis, four patients initiated hydrochlorothiazide (associated with increased free water intake) and one of them started dDAVP, which was replaced by hydrochlorothiazide 12 months later due to the difficult control of natremia. The dose used in the treatment varied from 2 to 5 mg/kg/day. At diagnosis, serum sodium levels ranged 151–173 mEq/L, and after starting hydrochlorothiazide, the median was natremia 144.5 (range: 141.5–148 mEq/L). One of the patients presented severe hyponatremia (123 mEq/L) during sepsis which was reversed with temporary discontinuation of medication. Three patients had other pituitary hormone deficiencies (deficiency of thyrotropin and corticotrophin) and multiple hospital admissions, which contributed to the difficulty handling. All patients had neurological disorders. Thus, the thirst mechanism in an attempt to normalize natremia and plasma osmolarity was not preserved.

Conclusion: There was improvement on natremia control after administration of hydrochlorothiazide and dietary manipulation. The use of hydrochlorothiazide associated with renal solute load formula can be a treatment option.

P-18

When Should We Suspect That a Child Has a Craniopharyngioma?

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Introduction: Childhood craniopharyngioma is a benign neoplasm that has variable clinical presentation, such as incidental findings on imaging, neurological and visual deficit, even multiple endocrine deficiencies. The initial clinical findings may have an impact on morbidity and mortality of these patients in the long run.

Design and Methods: A retrospective analysis of medical records of 57 patients diagnosed with craniopharyngioma, from June 1999 to June 2014. In that, were analyzed the initial clinical features, variables such as age, weight, height and the first clinical symptoms. Body mass index (BMI) was calculated (kilogram/meters^2). Anthropometric data was calculated by z-score for height and BMI, based on the National Center for Health Statistics (NCHS) growth charts.

Results: Of the 57 patients studied, 35 were male and 22 female, aged 6 to 32 years, mean of 16.3 years. Among the main complains at diagnosis, 78.9% (45/57) had headache, 28% (16/57) visual disorders, 19.2% (11/57) vomits, 5.2% (3/57) growth retardation, 8.7% (5/57) polyuria and/or polydipsia, 19.2% (11/57) other (incidental findings) and 1.7% (1/57) asymptomatic. The anthropometric analysis, showed that 14% (8/57) of the patients had adequate height (z-score> –2), 21% (12/57) short stature (z-score –2 to –3) and 8.7% (5/57) severe short stature (z-score <-3). In concern of the BMI, 49.1% (28/57) were healthy weight (z-score +1 to –2), 29.8% (17/57) overweight (z-score +1 and +2), 14% (8/57) obese (z-score> +2).

Conclusions: Craniopharyngioma usually has a clinical presentation dominated by visual and neurological deficits. Symptoms like headache were found in more than 50% of the sample and visual impairment in 28% of the patients. Although, only 5.2% complains of growth retardation at the first consultation, by the anthropometric examination was detected short stature in 29.7% of patients, which reasons for the slowdown of growth was not described. Preoperatory diabetes insipidus should be better investigated. An early recognition of this condition and proper management of hormones deficit can have a positive impact on the quality of life in long-term patients.

P-19

Characterization of 185 Patients with 46,XX Disorders of Sex Development

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Disorders of sex development (DSD) are congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical. The aim of this study is to characterize a cohort of 46,XX DSD patients followed at the Garrahan Pediatric Hospital, Buenos Aires, Argentina. Medical records of all patients followed at the Endocrinology Department because of DSD between January 2000 and June 2015 in whom laboratory tests were requested were reviewed. We analyzed the records of 185 patients with 46,XX karyotype. In 83.2% the final diagnosis was congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (CAH/21-OHaseD). This diagnosis was established on the basis of consistent hormonal measurements and it was confirmed by genotyping of the CYP21A2 gene in 72.7% of the cases. Diagnoses of the remaining patients were the following: in 17 patients it was made by histological examination of the gonads and gene analysis, ovotesticular DSD 5.4% and testicular DSD 3.8%; while in the other 14 patients by gene analysis, aromatase (CYP19) deficiency in 3.2%, oxidoreductase (POR) deficiency in 2.7%, CAH due to 11β-hydroxylase deficiency in 1.1%, and CAH due to 3β-hydroxysteroid dehydrogenase deficiency in 0.5%. In patients with testicular and ovotesticular DSD, the presence of the SRY gene was investigated in genomic DNA from mononuclear cells and gonadal tissue. The genes NROB1, FOXL2, RSPO1 and WNT4 were automated sequenced, while the copy number variations of SRY, SOX9, NROB1, NR5A1 and WNT4 were assayed by MLPA. SRY resulted positive in two patients, one with testicular DSD and the other with ovotesticular DSD. Nevertheless, there were neither variations in the sequence nor alterations in the copy number of the remaining genes studied. As it is known, CAH/21-OHaseD is the most common diagnosis in 46,XX DSD and testicular and ovotesticular DSD was the second. Further studies should be performed to better characterize this population in order to arrive to an etiologic diagnosis which enables the optimization of long-term monitoring and improves genetic counseling. Moreover, it is suggested the implementation of next generation sequencing as well as compared genomic hybridization (CGH) techniques to reduce the costs and increase the throughput and accuracy.

P-20

Molecular Analysis of the Androgen Receptor Gene in 35 Index Patients with 46,XY Disorder of Sex Development

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Background: Androgen insensitivity syndrome (AIS) is the most frequent monogenic cause of 46,XY disorders of sex development (DSD), an X-linked recessive condition. Mutations in androgen receptor (AR) gene are associated with a wide phenotypic spectrum, ranging from complete androgen insensitivity syndrome (CAIS) to a partial form (PAIS).

Objective: To characterize the contribution of the AR gene to the molecular cause of 46,XY DSD in our population.

Clinical Cases: We studied 35 non related 46,XY DSD patients, with different clinical and hormonal characteristics, adecquate testosterone production and no evidence of gonadal disgenesis in whom the AR gene was the first candidate to molecular analysis.

Methods: AR exons (1 to 8) and intron boundaries were direct sequenced in all patients and in 13 family members (65% of affected patients).

Results: AR gene mutations were found in 20 individuals (57% of index patients), of whom 11 (55%) were CAIS and 9 (45%) PAIS. Eighteen different mutations were found: 11.1% located in N-terminal transactivational domain; 11.1% in the DNA-binding domain (DBD); 72.2% in the C-terminal ligand binding domain (LBD) and 5.6% of gross deletions. Eleven mutations (61%) had been previously described and 7 (39%) were novel. Somatic mosaicism is present in four individuals (20% of AR-mutated gene patients). Ten percent (10%) of androgen insensitivity syndrome patients had other affected relatives.

Conclusions: Androgen receptor gene mutations are the main cause of 46,XY DSD. Mutations in the AR gene are distributed throughout the gene with a preponderance located in the ligand binding domain. The most severe mutations are generally associated with a CAIS phenotype, but the correlation is less defined in PAIS. Some patients with severe mutation display a partial androgen insensitivity syndrome phenotype, which is explained by somatic mosaicism.

P-21

Sex Reversal Secondary to CYP17A1 Gene Mutations in a 46,XY DSD Girl

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Background: P450c17 deficiency, secondary to CYP17A1 gene mutations, is a rare cause of congenital adrenal hyperplasia (CAH) affecting cortisol, adrenal androgens and gonadal steroids synthesis. These mutations lead to 46,XY DSD and pubertal delay in both sexes. Adrenal insufficiency is rare, presumably cortisol deficiency is compensated by ACTH-stimulated corticosterone secretion, and patients might present hypertension (HT) and hypokalemia because of DOC excess. Treatment mainly involves the administration of hydrocortisone, sex steroid replacement and management of HT.

Case Report: We report the clinical, biochemical and molecular findings in a 9-year(y)-old 46,XY DSD patient presented with female external genitalia.

Inguinotomy, performed in another institution at 4 years of age because of left inguinal hernia, showed the presence of one testis that was removed. A wrong diagnosis of CAIS was made.

In our Institution, at 9 y, physical examination showed normal normotensive patient with female prepubertal external genitalia. No gonad was palpated in the right inguinal region. Laboratory tests showed no detectable serum SDHEA levels. An ACTH stimulation test revealed serum cortisol insufficiency and a high increment of serum progesterone levels. The presence of an intra-abdominal gonad was suggested by detectable basal serum AMH levels. Furthermore, a right immature testis was found by laparoscopy. Histology showed seminiferous cords with immature Sertoli cells and scarce germ cells, vacuolated germ cells and centrally located germ cells and Leydig cell hyperplasia. Mutation analysis revelead two previously described compound heterozygous mutations in the CYP17A1 gene, p.Arg358Gln and c.1434-1437dupCATC.

Conclusion: P450c17 deficiency is a rare cause of CAH and DSD XY. This is the first case of our 128 46,XY DSD patient series.

A combination of impairment of adrenal androgens and gonadal steroid synthesis should orientate the diagnosis and a complete steroid profile. It is mandatory to evaluate steroidogenesis at a whole. A misdiagnosis can lead to severe HT early in life. An early diagnosis could improve our knowledge on the physiopathology of the prepubertal and pubertal period, optimize clinical management and offer genetic counseling to the parents.

P-22

Molecular Analysis of Androgen Receptor Gene in a Cohort of Brazilian Patients with Androgen Insensitivity Syndrome

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Androgen Insensitivity Syndrome is a common cause of 46,XY DSD. AR mutations are identified in 85–90% of patients with Complete (CAIS) but only in 30% of Partial form (PAIS).

We sequenced the whole coding region of the AR gene by PCR in 63 patients with clinical suspicion of AIS (testo and LH levels, hernia, gynecomastia and X-linked inheritance (33 patients from 21 PAIS families and 30 patients from 20 CAIS families). In patients without exonic mutations, the 5'UTR region of AR were sequenced. Allelic variant with a very low frequency in databases (ExAC and 1000 genomics) were analyzed for deleterious potential by mutation taster, Polyphen and Mutation Assessor sites. Intronic and silent mutations were analyzed for splicing alteration by Netgene2 and Human Splicing Finder sites. In these cases we performed a partial sequencing of AR cDNA, flanking the mutation region to verify protein size change.

Exonic missense mutations were identified in 88% of PAIS and in 73% of CAIS patients. Silent mutations causing splicing alteration were identified in one PAIS patient (p.S889S) and a novel mutation in two CAIS families (p.S5010S). Heterozygous mutations were identified in 3 PAIS. The analysis of 5UTR (including the promotor region) identified a large insertion in a family with 9 affected individuals.

We were able to establish the molecular diagnosis in 90% PAIS and 100% in CAIS. The The use of phenotype approach and sequencing of exomic and promoter regions allow the identification of deleterious mutation in AR, including silent ones, in almost all AIS patients from our cohort.

Table 1. AR mutations in CAIS and PAIS Brazilian patients (for Abstract P-22)

Parameters	CAIS	PAIS
Patient/families	30/20	33/21
Missense MUT	15	17
Heterozygous MUT	–	3
Silent (splicing) MUT	1	1
Promoter region MUT	–	1
Novel mutations	7	8

P-23

45,X/46,XY Chromosomal Disorders of Sex Development. Experience from a Cohort of 50 Patients Followed in One Single Institution

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Background: Disorders of sex development (DSD) are those congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical. 45,X/46,XY mosaicism results in a large clinical spectrum of disorders of sexual development (DSD) including from female patients with Turner's syndrome to normal appearing males.

Objective and Hypotheses: The main aim of this study is to review the clinical and gonad histological findings in a cohort of chromosomal DSD patients followed between January 1/2000 and January 1/2016 at our institution.

Method: We analyzed the records 50 patients with 45,X/46,XY karyotype or variants. Patients were divided according to external genitalia into 2 groups (Gr): normal female phenotype (Turner syndrome, n18, Gr1), and atypical genitalia (n32, Gr2). We also identified one patient with normal male phenotype evaluated because of short stature that was not included in the analysis.

Results: Gr2 was more prevalent than Gr1 (64% vs. 36%, p 0.009). Male assigned patients in Gr2 (n = 22, 69%) presented higher mean external masculinization score (EMS) than female assigned ones (8.2 ± 0.9 SD vs. 5.6 ± 1.6 SD respectively, p 0.0017). In all male assigned patients in Gr2 that have reached pubertal years, spontaneous pubertal development was observed (n9). Gonadal neoplasia was found in 5/34 gonads from Gr1 (15%, chronological age at diagnosis 15–18 ys), and 2/50 gonads from Gr2 (4%, 3 ys). Adult height was available from 18 patients and it was significantly lower in Gr1 vs. Gr2 (145.3 ± 5.1 cm vs. 151.81 ± 5.1 cm, respectively, p 0.016) even though in Gr1, 55% (6/11) received rhGH treatment vs. only 30% in Gr2 (2/7).

Conclusion: In our cohort of 45,X/46,XY chromosomal DSD patients atypical genitalia was the most frequent phenotype. A tendency to a higher gonadal malignancy risk was observed in Turner syndrome patients. External genital phenotype might be a useful predictor for adult height.

P-24

Recurrent Orchitis in a Patient with True Hermaphroditism

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Ovotesticular Disorder of Sex Development (OTDSD – true hermaphroditism) is rare, characterized by the presence of both; presence of both testicular tissue and ovary tissue. Usually, these patients seek medical attention due to ambiguous genitalia.

Case Presentation: A 15-year-old boy, with 'atypical' genitalia and breast enlargement came for surgical correction. His genitalia had a more masculine aspect at birth and he had been submitted to six corrective surgeries. Karyotype is 46, XX[20]. His complaint was recurrent episodes of painful testicular swelling and gynecomastia for the last five years. Tanner stage G4P3 and breast enlargement (T_4), hyperpigmented scrotum fused with palpable gonads and a penis 6 cm long with distal hypospadia. Lab work-up: Estradiol = 73.4 pg/ml (<20), Pubertal LH and FSH levels. Testosterone = 156 ng/dl. Ultrasound revealed testes with microlitiasis, bilateral hydrocele and cysts in the left testis. A structure which could resemble a rudimentary uterus or vaginal fornix was also shown. Bilateral mastectomy and a laparoscopy was performed in order to explore the gonads, which turned out to be ovotestis. The left gonad was totally excised, whereas in the right one, the macroscopic testis component was preserved.

Conclusion: In OT DSD, the ovarian portion of the gonad in the scrotum may enlarge during the ovulatory phase, which may be misdiagnosed as 'orchitis', but the cyclical nature of the episodes should raise the possibility of ovarian tissue present in the gonad. In the ovotestis, the testicular component may be dysgenetic, opposing to the usual normal function of the ovarian portion, which favors the maintenance of the ovarian portion when possible. In our patient, the social male gender was well established therefore testicular tissue was preserved. The possibility of neoplastic degeneration is minimized once Y chromosome was not present but follow-up is mandatory, with the dosage of markers of malignization.

P-25

The Action of Paracrine Inhibitory Factors in the Absence of Spermatogenesis Impairs in vivo BetaB Inhibin Subunit Synthesis in Human Seminiferous Tubules

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The inhibin production and its hormonal regulation in cultured seminiferous tubules (ST) from a puberal patient with DSDXY were studied. The serum profile, the presence of inhibin subunits in the testis by immunohistochemistry and the hormonal regulation of ST inhibin production in vitro were determined. Serum inhibin B (InhB) was not detectable; levels of inhibin a-subunit (Pro-aC), FSH and LH were very high in relation to age. The histopathological examination revealed the predominance of mature Sertoli cells in the ST; the immunohistochemistry showed the presence of inhibin a-subunit and the absence of bB-subunit. Under basal conditions, the cultured ST produced detectable levels of both inhibin molecular forms, InhB and Pro-aC. The addition of FSH to the cultures stimulated Pro-aC production ($p < 0.01$). In contrast, no changes were observed in both inhibins production under other experimental conditions studied. These results confirmed that FSH is not able to sustain InhB production in a pubertal testis in the absence of the stimulatory factors produced by germ cells; these findings also suggest the existence of inhibitory mechanisms that may have impaired in vivo testicular InhB production in this patient. TNF-a, among others locally produced factors, may be involved in this inhibitory mechanism. It cannot ruled out that these factors could exert their action under other physiological and/or pathological conditions.

P-26

Sertoli Cell Function during Chemotherapy in Pediatric Patients with Acute Lymphoblastic Leukemia

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Background: Most reports on gonadotoxicity associated with chemotherapy of acute lymphoblastic leukemia (ALL) comes from studies in adults, and they are mainly focused on the sensitivity of testicular germ cells. Little attention has been placed on Sertoli cells in prepubertal patients, even though Sertoli cell function is essential for adult spermatogenesis.

Objective: To evaluate Sertoli cell function in prepubertal boys who receive chemotherapy for acute lymphoblastic leukemia.

Materials and Methods: A prospective study including prepubertal male patients with ALL. Main outcome measure was serum AMH level after each phase of chemotherapy and 1 year after treatment completion. Secondarily, FSH levels were measured. Results are expressed as medians (range).

Results: 26 boys with ALL were included: 24 had LLAB and 2 LLAT (4 standard, 14 medium and 8 high-risk ALL), age at diagnosis was 4.2 yr (0.4–14.3).

Serum AMH was: at diagnosis, 605 pmol/L (152–1333); at the end of induction (n = 19), 833 (170–1697) = 143% of pre-treatment level (92–274); after intensification (n: 23), 742 (240–1660) = 138% (58–251); after Phase 1 (n = 14), 644 (265–1095) = 112% (53–150); prior to start of maintenance (n = 16), 674 (351–1300) = 109% (67–199); at 6 months of maintenance (n = 11), 695 (312–1386) = 104% (63–215); at the end of treatment (n = 7), 817 (523–1563) = 131% (87–291); and 3 months after the end of treatment (n = 5), 738 (396–1336) = 107% (75–123) of pre-treatment AMH level. Serum AMH decreased below 70% of pre-treatment level during chemotherapy in 6 of 8 patients with high risk ALL, in 1 of 14 with medium risk and in none with standard risk. Only 6 patients (23%) had a transient mild FSH elevation.

Conclusion: These preliminary results showed that Sertoli cell function is not affected by chemotherapy in prepubertal boys with standard or medium risk ALL, but is at least transiently affected in those with high risk LLA.

P-27

Germline Stem Cells in Testicular Tissue of Cryptorchid Boys: A Retrospective Study

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Gonocytes remain one the least analyzed germ cell types in mammals (Culty, 2009; Manku & Culty, 2015). In humans, these cells may have important prognostic value in gonadal tumors. The aim of the present work is to define the morpho-functional identity of the poorly differentiated germ cells, observed in patients with cryptorchidism and in controls. Testicular biopsies from 76 samples of cryptorchid boys (2 months-14 years old) and controls, from an archival tissue collection, were analyzed by EM, conventional and high-definition light microscopy, and by immunohistochemistry (IHC) using specific protein markers, such as MAGE-A4 (gonocytes and spermatogonia) and AMH (immature Sertoli cells). For IHC, a specific pretreatment of the paraffin sections with dithiotreitol was used for the first time, in order to retrieve archival tissues. The analysis of the testicular biopsies in cryptorchid boys showed the following results: 1) presence of germ cells in 47/79 of the analyzed biopsies; 2) neonatal gonocytes were observed in 68% of the testicular biopsies having germ cells; 3) only few numbers of Ad spermatogonia/tissue area was observed (0–10 Ad/mm^2); 4) there is no pachytene spermatocytes before 12 years old. Neonatal gonocytes were clearly distinguished as a poorly stained cytoplasm due to the scarcity of organelles; lack of ER cisternae and a well-developed Golgi apparatus; scattered polyribosomes; very large mitochondria with intermitochondrial 'cement', localizing as a 'crown' around the nucleus; a lightly stained nucleus with homogenously distributed chromatin fibers; and a nucleolus attached to the nuclear envelope. Most of gonocytes were seen near the basement membrane (but not sat on it like spermatogonia), and surrounded by immature Sertoli cells. Functionally, MAGE-A4-positive germ cells per 100 Sertoli cells were significantly larger in pubertal boys with cryptorchidism compared to younger cryptorchid boys. Apparently healthy neonatal gonocytes may remain in cryptorchid testis up to puberty. The failure of these gonocytes to attain its correct final 'niche', is probably related to their persistence as immature germ cells and seems to go along with the failure of Sertoli cells to reach the adequate maturity.

P-28

DICER1 Syndrome, Novel Germline Mutations in Paediatric Patients

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Carriers of germline DICER1 mutations are predisposed to a rare cancer syndrome, the DICER1 syndrome, associated with tumors such as pleuropulmonary blastoma (PPB), ovarian Sertoli-Leydig cell tumors (SLCT), multinodular goiter (MNG), cystic nephroma (CN), embryonal rhabdomyosarcoma (ERMS) or primitive neuroectodermic tumor. DICER1 is involved in the generation of microRNAs (miRNAs), short, double-stranded, non-coding RNAs that modulate gene expression at the post-transcriptional level. Germline mutations in DICER1 might cause an alteration in miRNAs processing deregulating target oncogenes and leading to elevated risk of tumorigenesis. In most reported cases, there is an heterozygous germline mutation detected and a somatic second hit mutation in the wild type allele.

To analyze the presence of DICER1 germline gene alterations in 4 patients with pediatric tumors associated and a possible somatic mutation in one MNG tissue sample.

Automated sequencing of DICER1 gene from gDNA extracted from blood of affected subjects and relatives. Clinical Cases: 3 girls (P1, P2, P4) and 1 boy (P3), chronological age at diagnosis were: 5, 12, 15, and 2 years, respectively. Pathological studies revealed in P1: bilateral ovarian SLCT, P2 and P4: ovarian SLCT and MNG, P3: CN.

P1, P2 and P3 were found to be heterozygous for the novel p.Trp1098*, p.Phe351fs*1 and p.Asp244Glyfs*27 variations respectively while P4 was found to be heterozygous for the previously described p.D1437Mfs*16 mutation. In P2 and P3 familial molecular studies the same alteration in one parent was detected. It's predicted that these alterations would lead to a truncated protein above the RNAsa IIIa and RNAsa IIIb domains that includes metal-binding sites, and therefore without catalytic enzyme activity if translated. Sequence analysis of P2 MNG tissue sample revealed the presence of the heterozygous germinal mutation p.Phe351fs*1 and the absence of a somatic second hit mutation.

We report three novel heterozygous frameshift mutations in the DICER1 gene. Our results show that unlike thyroid carcinoma in which somatic mutations are described, a second hit would not be involved in the physiopatological mechanism of MNG. Molecular analysis of DICER1 gene allows identification of high-risk families, to perfom an early diagnosis and to offer a genetic counselling about familial recurrence risk.

P-29

Vaginal Bleeding in Infants: Case Series

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Vaginal bleeding in infants have different etiologies and needs investigation. We report 4 cases: *Case 1:* Newborn 7 days old, full term, AGA, Apgar score 7/9, presented with macroscopic genital bleeding, with 4 exchanges diaper/day. On physical exam: Tanner M2Ph1, intact hymen, absence of vaginitis or external vaginal tumor. Regular pelvic ultrasound. Patient had bleeding for 5 days and ceased spontaneously. Diagnosis: Bleeding for puerperal hormonal crisis. Conduct: Expectant. *Case 2:* Infant 9 months old, with monthly vaginal bleeding since 4 months. Normal development, except significant speech delay. Physical exam: weight and height more than 95th percentile, one coffee & milk spot and Tanner M4Ph1. Pelvic ultrasound: uterus 6.1 cc, 0.1 cm endometrial line, right ovary (RO) 1.3 cc with microcyst formation of 0.9 cm and left ovary (LO) 2.3 cc. Laboratory: Testosterone 10 ng/ml, 17OHprogesterone 148 ng/dL, Prolactin 25.34 ng/mL, DHEAS 17 µg/dL, LH 3.84 mU/L, FSH 3.05 mU/L, Estradiol 178 pg/mL. Magnetic resonance with pituitary microadenoma of 0.3 cm. Normal bone scintigraphy. Xray hands and wrists: >2 SD. Test 2 hours after leuprolide LH 82.4 mU/L. Diagnosis: Central Precocious Puberty. Conduct: leuprolide. *Case 3:* 11-month old girl, with vaginal bleeding from 6 months on. Pelvic ultrasound: uterus of 35.7 cc and endometrium of heterogeneous content to clarify. Physical exam: Tanner M1Ph1, active vaginal bleeding in moderate amounts; vaginoscopy with expansive injury to the middle third of the vagina. Laboratory: αfetoprotein 28,053 ng/mL. Tomography with lung and liver metastases. Pathology: endodermal sinus tumor. Diagnosis: germ cell tumor. Conduct: Chemotherapy. *Case 4:* Girl with active vaginal bleeding since 2.1 years old. Clinical examination: intact hymen, vulva with estrogenic stimulus, Tanner M2-3Ph1, discrete hyperchromic spots on the thigh, at flank and right occipital region. Laboratory: LH 0.1 mU/L; FSH 0.2 mU/L; Estradiol 32 pg/ml. Ultrassonography: increase in uterine volume and right ovarian cyst. At 3.3 years, Xray bone age of 7 years; Bone scan: increased osteoblastic activity in the skull. Diagnosis: Mc Cune Albright Syndrome. Conduct: Tamoxifen + Pamidronate. Comment: the appropriate clinical and laboratory test evaluation is crucial for assertive diagnosis and proper conduct in vaginal bleeding in infants.

P-30

Treatment with GnRH Analogs: Case Report with Discrepancy between Clinical and Laboratory Response

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Background: Central precocious puberty (CPP) is defined by the early maturation of the Hipothalamus-Pituitary-Gonad axis. The classical definition of precocious puberty is the development of secondary sexual characteristics before 8 years or menarche before 9 years in girls. The most accepted criteria to confirm the clinical suspicion is the stimulated LH after gonadorelin above 5 UI/L. When confirmed, the most appropriated treatment for CPP is GnRH analog.

Case Report: 5.6 years old girl was sent to evaluation by Pediatrician after breast enlargement and rapid growth after 5 years, when also has started underarm odor. Born term, healthy weight without significant pathological history. Healthy and not consanguineous parents, target height in the 50th percentile. At the initial examination, height 75–90th percentile (p) and weight in 75th percentile, Tanner B3 turgid, Ph1 (lanugo). Investigation: bone age of 7 years and 10 months; pelvic ultrasound: uterus 5 cc, right ovarian 4.6 cc (9 follicles), left ovary 2.5 cc (5 follicles) and doppler uterine artery pulsability index 1.5. Initial laboratory: LH 0.1 UI/L; FSH 1.4 UI/L; Estradiol <0.5 ng/dL; OHP 17 0.21 ng/mL; Androstenedione <30 ng/dL; Testosterone 9 ng/dL; SDHEA 15 µg/dL. LH after gonadorelin 6.4 IU/L after 60'. MRI: choroidal fissure cyst on the right. Started with GnRH analogue (aGnRH), leuprolide quarterly 11.25 mg. In the first post treatment revaluation presented an increase in left breast (Tanner B3) and regression of right breast (Tanner B1) was observe, with adequate suppression of LH. Throughout treatment with aGnRH, she presented satisfactory laboratory block (LH after 2 h aGnRH <4.0 UI/L), but not regressed breasts, otherwise progressed and also ovarian volume. Bone age, however, remained steady, at the start was in the 3th and after 3 years block in 50th percentile.

Conclusion: We describe a case with adequate laboratory and bone maturation response with leuprolide, yet without breast and ovarian blockade, but without evolution to early menarche. The hypothesis of exaggerated thelarche has been contemplated, however estradiol levels were never high, as expected. It follows a different tissue or ovarian sensitivity range in this case.

P-31

Clinical Experience with Radioactive Iodine in Treatment of Childhood and Adolescent Graves' Disease

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Graves'Disease (GD) is the most common cause of hyperthyroidism in pediatric patients. First line treatment is methimazole (MMI) but the rate remission is 20–30% and patients often require a definitive treatment with Radioactive Iodine (RAI) or surgery.

Aim: Report our experience in a pediatric third level center with radioactive iodine (RAI) and its effectiveness as definitive treatment of Pediatric GD.

We reviewed retrospectively the hospital record of 151 patients with hyperthyroid syndrome due to GD who were followed between 2003 and 2016. The study group was formed by 51 patients who received RAI.

Results: (mean ±SD): Age at first consult was 12.89 years (3.32), they were 38 female (74.5%) and 13 male (25.5%).

The patients who received RAI were treated first with MMI for average 29.27 months (±18.19). Mean TRAB title before RAI was 103.1 U/L (±129.1 U/L).

At the time of initial RAI the patients were 14.99 y (±2.67).

Indications for RAI were persistence of GD with MMI (48.21%), relapse after cessation of MMI (26.8%), bad compliance to MMI (16.1%) and adverse events to MMI (8.9%).

Forty-two patients received only one dose and nine patients (female: male 8:1) required a second dose of RAI. One patient underwent thyroidectomy after first dose of RAI.

Dose of RAI was calculated to induce hypothyroidism; first RAI dose was 12.47 mCi (±3.24) and second dose 11.22 mCI (±2.9).

Thirty-two patients achieved remission with a single dose in 4.40 m (±2.67) and eight after the second dose in 4.12 m (±2.85). Ten patients abandoned follow-up and returned with hypothyroidism.

80% of patients that achieved remission after a single RAI dose did so within 6 months.

As final outcome of treatment, 47 (92.2%) patients progressed to hypothyroidism.

Conclusion: We found RAI therapy is effective as definitive treatment of pediatric GD, achieving hypothyroidism in most of our patients. We found no correlation between age and time to remission and RAI dose and time to remission.

Given RAI's high effectiveness, it's important to ensure a close follow-up of patients after this treatment to avoid prolonged untreated hypothyroidism.

P-32

Neonatal Thyrotoxicosis: An Endocrine Emergency Rarely Recognized

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Thyrotoxicosis is a rare disorder in newborns; frequency is <1% of childhood hyperthyroidism. Maternal Graves'disease is the main risk factor.

Reviewed medical records of newborns in last 2 years in our hospital; we got 3 patients with thyrotoxicosis. We emphasize the importance of early recognition of this disease.

Case 1: He was born at term by caesarean section for acute fetal distress, was SGA; required resuscitation. Mother received levothyroxine during pregnancy. 3rd day of life he was irritable, tachycardic and appeared a heart murmur. Diagnosis: Heart Failure. Despite treatment, persisted tachycardic (HR 220x`), increased irritability, tremors, exophthalmos. Thyroid profile at 5th day of life was TSH <0.004 mcU/ml, FT4 >6 ng/dl, FT3 17.4 ng/dl, with antithyroid antibodies and TSI elevated. Diagnosis: thyroid storm. Immediately he received: lugol, methimazole and propranolol. He improved at 24 hours, continued with methimazole and propranolol. Thyroid profile improved at two weeks: FT4 1.88 FT3 7.76, TSH 0.006. Two months later: TSH 0.25, FT4 0.61, treatment was stopped. He is one year old, remaining euthyroid.

Case 2: Patient was born premature by caesarean section due maternal HELLP syndrome. At birth, he had respiratory distress, diagnosis: probable sepsis. 10th day, he had tachycardia (HR 180), exophthalmos. We requested thyroid profile: TSH <0.004, FT4: 4.39, FT3 6.43, antithyroid antibodies and TSI high. Immediately he received methimazole and propranolol, two days later improved. He was treated until two months of age (TSH: 1.34, FT4 0.7). He is 6 months old and remains euthyroid, with negative antibodies.

Case 3: Mother with preeclampsia, without known thyroid disease. Patient was born at term. 1st day of life, he had tremors, irritability and mild exophthalmos. Diagnosis: probable sepsis.10th day, had tachycardia and symptoms persist. We requested thyroid profile: TSH <0.004, FT4:5.1, TSI high. Started treatment with methimazole and propranolol. He improved and continued treatment until 3 months of life. He remains euthyroid, without treatment (TSH 1.64 FT4 0.93).

All patients are male. Two of them were born of mothers with hypothyroidism who had Graves' disease treated with radioactive iodine before pregnancy. In the last patient, mother was diagnosed with Grave's disease in postpartum.

Neonatal thyrotoxicosis is a life threatening condition rarely recognized and can be confused with other diagnoses such as sepsis or heart failure. If we don't diagnose timely and start treatment immediately, the outcome will be catastrophic.

P-33

Unilateral Graves' Orbitopathy in a Pediatric Patients Clinically Euthyroid

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Grave's disease (GD) is rare in childhood; however it is the most common cause of hyperthyroidism in children and adolescents. Graves's orbitopathy (GO) is the most common extrathyroid manifestation of GD but it can be present in 5 to 10% of euthyroid patients. The GO pathogenesis is still enigmatic, the evidence indicates that anti-TSHR antibodies are probably responsible for the genesis of the GO, there are poor genetic influences and a strong association with cigarette exposure. The most common clinical manifestations of the GO are upper eyelid retraction, proptosis, periorbital edema or erythema and conjunctival injection. The diagnostic evaluation should include a complete ophthalmological exam, evaluation of thyroid function and imagenological assessment (CT, MRI and US).

An 8 year-old boy presented with painless right exophthalmos without diplopia for a month period. Initially the ophthalmologist evaluated the patient; the CT reports a right eyeball protrusion and an increase in periocular soft tissue. MRI evidence pre- and postseptal right orbit commitment regarding with possible idiopathic orbital inflammatory disease, with differential diagnosis of non-Hodgkin lymphoma, leukemia or histiocytosis infiltration. Endocrine evaluation was requested, he was clinically euthyroid but his thyroid profile showed a persistent subclinical hyperthyroidism (FT4 1.35 ng/dL, FT3 3.81 pg/mL and TSH 0.023 mIU/mL) with antibodies TPO and TGB negatives. TRABS were positive (6.91 U/L). The thyroid scintigraphy shows a mild diffuse hyperintense goiter. Other organic, infectious and tumoral causes were ruled out during evaluation. In the clinical follow-up the patient had a marked improvement in his exophthalmus only with symptomatic treatment but still persists with subclinical hyperthyroidism.

Unilateral pure GO is rare; usually it progresses and becomes bilateral. This unilateral presentation in a clinically euthyroid patient is unusual in pediatrics. The clinical approach and diagnosis represented a challenge and always is necessary to rule out other causes. This case allows us open the spectrum of presentation of GO in children and helps to understand the behavior in order to facilitate the diagnosis.

P-34

Good Agreement between Two Methods – Of 1st- and 3rd-Generation – For the Detection of Autoantibodies to the Thyrotrophin Receptor (TRAbs)

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Introduction: Graves' disease (GD) is the most common cause of hyperthyroidism in children, caused by autoantibodies that bind to the TSH receptor and stimulate the signal transduction cascade.

Measurement of TRAbs is therefore used to confirm the diagnosis of GD. Currently, traditional radio-binding assay methods are being replaced by automated methods.

Aim: To evaluate agreement between two methods to measure TRAbs in different diagnosis-related groups.

Subjects and Methods: A total of 98 serum samples from 98 patients seen at our center aged (X±SD) 9.7 ± 5.27 years (ys); sex M/F: 32/66. Patients were divided into four diagnosis-related groups: Hyperthyroidism (HT) n = 40, 11.0 ± 4.45 ys; Hypothyroidism due to chronic lymphocytic thyroiditis (CLT) n = 10, 13.1 ± 3.50 ys; Non-autoimmune hypothyroidism (NAH) n = 25, 5.7 ± 5.87 ys; and Autoimmune disease with normal thyroid function (ADNT) n = 23, 10.5 ± 4.22 ys.

TRAbs were assessed by two methods: 1st-generation TBII assay RSR (RSR) cut-off point <10% and 3rd-generation anti-TSHR assay using the Cobas electrochemiluminescence Roche Diagnostics (ECLIA) cut-off point <1.75 IU/L. ATPo and ATgU were assessed using chemiluminescent immunoassay Immulite 2000–Siemens. For statistical analysis Passing-Bablok regression, contingency tables, and Cohen's Kappa coefficient (K) were used.

Results: The methods showed a positive correlation with significant deviation from linearity ($p < 0.01$). Overall, K was good (K = 0.70); however, in 11 samples (11.2%) disagreement was observed. Indeed at least one thyroid autoantibody (ATPo/ATgU) was detected in these samples 7/11 (63.6%). In all diagnosis-related groups, K was good to almost perfect (HT K = 0.70; CLT K = 1.00), for methodological reasons K could not be calculated in NAH and ADNT, disagreement was greatest in HT at 20% (disagreement % CLT = 0.0; NAH = 7.7; ADNT = 4.3). In samples with discordant results TRAbs levels were near the cut-off point.

Conclusions: In spite of the different characteristics of the methods, acceptable agreement was found. In the diagnosis-related groups TRAbs levels were similar for both measurement methods, in samples with discordant results TRAbs levels were near the cut-off point. The methodological shift to a 3rd-generation automated method seems to be reliable for the diagnosis of GD.

P-35

Incidence of Childhood Ophthalmopathy in 157 Patients with Graves' Disease. Clinical Implications

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Introduction: Childhood Graves' ophthalmopathy (GO) manifests with: proptosis, exophthalmos, and eyelid retraction. Unlike adults, in children these manifestations resolve when the patient becomes euthyroid.

Aim: To determine the prevalence of GO in a cohort of children and adolescents with a diagnosis of hyperthyroidism and to define the frequency according to age and sex. To analyze the correlation between response to antithyroid treatment and the presence of GO.

Material and Methods: A retrospective descriptive study was conducted assessing 157 children and adolescents with autoimmune hyperthyroidism seen between September 2005 and May 2012. Mean age at diagnosis was 10.78 ± 3.17 years.

Results: In our series, the frequency of GO was 44.6% (n:70), 55.4% was younger than 10 years of age with a statistically significant difference ($p = 0.043$).

The difference in sex was not statistically significant ($p = 0.74$); GO was found in 45.2% of the female patients and in 41.9% of males.

T3 ($p = 0.0001$), fT4 ($p = 0.0006$) and TRAb ($p = 0.308$) levels at diagnosis were significantly higher in patients with GO.

The presence of GO in patients with hyperthyroidism was predictive of a worse response to pharmacological treatment (p:0.002).

All but one patient resolve GO when became euthyroid. The latest required specific ophthalmological treatment with corticosteroids and surgical decompression.

Conclusion: In our series, the frequency of GO was 44.6%, being more common in younger children. These patients present with higher levels of T3, fT4, and TRAb. The presence of GO is predictive of a worse response to medical treatment.

If vision is not at risk, children with GO should be managed conservatively.

P-36

Therapeutic Outcome of Children and Adolescents with Graves Disease

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Introduction: Graves disease (GD) is the most common cause of hyperthyroidism. The management of the disease in children and adolescents is still debated.

Objective: To evaluate the outcome of therapeutic measures of children and adolescents with GD and identify predictors of disease remission.

Methods: A retrospective analysis of clinical and laboratorial parameters as well as the treatment provided was conducted with patients followed-up in a single pediatric endocrinology service in Brazil, between 1993 and 2015. Data were retrieved from medical records. SoftwareSPSS was used for statistical analysis, with a significance level of 0.05.

Results: At diagnosis, all the 20 patients were eutrophic, 65% of them were female with a mean age of 9.6 ± 3.9 years. Most of them presented with adrenergic signs and symptoms (90%), goiter (80%) and ofthalmopathy (60%). All had low serum TSH, elevated free T4 and positive TRAB levels (done in 65% of patients). The initial treatment was antithyroid drugs (ATD), 95% methymazol (MTZ), for an average period of 1.5 years (0.1–8.0). There was a moderate negative correlation between age at diagnosis and the duration of the ATD treatment ($r=-0.63$; $p < 0.003$). Two patients (10%) presented severe side effects under MTZ. Three patients were still using ATD. In contrast, seventeen had already discontinued the treatment. Among them, eight (47%) achieved disease remission (seven remained in euthyroidism for an average period of 6.7 ± 3.8 years and one developed hypothyroidism). The remaining nine who failed in achieving remission (53%) went to radioiodine therapy (RAI) and evolved into hypothyroidism. No patient underwent thyroidectomy. There was no difference in the age at diagnosis, in initial levels of TSH and free T4 and in the duration of ATD use among patients who achieved remission and those who did not ($p = 0.54$; $p = 0.44$; $p = 0.37$ and $p = 0.60$, respectively).

Conclusions: Treatment with ATD for an average time of 1.5 years led to a long time remission rate of 47%. In contrast, most patients didn't benefit from this therapy and RAI was necessary, with a high success rate. Predictors of disease remission were not identified.

P-37

Recombinant PTH (rPTH) in an Adolescent with Severe Hypoparathyroidism after Thyroidectomy

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Hypoparathyroidism is a disorder characterized by hypocalcemia and hyperphosphatemia by decreased or absent secretion of PTH. The most common cause is total thyroidectomy by inadvertent removal of the parathyroid glands. It is usually treated with calcium and vitamin D analogs.

A 14 year old female patient was admitted with thyroid storm, treated with methylmercaptoimidazole (MMI) 50 mg/d and propranolol 120 mg/d. Physical examination revealed a critical condition, tachycardia, arterial hypertension, no fever and goiter. Laboratory test: Leukocytes: 10.800/mm^3; T3: 529 ng/dl; T4: 25.1 ug/dl; FT4: 4.51 ng/dl, TSH: 0.06 mU/ml, negative antibodies, TRAb: 73%. MMI was gradually increased to 120 mg/d, propranolol to 240 mg/d, with no adverse effects and intravenous hydrocortisone was added. Intestinal malabsorption was discarded. She presented a psychotic crisis. Total thyroidectomy was performed. Prior to surgery Lugol, Lithium and vitamin D was administrated. Histological examination revealed bilateral multifocal papillary carcinoma classical variant without angiolynphatic invasion, a free lymph node neoplastic infiltration and two parathyroid glands. TNM: T1aN0Mx. Postsurgical laboratory was PTH: <10 pg/ml, T3: 161 ng/ml; FT4: 2.18 ng/dl and at 24 hours post Ca i: 1.13 mmol/L, P: 6.0 mg/dl, Mg: 1.5 mg/dl, Vitamin D: 23 ng/ml. Hypoparathyroidism was diagnosed. Calcium gluconate was increased up to 20 g/d and 1, 25-dihidroxyvitaminD up to 3 μg/d because of sustained hypocalcemia. Magnesium sulfate and vitamin D3 was administered. Once month later, euthyroid with levothyroxine and rPTH treatment she normalized serum calcium at 48 hours and she was given hospital discharged with rPTH. She had a normal systemic examination. She received rhTSH prior ablative dose of radioyodo131 (100 mci), confirming uptake in the thyroid bed.

Conclusions: rPTH replacement therapy was useful in this case of severe hypoparathyroidism that do not respond to conventional therapy constituting an option to reduce days of hospitalization and to improve the quality of life.

P-38

Predicting Hypocalcemia Post-Thyroidectomy with Intraoperatory PTH in Children: Validation of a Proposed Algorithm and Improvement in Hospitalization Days

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Background: In a previous report we proposed and algorithm with intraoperatory PTH at 5 and 60 minutes post thyroidectomy (TX) (PTH-5) (PTH-60) for predicting hypocalcemia (Freire et al, Surgery 2015)*.

Objetives:

To validate our cut-off values as predictors of hypocalcemia.

To evaluate the impact of the propose strategy on:

- Reduction on the occurrence of clinical and/or biochemical hypocalcaemia.
- Reduction on the period of hospitalization post TX and serum calcemic controls (sCa+).

Methods: Patients were prospectively classified according to their risk of hypocalcaemia in:

G1: High risk: PTH-5: ≤16 pg/mL or PTH-5 16–20 pg/ml with PTH-60: ≤16 pg/mL; IV Calcium was infused immediately after TX, 1-25OHVit D and oral Calcium were introduced within 24–48 hs after TX according to oral tolerance.

G2: Low risk: PTH-5: >20 pg/mL or PTH-5 16–20 pg/mL with PTH-60: >16 pg/mL, underwent clinical controls of hypocalcemia every 6 h and sCa+ performed when present; sCa+ was checked at 24 and 48 h after TX, if normal, patient was discharged.

Presence of signs/symptoms of hypocalcaemia, days of hospitalization and number of sCa+ in low risk patients were recorded and compared with those of our historical thyroidectomized group (HG) (32 patients, 15 with hipocalcemia)*.(PTH assay: ECLIA, COBAS e-411, Roche Diagnostics).

Results: 21 children, aged (median, range) 12.7 (3.8–19) years, 18 girls) were included. Seven fell in G1 and 14 in G2. Five patients from G1 remained asymptomatic and had transient hypoparathyroidism. The remaining 2 developed mild hypocalcemic symptoms with definitive hypoparathyroidism. None of G2 patients developed hypocalcaemia due to hypoparathyroidism, 1 hyperthyroid girl had mild hypocalcemia related to hungry bone syndrome. Hospitalization lasted 3 (4–6) days in G1, vs. 6 (3–18) days in HG ($p < 0.01$). G2 remained hospitalized 2 (1–3) days and their sCa+ controls were 2 (1–4) vs. 5 (4–6) in HG ($p < 0.001$).

Conclusions: This study has validated our proposed algorithm to identify patients at risk of hypocalcaemia post TX and allowed avoiding hypocalcaemia, decreasing days of hospitalization and calcemic controls post-TX. Therefore, this strategy consequently reduced health costs related to the surgical procedure.

P-39

Hypophosphatasia: Experience in the Multidisciplinary Team in a Referral Paediatric Hospital in Buenos Aires Argentina

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Hypophosphatasia is a rare heritable metabolic disorder characterized by defective mineralization of bone and/or teeth in the presence of reduced activity of serum alkaline phosphatase. More than 300 different mutations within the ALPL gene that encodes the tissue-nonspecific isoenzyme of alkaline phosphatase have been reported. The clinical spectrum range from stillbirth to fractures of the lower extremities in adulthood at mild end or even no bone manifestations. Different clinical forms are recognized according to the age of onset and severity as perinatal, infantile, childhood adult, and odontohypophosphatasia. The prevalence of severe forms of the disease has been estimated to be 1/300,000 births in Europe. In our 20 years as a skeletal dysplasia multidisciplinary team, in a referral paediatric Hospital in Buenos Aires Argentina we detected three perinatal forms, one infantile and one with odontohypophosphatasia. The follow up of two patients, a 8 years old girl that was diagnosed at 8 months old with perinatal form due to craneosynostosis, poor mineralized bones, severe short stature and development delay and a 3 years old boy, infantile form with premature loss of primary dentition, rickets and deformity, bony craneosynostosis and delay in motor development milestones are reported.

P-40

Familial Hypomagnesemia with Hypercalciuria and Nephrocalcinosis (FHHNC) Due a Mutation in CLDN19

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Background: FHHNC is an autosomal recessive renal disease characterized by calcium and magnesium wasting. It is caused by mutations in the CLDN16 and CLDN19 genes that encode the tight junction proteins claudin-16 or claudin-19, respectively. Patients exhibit nephrocalcinosis (NC) and progression to renal failure.

The aim of this report is to describe two siblings affected by this rare disease due to a mutation in CLDN19, whose diagnosis was confirmed by specific molecular analysis.

Case Report:

Case 1: A 7 year-old boy with a history of recurrent abdominal pain; he was referred after detection of nephrocalcinosis (NC) in abdominal x-ray and renal ultrasound. Laboratory analysis revealed: mild increment on iPTH (72 pg/mL), elevated serum creatinine, (Barrat Index 88 mL/min/m^2), nomal 25OHVit D, hyperuricemia, normal serum Ca^+ and $PO4^-$ but normal to low serum Mg^{++}. He presented hypercalciuria, microalbuminuria and hypocitraturia in 24-hour urine sample. Ultrasound and TC 99 Smibi scintigraphy of parathyroid glands were normal.

Case 2: A 2 year-old asymptomatic girl; NC by ultrasound was detected by family screening. She presented elevated serum iPTH (189 pg/mL) and similar urine findings as her brother.

Fractional Magnesium Excretion calculated ($FEMg^{++}$) in both were 8.9 and 10.45% (NV: <4%), respectively, fulfilling the clinical phenotype of the FHHNC.

Genetic molecular analysis revealed an homozygous mutation (c.59G>A, p.Gly20Asp) of the CLDN19gene (1p34.2) in both siblings that has been described as the classical Hispanic founder mutation.

Although there is no specific treatment for this disease, treatment with thiazide diuretics was introduced to reduce calciuria and potassium citrate to prevent renal failure progression. Six months after onset of treatment, both patients achieved normal calciuria and stable kidney function.

Conclusion: In FHHNC, the PTH increment is characteristic but not related to a primary disorder of the parathyroid gland. $FEMg^{++}$ was essential to establish the diagnosis and genetic confirmation. The early diagnosis and implementation of specific treatment could modify renal failure progression in those patients and enhance their quality of life.

P-41

Assessment of Bone Mass in Patients with Chronic Liver Disorders

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Introduction: Assessing bone mineral density in a series of patients with chronic liver disorders in order to consider the need for preventing deterioration of bone mass.

Material and Methods: Bone mass by densitometry and laboratory analysis of 13 patients younger than 20 years (: average age 13.23 years) were analyzed. Of all patients 10 have autoimmune hepatitis, sclerosing cholangitis 1, 1 biliary atresia, 1 glucogenosis type 1. Bone mass was assessed by bone mineral densitometry of the lumbar spine by LUNAR team (L2-L4); laboratory and analyzed 25-OH-Vitamin D, calcium levels, phosphoremia, alkaline phosphatase and parathormone. It was also assessed whether taking steroids at the time of evaluation.

Results: Of the 13 patients 10 take corticosteroids (76.92%) with a mean dose of 24.7 mg/day Hydrocortisone. Densitometry in relation to the average Z-score was –1.36. 2 patients had low

bone mass (as measured by Z-score) by definition under 20 years: Z-score less than –2.0 (Z-score of the patient: –2.6 and –3.1). While the rest of patients have bone mass >–2.0; 6 they had a Z-score <–1.0 (mean –1.68). All patients have normal levels of calcium, phosphorus, alkaline phosphatase and serum parathyroid hormone (keep in mind that 8 they took calcium daily (61.53%). When analyzing the levels of vitamin D (the average of all patients was 28.67 ng/ml) it was considered whether they ingested vitamin D; 7 of the 13 patients did (53.84%), however 8 of the 13 patients have insufficient levels of vitamin D (<30 ng/ml, average: 22.94 ng/ml) whereas 50% of them ate vitamin D.

Conclusions: Of the total patients studied them 8 (61.53%) had low bone mass (considering a Z-score less than –1.0) despite receiving a percentage of them calcium as part of treatment. 76.92% of them taking corticosteroids (average hidrotisona 24.7 mg/day). The average vitamin D was insufficient despite that 7 of the 13 the ingested. It is important to do more stress upon the prevention of bone mass in children and adolescents with chronic liver disorders.

P-42

Hypophosphatasia: Case Report

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Hypophosphatasia is an inborn error of metabolism characterized by defective bone mineralization and biochemically by deficient activity of the tissue-nonspecific isoenzyme of alkaline phosphatase. Enzyme replacement with asfotasa alfa, a human recombinant form of alkaline phosphatase was recently approved.

Such deficiency generates alterations in the bone mineralization process. It is estimated that its incidence in general is one in every 100,000 newborns, although in some regions it may be greater. Its presentation spectrum is broad and varied ranging from mild to severe forms of neonatal impairment which may even threaten the life of the newborn. Clinically, it is characterized by a generalized failure in bone mineralization manifested by stunted growth including early loss of deciduous teeth, chest malformations, large anterior fontanelle, etc. In some severe cases, pyridoxal-dependent seizuresmay occur. A marked decrease in alkaline phosphatase activity is characteristic accompanied by normal or elevated levels of calcium and phosphorus with decreased PTH and normal vitamin D.

The case of a 12 year old girl is shown. At 9 months of age, her height and weight < – 3 DE is stunted. Pregnancy was normal with no complications. She experienced delay in motor development requiring physical therapy. There is no history of consanguinity or relatives being affected. Clinically, she presented dolichocephaly, partial absence of teeth, no chest malformations and she was in the final stages of puberty. Radiology andbone densitometry studiesrevealed marked hypomineralization. Biochemical profile: phosphorus: 3.97 mg/dl, very low alkaline phosphatase (30 UI/L), ionized calcium 1.3 mmol/l, total calcium: 9.4 md/dl, creatinine 0.41 mg/dl, PTH: 17.4 pg/ml and hypercalciuria. Renal echography was abnormal. Genetic test has been ruled out.

Conclusion: Hypophosphatasiamay occur in a mild form and late, with no fractures nor chest deformities or seizure episodes. Short height and low bone mineralization together with reduced alkaline phosphatase provide the diagnosis.

P-43

Adolescent with Type 1 Diabetes on Insulin and Dapaglifozin a SGLT2 Inhibitor Developed an Euglycemic Diabetic Ketosis

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Dapaglifozin, an inhibitor of the sodium-glucose cotransporter 2 (SGLT2), increases glucosuria and reduces hyperglycemia, but it is not approved in T1D nor in adolescents. We present an euglycemic diabetic ketosis in 17 years old girl who never had ketones before during 9 years with Type 1 Diabetes (T1D). She was started on Dapaglifozin 10 mg/day expecting to reduce her insulin dose, weight and her clinical hyperandrogenism. As expected she presented polyuria, polydipsia and dry mouth without hyperglycemia. Capillary beta-hydroxibutirate randomly measured was <0.4 nmol/l or undetectable. During 11.5 months on dapaglifozin, she reduced BMI 23.9 to 21.1 kg/m^2, basal insulin 40 to 17 U and metabolic control was improved, decreasing HbA1c 8.3 to 7.5%, mean blood glucose 175 to 161 mg/dl and glucose variability (blood glucose SD) 85 to 77. Suddenly, after 11.5 months on dapaglifozin, she presented with nausea and vomiting. She was on an insulin pump (Medtronic 640G) and continuous glucose monitoring (CGM). The glucose sensor was well calibrated and interstitial glucose readings were concordant with capillary blood glucose. The CGM showed a stable glucose level under 200 mg/dl. Blood glucose was 180 mg/dl, and the pump delivered a correction insulin bolus. She had several vomits without hyperglycemia. Three hours later she was severely dehydrated and fainting. Capillary beta-hydroxibutirate was 4.6 nmol/l and blood glucose 224 mg/dl. She received IV physiological saline fluid (1.8 L), ondansetron, oral carbohydrates and SC insulin boluses. Hydration and general condition improved soon, but despite several insulin doses, ketones production continued during 24 hours. Interestingly the pump was working well and the cannula was not changed, after the ketosis was resolved, she continued using the same cannula with good metabolic control and no ketones. We report an atypical case of euglycemic diabetic ketosis related to Dapaglifozin where CGM confirmed that ketones were present without hyperglycemia. This condition may be life threating and should be suspected in the absence hyperglycemia.

P-44

Real Life Impact of Changing a Traditional Blood Glucose Meter to a Meter with a Built-In Automated Bolus Calculator in Children with Type 1 Diabetes

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All our patients are trained in multiple daily insulin injections, whereas calculation of insulin doses is challenging for many children. In 2014, our public hospital, that provides the same meter to all affiliates, changed the traditional meter (TM) (Accuchek Active/Roche) to a meter with a built-in bolus calculator (MBC) (Free Style Insulinx/Abbott).

Our aim is to describe the real life impact of changing a TM to a MBC on metabolic control, among children who did not choose to have this meter and are not being paid in a study to use the devise.

We review the medical records and meter downloads of 45 children with Type 1 Diabetes (honey moon excluded), who had an HbA1c before and within 6 months from the meter change and had respond a brief poll regarding their meter preference.

Children were 13.7 ± 3.5 years old, 76% with pubertal development, 59% male, had diabetes during 4.9 ± 2.2 years and a mean HbA1c 9.5 ± 2.1 (%).

Subjects classified as who increased or decreased HbA1c after changing the meter, are shown in the table. We found no differences in gender, age at diabetes onset, presence of pubertal development or in the poll answers, where 97% believed that the use of the MBC could ameliorate glucose control, 97% trusted the MBC and 100% preferred the MBC compared to the TM.

In population studies the highest HbA1c is attained around 16 years old, since our cohort is 12.8 years old we expected a sustained increase in mean HbA1c but no significant change was observed (9.5 ± 2.1% on TM and 9.3 ± 2.1% on MBC).

All subjects preferred the MBC and those who improved HbA1c (59%), were older, had longer duration of diabetes and had higher previous HbA1c. The MBC has been helpful to our patients.

P-45

Does Excess Weight Modify the Expression of Insulin Resistance in Subjects with Family History of Type-2 Diabetes? A Study in Adolescents from a Chilean Birth Cohort

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Introduction: Along with obesity, the incidence of type-2 diabetes (DM2) has increased in recent years, including children and adolescents, due to changes in lifestyle, diet and exercise. The early presence of DM2 predispose to cardiovascular disease and death in early adulthood. Insulin resistance (IR) is an important determinant in the development of cardiovascular diseases and DM2. A genetic susceptibility to injury of β-cells might explain DM2 in early ages. While IR in young people is associated with family history of DM2 (FHDM2), other environmental and biological factors might contribute to its phenotypic expression. We aimed to determine whether weight status is more salient than FHDM2 in predicting insulin sensitivity in adolescents.

Methods: Cross-sectional study in 534 16 years-old adolescents, of middle-to-low SES, from a Chilean birth cohort. FHDM2 was reported by the participant's parents/legal guardian. Anthropometric variables were measured in duplicate and fasting blood tests were performed. Body-Mass Index, fasting blood glucose and insulin were measured. HOMA-IR was estimated and values ≥2.6 were considered IR, according to previous studies in this population. ANCOVA was conducted to model the effect of FHDM2 on participants HOMA-IR levels, after adjusting for weight status and sex.

Results: 72% of participants had FHDM2 in parents/grandparents, 38% had excess weight (23% overweight and 15% obese) and 17% had IR. Adolescents with excess weight had higher values of HOMA ($P < 0.05$), especially the obese group (HOMA-IR = 3.4). Having FHDM2 in ≥3 first-degree relatives was significantly associated with higher values of HOMA-IR in participants with overweight and obesity. The association was positive but non-significant in normal weight participants.

Conclusion: In Chilean adolescents of mid-to-low SES, there was a high prevalence of FHDM2 in first degree relatives. FHDM2 predicted higher levels of HOMA-IR only in excess weight participants. Weight status might modify the influence of FHDM2 in the expression of IR. Funding: NHLBI/NIH (grant R01HL088530).

Table 1. Characteristics of subjects that increased or decreased HbA1c after changing the TM for the MBC (for Abstract P-44)

Change in HbA1c (%)	DM duration (year)	Age (year)	HbA1c (%) on TM	HbA1c (%) on MBC
Increased 41	3.9±2.3	11.7±3.0	9.0±2.1	10.1±2.2
Decreased 59	5.7±3.1*	13.7±3.5*	9.8±2.2*	8.8±2.0**
Total Group 100	4.9±2.9	12.8±3.4	9.5±2.1	9.3±2.1

* $p < 0.05$; ** $p < 0.01$.

P-46

Association between Early Life Events and Precocious Development of Type 1 Diabetes

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Introduction: Type 1 Diabetes (DM1) is believed to develop as an autoimmune disease in genetically susceptible subjects following exposure to environmental factors. These environments factors could be associated with the rising incidence of DM1, especially in the age group between 0 and 4 years of age.

Objective: The aim of this study was to evaluate the relationship between age of diagnosis, early life events and social economic factors in patients who attended a Brazilian pediatric endocrinology service.

Materials and Methods: Data was obtained from the Pediatric Diabetes Group of the University Hospital through a standardized questionnaire. Information obtained included: age at diagnosis, perinatal factors (gestational age, delivery type, birth anthropometry, mother's age at birth), first-year feeding (time period of breastfeeding, time of introduction of cow's milk, solid foods and gluten), sickness until 12 months old and socioeconomic factors (parents degree, number of people in the house, socioeconomic status). We used the software SPSS version 18.0 for comparisons.

Results: Data was obtained from 663 children and adolescents diagnosed with DM1 who attended the University hospital between 1969 and 2015. Analyzing the records from 283 patients who provided information about the number of people living at the same house at the time of diagnosis, an association was observed between DM1 before 5 years old and a higher number of people living at the same house (OR: 2.41 CI 95%: 1.45–3.98 $p < 0.001$). We found no association between perinatal factors (n = 332), first year feeding (n = 226), sickness before 12 mo (n = 289), and other socioeconomic factors with the development of DM1 before 5 years of age.

Conclusions: In our study, we observed an association between living in crowded house and developing DM1 in a younger age. The Acceleration Theory could explain this finding, considering that children living in worse sanitary conditions are more susceptible to infections at a younger age. However we didn't find association of DM1 before 5 years old with other related events like duration of breastfeeding or getting sick before 1 year old. Studies with larger populations could clarify this information.

P-47

Assessment of Therapeutic Education in Type I Diabetes Children by Two Different Modes: Workshops and Camps

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Introduction: Therapeutic education of diabetes patients is an ongoing and essential process that starts at diagnosis to optimize treatment outcome and improve quality of life. Such education should provide knowledge, develop skills ability and induce changes in attitudes.

Objective: To evaluate the impact on knowledge about treatment pillars and metabolic control in a group of type1 diabetes children through group games limited to two different educational modes.

Materials and Methods: Cohort study between two groups with therapeutic equipment intervention: patients attending educational workshops (G1) and patients attending an educational camp (G2). Two educational workshops took place from August to November 2014, lasting 2 hours each, followed by a session of physical activity. The first one was developed at the beginning of the month and the second at the end. The camp took place from May 22 to 25th 2015. The following topics were addressed in both workshops with games modality: insulin therapy, importance of metabolic control (hypoglycemia, hyperglycemia, variability), identification of nutrients (carbohydrate counting and selection). A 20 items questionnaire was performed. Maximus level of qualification was 20 points. Games used in both groups were similar. The analyzed variables were: previous HbA1C, 6 months later HbA1C, and knowledge questionnaire pre and post event. Statistics: Student's T test.

Results: G1: 27 children (M:13, F:14) with mean chronological age (CA) 10.78 ± 2.38 SD years, and G2: 19 children (M:9, F:10) with CA 11.53 ± 1.39 SD were evaluated. Significant differences were found between knowledge acquired in both groups. In G1 they achieved 12.93 ± 3.17 SD points pre workshop, and 15.7 ± 2.93 SD post workshop ($p = 0.002$); in G2 14.42 ± 3.24 SD pre camp and 17.16 ± 2.14 SD points post camp ($p = 0.004$). No significant differences were found between HbA1C previous and post intervention in both groups. There were no significant differences in acquired knowledge between workshops and the camp ($p = 0.07$).

Conclusions: Educational activity improved knowledge in both groups of type 1 diabetes children, although metabolic improvement was not achieved. Educational activities are of great importance for the diabetic patients to assume an active and responsible role about their treatment.

P-48

School Performance in Children and Adolescents with Type 1 Diabetes

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Hyperglycemia may affect cognitive functions but the impact of Type 1 Diabetes (T1D) on academic achievement is controversial.

Our aim was to examine the relation between school performance and metabolic control in children with T1D, and to compare their academic achievement with their peers.

We review clinical data on 66 children with T1D. School grades from year 2015 were obtained from the national registry and were correlated with parameters related to hyperglycemia exposure and metabolic control.

The academic qualifications of each subject with T1D were compared with the mean grades of peers from the same kind of school (public, private o subsidized private) and location.

Children were 13.4 ± 2.9 years old, 83% with pubertal development, 60% female, had diabetes during 5.3 ± 3.2 years, a mean HbA1c 8.6 ± 1.9, controlled capillary blood glucose 3.2 ± 1.2 per day, 26% had hypothyroidism under treatment and 32% had mental health issues. In Chile school grades range is 1 to 7. Subjects mean grades were: total 5.6 ± 0.7, math 5.2 ± 1.1, language 5.2 ± 0.7 and history 5.2 ± 0.9.

Average marks showed no correlation with HbA1c or with diabetes duration. Interestingly we found a significant correlation ($p < 0.05$) between school grades and number of capillary blood glucose readings per day, Pearson correlation coefficient 0.25, 0.41, 0.52 and 0.58 with total, math, language, and history respectively. No association was observed with hypothyroidism or mental health disturbances and school grades.

Characteristics of children whose grades were below or over the mean of the peers are shown in the table. We found no significant differences between both groups in any variable.

In this small group of children, T1D, HbA1c an diabetes duration were not associated with a decrement in school performance. Children who checked capillary blood glucose more often showed better school grades.

P-49

Peripheral Precocious Puberty as a Clinical Manifestation of Adrenocortical Carcinoma: Case Report

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Adrenocortical carcinoma has an incidence of 0.2 to 0.3 cases per million a year in children with bimodal age distribution, peak of presentation in children under 5 years and a sex ratio of 1.5–2.5: 1 female vs. male. Despite being a rare condition in childhood, it causes major endocrine disorders and poor prognosis of survival depending on the stage.

Male patient 2 years old, with no history of importance, who was admitted due to a clinical evolution of 1 year occurrence of left subcostal abdominal mass, painless and the length and girth increasing of the penis. On physical examination, the patient's weight was 17 kg (p > 97) Z+2.48, size 96.4 cm (p > 97) Z+2.1, BMI 18.2 (p85-90) Z+1.73. No hypertension or tachycardia were detected. An 8x8 cm tumor painless mass was found in the abdomen left flank with hard consistency fixed to deep planes extending to lumbar region. Genital somatometry: penis length 10 cm, 7.5 cm penis girth, PVI 44.8 cc (Z+17.4) RT 2.57 cc (Z+1.1) 2.57 cc LT (Z+1.09), no pubic hair growth or Cushing syndrome clinical data. Laboratories 17OHP 2.5 ng/mL, androstenedione >10 ng/mL, DHEA 42.3 ng/mL, DHEAS >1000 ug/dL, ACTH 37.1 pg/mL, cortisol AM 16.3 ug/dL, cortisol PM 1.01 ug/dL, urinary cortisol 57.6 ug/24 h, renine 18.6, FSH 0.1 mUI/mL, LH 0.2 mUI/mL, testosterone 96.2 ng/dL, BHCG <2.0 ng/mL, AFP 1.68 UI/mL, TSH 3.9 U/mL FT4 0.8 ng/dL. Abdominal CT Heterogeneous left adrenal mass with calcifications displacing adjacent structures. PET (18 DFG) without metastases. A tumor resection is performed with pathology report of adrenocortical carcinoma with high-grade invasion of the capsule and vessels.

The functional adrenal cortical carcinoma is a 60% functional tumor with a very broad spectrum of presentation according to its hormone type production. In pediatric age groups a secretion of one or more hormones can be found. Also, an isolated androgen secretion clinically translated into precocious puberty of peripheral origin is very frequent. This forces an immediate approach, taking into account the need for timely treatment, as it goes along

Table 1. Characteristics of children whose grades were below or over the mean of the peers (for Abstract P-48)

School grades (%)	HbA1c (%)	DM duration (year)	Age at onset (year)	Blood glucose/day (n)
Below 49	8.8±2.0	4.9±3.0	8.6±3.2	2.9±1.2
Over 44	8.1±1.2	5.3±3.4	8.3±3.3	3.4±1.2

with prognosis in this type of tumors. In addition, when suspicion of adrenortical carcinoma, it is necessary to discard the excess of adrenal hormones like cortisol or catecholamines that might trigger comorbidities during presurgical and postsurgical intervention.

P-50

Cushing's Syndrome Due to Pigmented Primary Nodular Adrenocortical Disease (PPNAD): A Challenge Diagnosis in a Young Patient

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Background: PPNAD is a very rare cause of Cushing syndrome (CS) in children and its diagnosis may be very challenging. Herein we report on a very young boy presenting with classical features of CS, including severe life-threatening blood hypertension and infections, caused by PPNAD.

Case Report: A two-years-old boy presenting with excessive weight gain, acne, axillary odor, hirsutism, and behavioral and mood changes for up to nine months. He presented with typical signs of CS including moon face, facial acne, hirsutism, mild virilization with pubertal Tanner stage G1Ph2, and tachycardia. Blood hypertension was severe and very difficult to manage, reaching up to 170x120 mm Hg. Biochemical investigation excluded exogenous CS (basal plasma cortisol 25 mcg/dL-698 nmol/L) and confirmed ACTH-independent (ACTH = 2.4 pg/mL-0.53 pmol/L) endogenous CS (morning plasma cortisol post-1 mg DEX = 23 mcg/dL-634 nmol/l). Abdominal MRI reveal slightly enlargement of both adrenals with a small isolated 5 mm nodule on left side. Then, the diagnosis of PPNAD was suspected. Left adrenalectomy was performed with intraoperative frozen section examination, which revealed architectural changes suggestive of PPNAD. Following, bilateral adrenalectomy was completed and the diagnosis was confirmed by pathology. After the adrenalectomy, the patient received stress-covering Hydrocortisone doses, which was subsequently reduced to physiological dose. Patient's outcome was favorable, with rapid improvement of acne and tissue infiltration but the regression of hypertension took longer time. He was discharged under oral glucocorticoid and mineralocorticoid replacement. Initial investigation clinical, biochemical and imaging screening (skin, testis, heart, thyroid, and pituitary) did not reveal signs of Carney complex. Molecular analysis did not reveal germ line pathogenic variants in the PRKAR1A gene.

Conclusion: In children, the diagnosis of CS may be challenging, mainly in the case of PPNAD, which accounts for less than 2% of ACTH-independent CS. In this situation, imaging exams may not show gross abnormalities and the diagnosis is only confirmed by pathology. In addition, up to 70% of the PPNAD patients and/or their families present or will develop other signs of Carney complex, a serious life-threatening condition.

P-51

Cushing Disease in Children: Experience of Five Years

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Cushing's disease (CD) is the most frequent form of ACTH-dependent Cushing's syndrome (CS), is a rare diagnosis in pediatric age. Near of 10% of new cases per year are reported in patients under 18 years old.

We report four patients with CD, they were diagnosed in the last five years in our hospital. We describe clinical characteristics which suggest this disorder for early recognition.

Four patients get diagnosed and treated in our hospital; three females and one male, the average age at diagnosis was 9.37 years (5.4–12.75). The most frequent clinical manifestations were: obesity and short stature in all of patients (4/4); striae rubra in three of four patients; hirsutism and acne in two (2/4) and hypertension in two patients.

In all patients was required: Bone Age (delayed in all). Urinary free cortisol was taken by twice (abnormal in all), cortisol am, pm and at midnight (all were elevated with rupture of circadian rythm). In three patients were perform dexamethasone suppression tests: Dexamethasone suppression test at low dose (LDDST: Dexa1) and high dose dexamethasone (HDDST: Dexa 8) all tests were abnormal in these three patients.

Selar MRI of these patients showed pituitary macroadenoma only in one of four (1/4) so it was necessary Bilateral Inferior Petrosal Sinus Sampling (BIPSS) in three of four to locate increased secretion site. Final diagnosis in all patients were CD-ACTH dependent.

Three Patients had hypophyseal surgery. Two of three patients required a second surgery because persistence of Cushing disease. Histopathology confirmed the pituitary adenoma in 3/4 patients but one patient is waiting for surgery. All patients with surgical treatment required replacement therapy according to their needs.

CD rarely occurs in children. Obesity, short stature and delayed bone age are the clues to suspect the diagnosis. Children with these characteristics must be studied for rule out this disease. Early diagnosis remains a challenge for the pediatrician.

P-52

Bilateral Inferior Petrosal Sinus Sampling: Diagnostic Difficulties in Pediatric Cushing Patients

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Introduction: Bilateral Inferior Petrosal Sinus Sampling (BIPSS) is the gold standard procedure to differentiate between Cushing Disease (CD) and Ectopic ACTH Syndrome (EAS), with a false negative rate of 1–10%, mainly because of technical difficulties. To reduce false negatives, previous investigators used prolactin as a marker of succesfull catheterization, and they 'normalized' peak ACTH IPS/P ratio (Central/Peripheral) in case of unsuccesfull catheterization.

Objective: Describe the use of prolactin during BIPSS in 2 pediatric patients with Cushing Syndrome (CS).

Material and Methods: ACTH and prolactin were determined at Right IPS (RIPS), left IPS (LIPS) and femoral vein (P) al time 0 and 3, 5 and 10 minutes after 10 mcg of desmopressin. The following indexes were calculated: ACTH RIPS/P; LIPS/P at each time and PRL IPS/P at time 0. Basal ACTH IPS/P >2 or peak ACTH IPS/P >3 was indicative of CD (positive test), while values below were indicative of EAS (negative test). A ratio PRL IPS/P above 1.8 (ipsilateral to the peak ACTH IPS/P ratio) was indicative of succesfull cathetherization, If PRL IPS/P was <1.8 (suggesting unsuccesfull cathetherization) we 'normalized' peak ACTH IPS/P by dividing it by the basal ipsilateral PRL IPS/P ratio; values >0.8 suggested CD, whereas those <0.6 implied EAS.

Results: Both patients are boys (10–13 years old), with CS (UFC p1:295; p2: 3500 mcg/24 hs, ACTH p1 65; p2 150 pg/ml, negative dexamethasone test and indeterminate MRI). They underwent BIPSS: Patient1: basal ACTH/P ratio of 1.08 and peak ACTH 1 (negative); basal PRL IPS/P ratio 1 (unsuccesfull catheterization) and normalized peak ACTH 1 (>0.8, consistent with CD). Patient 2: basal ACTH/P ratio of 1.33 and peak ACTH 2.13 (negative); basal PRL IPS/P ratio 1.53 (unsuccesfull catheterization) and normalized peak ACTH 1.39 (>0.8, consistent with CD). Both patients were surgically treated and CD was confirmed by biopsy. They remained asymptomatic.

Conclusion: In our patients PRL determination and normalization of ACTH improved diagnostic accuracy. Patients had negative BIPSS but positive after correction. We suggest using PRL during BIPSS as cathetherization of IPSS is troublesome in pediatric patients and a lower cathether positioning may be sufficient.

P-53

Congenital Adrenal Hyperplasia and Ehler-Danlos Syndrome: Molecular Analysis in Two Non Related Patients

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Background: The contiguous gene deletion syndrome, CAH-X, was described in 8.5% of congenital adrenal hyperplasia (CAH) patients with a TNXA/TNXB chimera resulting in deletions of CYP21A2, encoding 21-hydroxylase necessary for cortisol biosynthesis, and TNXB, encoding the extracellular matrix glycoprotein tenascin-X (TNX). There are three TNXA/TNXB chimeras described that differ in the junction site, as well as point mutations in TNXB gene resulting in TNXB haploinsufficiency or dominant negaive effect, disrupted transforming growth factor-b (TGF-b) signaling, and an Ehlers Danlos syndrome (EDS) phenotype. Recently, it has been described a biallelic form of CAH-X syndrome.

Objective: Molecular characterization of two non related patients with CAH and EDS phenotype. TNXB haploinsufficiency analysis in 12 CAH patients and/or carriers of CYP21A2 deletion was also carried out.

Methods: Ten most common mutations in CYP21A2 gene were analysed by allele-specific polymerase chain reaction, restriction fragment length polymorphism (RFLP). Large rearrangements (CYP21A2, TNXB) were detected by southern blot and MLPA analysis.

Results: Two CYP21A2 molecular alterations, CYP21A2 –8pb mutation in one patient and macroconversion in the other along with TNXB haploinsufficiency in both were detected, confirming EDS. Molecular studies revealed in the two patients, compound heterozygous for a TNXA/TNXB quimera, characterized by a 120 bp deletion in TNXB in exon 35.

Analysis in 12 CYP21A2 deletion alleles revealed TNXB haploinsufficiency in 6/12 alleles (50%).

Conclusion: We could characterize CYP21A2 molecular alterations and the presence of TNXA/TNXB chimera resulting in TNXB haploinsufficiency in both patients with EDS phenotype. Moreover, a high frequency of TNXB haploinsufficiency was found in deletion carrier alleles in our population. Clinical evaluation for connective tissue dysplasia should be routinely performed in CAH patients, especially those harboring a CYP21A2 deletion.

P-54

Polyglandular Syndrome Type 1 Autoimmune: Report of an Unusual Family Case

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The polyglandular syndrome type 1 autoimmune (SPA-1), a rare autosomal recessive disorder, caused by mutations in the AIRE gene (regulator autoimmune) and production of defective protein. The classic triad is characterized by chronic mucocutaneous candidiasis, hypoparathyroidism and adrenal insufficiency, though many organs may be affected resulting in varied clinical. We present a case of girl with 3 years and 6 months, referred for evaluation of generalized arthralgia 1 year. I had chronic diarrhea for 6 months, recurrent urinary infections and oral thrush and perineal before 1 year of age appropriate development weight and height. ICU admission in the previous month consultation symptomatic hypocalcemia. Physical examination showed no phenotypic changes, except for nails with grooves and Chvostek positive signal. Laboratory tests revealed hypocalcemia, hyperphosphatemia and hypocalciuria. During clinical follow-up at 4 years and 8 months old, other laboratory abnormalities were found: cortisol and aldosterone with values below the reference level and ACTH above the reference level, characterizing adrenal insufficiency. Faced with such celebrations held family genetic research and found mutation in AIRE gene (mutation deletion type with frameshift change in homozygous – deletion of 13 nucleotides at positions 967–979 of the AIRE gene) in the patient, brother and mother, however these two asymptomatic. Father and other brother did not have the mutation. Observed so that the parents had a matching polymorphism and children affected due to uniparental disomy mutation. Diagnosis for SPA-1 in the patient was performed in the presence of primary components of the syndrome, manifested early, associated with positive genetic research to mutation. The treatment should be performed for multiple endocrine diseases, maintaining screening for early diagnosis. Our patient was treated with calcitriol, prednisolone and fludrocortisone, with good clinical and laboratory control. Affected relatives keep on clinical and asymptomatic follow-up.

P-55

Primary Growth Hormone Insensitivity (Laron Syndrome): A Brazilian Familial Case Report

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Laron's syndrome (LS) is an autosomal recessive disorder characterized by insensitivity to growth hormone (GHI). There are only eight cases reported from South and Central America. We report two cases of a consanguineous family from Brazil. Parents are first cousins and had three children. They have no complaints and no remarkable family history. The oldest sibling was referred by short stature and reduced growth rate when she was four years old. She was born at full term with 3.450 kg (0.47 SD), 46 cm (–1.69 SD) and head circumference of 34 cm (–0.2 SD). According to previous data, her height has being maintained below –2 SD from birth. The physical examination revealed weight of 9.9 kg (–4.7 SD); length of 80.2 cm (–5.67 SD) and a typical fascies with broad forehead and low nasal bridge. She presented a bone age of 2 years. Most of the workup performed for disclosing short stature etiology was normal: blood count and kinetics of iron, urinalysis, antibodies for Celiac Disease, renal and hepatic function, acid-base equilibrium, calcium, phosphorus, alkaline phosphatase, sweat test and lipid metabolism, cortisol, TSH and free T4, but IGF1= 12.3 ng/mL (RV: 33.5–171.8) and IGFBP3= 0.70 mcg/mL (RV: 1.0–4.7) were low. She underwent two GH stimulation tests, clonidine followed by insuline tolerance and both exhibited stronger responses: peak GH level >40 ng/mL. Currently, she is 7 years old, 15.8 Kg (–3.45 SD) and 96.1 cm (–5.93 SD). Target height is 152.7 cm (–1.74 SD). The middle sister is 5 years old, 104.5 cm (0.7 SD) height, and had no complaints. The youngest sister was first examined at the age of one year. She presented with more typical features of LS: beyond the typical fascies she has sparse hair. She has 66.4 cm (–5.51 SD) length, 7030 g (–3.65 SD) and her biochemical profile is also suggestive of GHI: IGF1=79.0 ng/mL (RV: 55.0–303.0), IGFBP3 = 0.50 mcg/mL (RV: 0.7–3.9), and basal GH level = 11.48 ng/mL. Analysis of GH receptor mutations is in progress. The girls are not under treatment because the only effective therapy for LS is replacement with recombinant biosynthetic IGFI, which is not approved in Brazil.

P-56

Final Adult Height of Patients with Disorders of Sex Development (DSD) Associated with Sex Chromosome Abnormalities 45,X/46,XY or 45,X/46,X,+Y Variants

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Introduction: Patients with chromosomal 45,X/46,XY DSD present variable phenotypes. The external genitalia can range from normal female to a wide range of ambiguous genitalia. Turner syndrome stigma can be present and short stature is the main clinical sign of patients with 45,X/46,XY mosaicism.

Objective: Our aim was to determine the final height (FH) in patients with 45,X/46,XY DSD and compare the effect of rhGH in the FH.

Patients and Methods: Retrospective data of 25 patients, 12 with male social sex and 13 with female social sex were collected. Patients karyotype were: 45,X/46,XY, 45,X/46,X,mar(Y) and other karyotypes in 16, 7 and 2 patients respectively. Time of rhGH therapy and bone age at the beginning of the treatment were evaluated. Target height (TH) was established in 72% of patients and did not differ between the groups ($p = 0.10$). Student T test were used to analyze the difference of FH between rhGH.

Results: Ten patients (6 males, 4 females) received 0.15 U/Kg/day of rhGH for 58.2 months (51.2 in females vs. 62.8 in males) and 15 patients (6 males, 9 females) did not use rhGH. Mean FH was 150.4 ± 6.4 cm vs. 162.0 ± 6.6 cm in males and 148.7 ± 6.2 cm vs. 153.4 ± 5.6 cm in females of the rhGH untreated group and rhGH treated group, respectively. Mean FH was significantly higher in the male rhGH treated group than in the male untreated group ($p = 0.011$), but not for female group ($p = 0.20$). A significant difference ($p = 0.002$) in the mean FH was also observed when rhGH treated patients (158.6 ± 6.9 cm) vs. untreated patients (149.4 ± 6.1 cm) were compared without stratifying by sex. The FH/TH were 0.93 and 0.95 for males and females rhGH treated and 0.89 and 0.94 for males and females untreated, respectively.

Conclusion: The treatment with pharmacological doses of rhGH of DSD patients with sex chromosome abnormalities 45,X/46,XY or 45,X/46,X,+Y variants improved final adult height.

P-57

Growth Hormone Deficiency in the Transition Phase: Retesting with Insulin Tolerance Test and GHRH Plus Arginine

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Background: Retesting for GH secretion is needed to confirm the diagnosis in adolescents or young adults with childhood-onset GH deficiency (COGHD). The cut-off for a normal GH response to different provocative tests is not well established, although a recent consensus suggested the limit of 6 μg/L after insulin tolerance test (ITT, Ho et al., EJE, 2007).

Aim: To define the cut-off for GH peak after ITT or GHRH+arginine (GHRHarg) for the diagnosis of permanent GHD during the transition phase.

Patients and Methods: A total of 129 patients (median age 17.3 y, IQR 16.0–18.6 y) were included in the study. ITT was performed in 99 subjects, and GHRHarg in 122. IGF-I was measured in all subjects. Fifty-one had idiopathic GHD (iGHD), in 49 GHD was secondary to an intracranial tumor (tGHD) and in 29 it was congenital (cGHD). Isolated GHD (IGHD) was found in 83 patients whereas 46 had multiple pituitary hormone deficiency (MPHD). According to the current literature, subjects with a GH peak >6 μg/L and >19 μg/L after ITT or GHRHarg, respectively, were considered normal. Receiver operating characteristic (ROC) analysis was used to evaluate the optimal GH cut-offs and the diagnostic accuracy of provocative tests.

Results: tGHD and cGHD had similar biochemical and clinical characteristics and were considered as one group (sGHD). Patients with sGHD were significantly shorter, heavier and had lower GH peaks to both ITT and GHRHarg as well as lower IGF-I than the patients with IGHD. The optimal cut-off for ITT resulted 5.3 μg/L (sensitivity 68%, specificity 94%, AUC 0.88). The cut-off for GHRHarg which best discriminate MPHD from IGHD resulted 13.8 μg/L (sensitivity 80%, specificity 82%, AUC 0.86). The GH response to GHRHarg resulted inversely correlated with the BMI-SDS while the response to ITT did not. IGF-I values <-1.9 SDS (sensitivity 49%, specificity 96%, AUC 0.77) and <-1.5 SDS resulted the best cut-off for differentiating between iGHD and sGHD and between IGHD and MPHD, respectively.

Conclusions: We have validated the suggested cut-off of 6 μg/L after ITT and shown that the best cut-off for GHRHarg is lower than previously reported. IGF-I has low accuracy.

P-58

Argentinian References for the Assessment of Body Proportions from Birth to 17 Years of Age

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In clinical practice, body disproportion suggests the presence of skeletal disease.

Aims: To obtain age references for head circumference/height ratio (HC/H) and sitting height ratio (SHR) in Argentina and to study the usefulness of sitting height/height ratio to detect body disproportion in a group of children with skeletal dysplasia.

Methods: Correlations between the values of sDS of the measured variables were calculated. The 3°,10°, 25°, 50°, 75°, 90° and 97° centiles were estimated from a sample of 4818 girls and 4803 healthy children aged 0–17 years with the LMS method, using the Box-Cox transformation to normalized data distribution for each age.

Results: Median SHR decreased from 0.67 at birth to 0.57 at age 4, with mild decrease until 12 years, reaching 0.52 y 0.53 values for boys and girls respectively. Median HC/H ratio decreased from 0.45 at age 6 to 0.34 at 17 years in both sexes. The Z scores of SHR adjusted by age in 20 children with hypochondroplasia, under 1 year old, was a better predictor of disproportion than SHR not adjusted by age.

Conclusions: SHR by age better reflects the biological variables that influence growth from birth and allow earlier detection of body disproportion, being a useful tool in the clinic assessment of children with idiopathic short stature.

P-59

Growth and Puberty in Children with Congenital Hypothyroidism Detected by Neonatal Screening Program

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Introduction: Growth and puberty in children with congenital hypothyroidism (CH) detected by neonatal screening programs have been analyzed. The aim of this study was to describe pubertal development and final height (FH) in early treated patients with permanent CH. Study design. Twenty–six patients detected by neonatal screening were followed longitudinally between 1995 and 2013. They were studied from diagnosis and start of treatment up to the age of final height. The following parameters were assessed: age, levothyroxine dose (LTd), TSH and T4 at start of treatment; age, height (H), LTd and bone age (BA) at puberty onset; age and H at menarche. We also calculated final height (FH), total pubertal growth and target height (TH). BA was assessed by Greulich and Pyle method. Statistical analysis. T-test, Mann-Whitney test and Spearman correlation.

Results: Chronological age at diagnosis was 15. 5 days (12.3–17.8). Initial LTd was 13.2 mcg/kg/day (12.4–14.2). Serum TSH was 274.2 uUI/ml (100–450.8) and T4 was 1.85 ug/dl (0.48–3.98). LTd at puberty onset was 2.83 mcg/kg/day (2.34–3.39). BA was 10 years in females (10–11) and males (9.8–11.1). Other parameters are shown in table 1.

There were no significant differences between genders in height at puberty onset, FH and TH; and between FH SDS and TH SDS. There wasa high correlation between FH SDS and TH SDS (rho = 0.76; p = 0.001).

Conclusions: Pubertal development and menarche in these CH patients occurred within normal limits for age with according BA. FH was in the normal range and it was similar to target height.

Table 1. Growth parameters in CH children (for Abstract P-59)

	F	M
Age puberty onset (years)	10.03 (9.07–10.52)	10.77 (10.26–11.70)
H puberty onset (cm)/SDS	138.4±5.92/0.24±1.33	145.3±7.64/0.44±1.14
Age/H menarche (years/cm)	12.04±1.13/154.1±4.78	
FH (cm)/SDS	159.4±5.22/–0.35±0.7	173.4±7.87/0.2±0.92
Total pubertal growth (cm)	21.04±4.74	28.07±9.92
TH (cm)/SDS	159.6±4.56/–0.54±0.7	172.6±3.49/–0.55±0.48

P-60

Severe Acquired Hypothyroidism in Childhood and Adolescence. Impact on Growth

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Introduction: Hypothyroidism due Hashimoto's thyroiditis is the most common cause of thyroid dysfunction in children and adolescents. A delay in the diagnosis greatly affects growth and development of the child.

Aim: To describe a series of pediatric patients with severe hypothyroidism and its impact on growth.

Material and Methods: A retrospective, descriptive study was conducted analyzing 79 patients (62 girls) younger than 18 years (2–16 years of age), seen between 2008 and 2014 with severe hypothyroidism (TSH levels >50 microIU/ml), without other disorders that may affect growth. All patients received thyroid replacement after diagnosis. Evolution of growth up to final height (FAH) was analyzed in a subgroup of patients (ANOVA, n = 33).

Results: Patients who presented with goiter, 56% (n = 45), showed higher height at diagnosis than those who did not. Mean height SDS: 0.2 vs. –2.42 ($p < 0.0001$). Precocious puberty was observed in five girls (7%). Patients who reached final height (n = 33, HSDS < –2.5) were divided in four groups, pubertal or prepubertal at diagnosis, with or without short stature (SS) None of them received growth hormone therapy. Height differences over time were associated with initial height ($p < 0.0001$), showing a positive outcome for those who had SS at diagnosis. FAH in the pubertal group with SS (mean HSDS:-2.82) was significantly less than in the prepuberal with SS group (mean SDS:-1.52) ($p = 0.0311$).

Conclusion: Late diagnosis of severe hypothyroidism has a negative impact on FAH. Treatment of hypothyroidism plus adjunctive growth promoting therapies should be an alternative to improve potential growth especially in the pubertal group.

P-61

Predictive Factors for Height Gain in Predicted Height in Girls with Central Precocious Puberty Treated with GnRH Analogues

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Introduction: GnRHa is the first line treatment for Central Precocious Puberty (CPP), however there are controversies in the selection of patients who would benefit from treatment and what factors could influence the therapeutic response.

Objective: To evaluate predictive factors for height gain in predicted height in girls with precocious puberty treated with GnRHa

Methods: A retrospective study was performed; 17 girls with CPP treated with GnRHa were included. The following variables were assessed: anthropometry, bone age (BA), target height (TH), duration of GnRHa treatment, and predicted height (PAH) by Bayley Pinneau method. For statistical analysis Pearson's linear correlation was used and multiple linear regression analysis; It was considered statistically significant $p < 0.05$.

Results: The mean age at the beginning of treatment was 7.8 years (7.3–8.4, CI 95%), the average BA was 10.1 (9.4–10.8 95% CI), the average TH was 155 cm (152–157.3, CI 95%), the average pre-treatment PAH was 150.4 (146.9–155.2, CI 95%), post-treatment PAH was 154.0 cm (150.4–159.6, CI 95%), the average gain height was 3.6 cm (1.2–6.1, CI 95%), the average duration of GnRHa treatment was 2 years (1.5–2.5, CI 95%). Brain MRI was normal in 75% of girls and abnormal in 25%. The increase in post-treatment PAH was significant ($p = 0.0067$), and correlation was found between the target height and the post-treatment PAH ($r = 0.51$, $p = 0.035$). Predictive factorfor gain in PAH was BA under eleven at the beginning of treatment adjusted to the TH, no correlation was found with pre-treatment height, BMI and duration of GnRHa treatment.

Conclusions: Girls with bone age under eleven at the beginning of GnRHa treatment was the only predictive factor for Height Gain in PAH.

P-62

Multiple Pituitary Hormone Deficiencies – Experience of a Single Pediatric Endocrinology Group

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Background: Hypopituitarism is defined as the partial or complete deficiency of one or more hormones produced by the pituitary gland. The prevalence of hypopituitarism ranges from 300 to 455 per million inhabitants. The clinical manifestations of hypopituitarism are variable, depending on the severity and the amount of deficient hormones. The treatment is directed to substituting the deficient hormone(s). The aim of this study is to show our casuistic on congenital causes of panhypopituitarism (multiple pituitary hormone deficiencies – MPHD).

Methodology: This is a retrospective descriptive cross-sectional study of patients with multiple congenital pituitary-hormone deficiencies seen in the Department of Pediatric Endocrinology. We correlated the initial clinical features with the laboratory and radiologic data.

Results: 37 patients with MPHD, 67.5% male, with mean age of 12.4 years old (2–18 years old). The initial clinical manifestations were: short stature 56.7% (21); hypoglycemia 18.9% (7); micropenis 18.9% (7); cryptorchidism 13.5% (5); visual alterations 13.5% (5), polyuria 8.1% (3) and others 24.3% (9) – one of these patients was diagnosed septo-optic-dysplasia (SOD) while intrauterus. The mean age of the diagnosis was 4.7 years. The MRI find-

ings were: absence/hypoplasia of corpus callosum 10.8% (4), absence/hypoplasia of septum pellucidum 8.1% (3), hypoplastic/ectopic pituitary 70.2% (26) and no alterations 10.8% (4). Seven patients have SOD (Morsier's Syndrome).

Conclusion: MPHD is a rare condition and the diagnosis is based on the combination of the following features: clinical history and physical examination, baseline lab work-up, provocative tests checking the hypothalamo-pituitary axis and magnetic resonance imaging (MRI). Every child with hypopituitarism should be evaluated for the whole pituitary function that, if present, indicates specific substitution hormonal therapy.

P-63

Septo-Optic Dysplasia: Hormonal and Neuroradiological Abnormalities in Case Series

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Introduction: Septo-optic Dysplasia (DSO) is a rare congenital disorder characterized by the presence of at least two components of the triad: optic nerve hypoplasia (ONH), midline brain abnormalities and pituitary hormone deficiencies. Most cases are sporadic of unknown cause. Mutations in genes as HESX1, SOX1, SOX2 and OTX2 have been identified in few cases. Other genetic and environmental factors may contribute to the etiology. Most commonly reported associations include young maternal age and/or primiparity. The clinical diagnosis is based on the presence of the classical triad features. About 30% manifests the complete triad. Hypopituitarism is reported in 60–80%, and the GH deficiency (GHD) is the most common endocrine disease.

Study Design and Patients: A retrospective study of case series. The study describes age at diagnosis, gestational history, frequency of triad features, neuroimaging abnormalities, and hormonal dysfunctions.

Results: The medical records of thirteen (7 females) patients mean age 9.13 ± 6.69 years were reviewed from June 2004 to May 2016. The mean maternal age was 26 ± 7.80 (19–41) years, 4 had history of primiparity and 3 had premature delivery. ONH was diagnosed bilateral in 8/13 and unilateral in 2/13 at average age of 1.39 ± 1.91 years. Nine had impairment vision or blindness. Neuroimaging revealed corpus callosum agenesis/hypoplasia (n = 7), absent/hypoplasic septum pellucidum (n = 8), ectopic posterior pituitary and/or anterior pituitary hypoplasia (n = 7). Ten patients presented development impairment. Ten patients had hypopituitarism (76.92%). ACTH deficiency was the most common (n = 9/69.23%), followed by central hypothyroidism (n = 7/53.85%), diabetes insipidus (n = 5/38.46%), GHD (n = 4/30.77%) and gonadotropin deficiency (n = 2/15.38%). One patient had isolated ACTH deficiency (7.69%). Age at diagnosis of the first hormone deficiency ranged from birth to 7.75 (2.48 ± 3.16) years. Seven (53.85%) patients had the complete triad.

Conclusions: The complete triad was present in half of the patients and the most frequent hormonal dysfunctions was ACTH deficiency. These data are in disagreement with that reported in the literature.

P-64

Short Stature and Hypothyroidism in a Child with Nail-Patella Syndrome. Case Report and Review of the Literature

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Background: Nail-Patella syndrome (NPS) (OMIM: 161200) or hereditary onycho-osteodysplasia is an autosomal dominant disorder characterized by skeletal anomalies, such as patellar aplasia/hypoplasia, iliac horns on X-ray as well as nail dysplasia, renal and ocular abnormalities. Males and females are equally affected. The diagnosis is based on clinical and radiological findings and confirmed by the identification of a heterozygous pathogenic variant in the LMX1B gene. Management of these patients involves continuous follow-up and treatment of the orthopedical, ocular and renal problems that may occur. The association with short stature has been barely described in the literature.

Case Report: An eleven-year-old boy with a height of 130 cm (–2.01 DS) was referred to our Endocrine Unit at the age of 2 years due to hypothyroidism (TSH 7.46 mIU/ml, FT4 1.33 ng/dl). At that time dysplastic nails and disproportionate short stature were detected (Upper-to-lower segment ratio of 1.6). His target height was 170 cm (father's height 167.8 cm, mother's height 159.3 cm). Radiological abnormalities initially suggested a skeletal dysplasia. Repeated thyroid hormones confirmed a primary hypothyroidism without anti-thyroid antibodies and a normal thyroid ultrasound. Levothyroxine treatment was initiated. The diagnosis of NPS was confirmed with a single nucleotide variant in the LMX1B gene that causes a nonsense mutation (c.661C>T; Arg221Ter). His father presented a similar phenotype with normal stature. Bone age was consistent with his chronological age. Laboratory screening for short stature and a GH stimulation test were normal.

Conclusion: We present a child with proven NPS associated with short stature (–2.01 DS) and hypothyroidism. We found just a few publications that described this association. Further studies are needed to find if the LMX1B gene plays a role in the development of both dorsal structures and thyroid tissues.

P-65

Prospective Genetic Analysis of Patients with Congenital Growth Hormone Deficiency by Massive Parallel Sequencing Using Target Gene Panel

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Background: Congenital GH deficiency (GHD) can be isolated (IGHD) or combined with other pituitary hormone deficiencies (CPHD). The identification of mutations has clinical implications for the management of patients and genetic counseling.

Objective: To prospectively conduct a molecular-genetic analysis in genes associated with IGHD or CPHD.

Method: Forty patients with IGHD (n = 8) or CPHD (n = 32) were studied using target gene approach. Targeted regions (involving 26 genes associated with GHD and 57 genes associated with growth disorders without GHD) were captured using Agilent Sure Select technology. Sequencing was performed with Illumina Next-Seq. Variants were analyzed considering allele frequency in the normal population and in silico prediction. Copy number analysis for targeted resequencing method was used to evaluate gains or losses in the regions of interest.

Results: We identified 31 rare allelic variants (excluding synonymous) located in exons or splice sites in 17 of 26 genes associated with GHD in 19 patients. Of these, 3 variants were considered pathogenic: one patient was compound heterozygous for a PROP1 mutation c.[109+1G>A];[301_302del]; the second one, was heterozygous for a TGIF1 variant (c.707A>T:p.Q236L) and the last one was a compound heterozygous [c.2212C>T:p.Q738]; [c.494G>T:p.R165L] for LZTR1 gene – a gene recently associated with Noonan syndrome (NS). Although, this last patient had clinical criteria for diagnosis of Noonan syndrome, he also presented laboratory data compatible with isolated growth hormone deficiency. There is only one Noonan Syndrome gene (SHOC2) previously associated with IGHD but he was negative for this condition. Five other variants in 5 different genes (LHX3, GLI2, GHSR, SHH and PROKR2) were considered possibly pathogenic, mainly because several in silico models predicted them to be deleterious. In the majority of cases, only one pathogenic or possibly pathogenic mutation was identified in each patient. One patient, however, is heterozygous at two loci: one variant in GLI2 and another in SHH, indicating a possibly digenic condition.

Conclusion: The panel established the diagnosis of 3 patients and possibly 5 additional patients with GHD. The patients with negative results are candidates for whole exome sequencing.

P-66

Report of Critical Values in Pediatric Endocrinology: Clinical Utility

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Critical values (CV) of laboratory are biochemical determinations that require immediate information to the physician, in order to determine if an urgent clinical care is necessary. Several accreditors of Health Systems include them among the quality parameters.

The process includes: biochemical report, medical evaluation, registration and conduct.

Objective: To analyze the reported CV observing the frequency of different determinations and evaluating how many of them which required only passive conduct were useful.

Retrospective observational study. We reviewed electronic pediatric medical records (MR) (May/2013, June/2016) in an University Hospital.

Laboratory CV based on international recommendations were: cortisol <5 mcg/dl, TSH >100 mIU/L, T4>20 mcg/dl, free T4<0.4 ng/dl, T3>4 ng/ml.

We analyzed biochemical determination, age, requesting service (endocrinologist, pediatrician or specialist), medication, registration in MR and adopted conduct (active or passive). Active conduct (A): medical intervention and/or notification to the family. Passive conduct (P): no medical intervention.

The laboratory performed 67.166 determinations, of which 86 were reported as pediatric CV (cortisol determinations 68 [79%], TSH 11 [12.7%], T4 3 [3.4%], Free T4 3 [3.4%], T3 1 [1.1%]). Request services were: endocrinology 50%, pediatric 23.25% and another speciality 26.75%. It was observed a high rate of report in MR performed by laboratory (97.5%), and clinical request services (79%) with non-registration only in 2 cases (2.3%).

70% of cases required active conduct. 30% of cases need only passive conduct; 96% were cortisol dosages, which 44% were with systemic or inhaled corticosteroid treatment and 20% with a history of previous treatment. Passive conduct was significantly associated with a history of corticosteroid therapy (P 64% vs. A 27%, p0.004); active management was associated with age less than 3 months (A 60% vs. P 24% p0.002) and the condition of admission to hospital (A 51% vs. P 28% p0.05).

MR registration of CV is considered a measure of hospital quality. More future medical education is needed to define the usefulness of cortisol dosage in order to decrease misuse of human and health resources.

P-67

Male 46,XX/45,X: Turner Syndrome Mosaicism in a Boy?

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Introduction: Turner Syndrome in male phenotypic patients has rarely been described in the literature so far, and its association with Disorders of Sexual Developement (DSDs) can be considered an interesting subject for pediatric endocrinologists.

Objective: Describe a curious case of DSD with male phenotype and a Turner syndrome mosaicism.

Case Report: A.L.M, 10 months old, sent to Pediatric Endocrinology service by the Pediatric Surgery unit due to ambiguous genitalia. At the age of 5 months, the child had had clinical suspicion of Down's syndrome and revealed karyotype 46,XX, despite presenting male phenotype and being raised as a boy. In our service were observed labioescrotal fusion, 3 cm falus, 0.5 ml and 1.0 ml gonads, almond-shaped eyes, round face, ogival palatus and nipple hypertelorism. Pelvic ultrasound showed no uterus, research for the SRY gene was positive while other Y gene markers were negative and a new G band karyotype evidenced 46,XX/45,X [30]. Abdominal video laparoscopy did not show müllerian structures and gonad biopsy revealed bilateral testicles. Testosterone level after stimulation with hCG was 422 ng/dL and others androgenic markers were in the reference range. In the following years, a short neck became evident. The diagnostic hypothesis was then made for DSD and Turner syndrome variant in a male phenotype. No positivity of thyroid or antiendomisium antibiodies were found, neither kidney or heart malformations, ALT and AST were normal. The child has received growth hormone for six months, due to short stature, that was suspended due to no response. At age 4, received 3 doses of testosterone due to penis size shorter than 2 SD. Currently, the patient is 8 years old, eutrophic, penis size normalized (4.8 cm), and shows learning difficulties.

Conclusion: Turner syndrome in female patients has been widely discribed, including several cromosome mosaicisms and gonadal dysgenesis. However, this patient showed clinical features and cromosomic findings that differ from what is usually seen in 46,XX testicular DSD. The hypotesis of a Turner variant in a 46,XX/45,X boy is discussed.

P-68

Clinical Presentation of Klinefelter Syndrome and Other Causes of Hypergonadotropic Hypogonadism

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Introduction: Klinefelter syndrome (KS) results from one or more additional X chromosome in men and is the most common cause of hypergonadotropic hypogonadism. KS is associated with neuropsychological dysfunction, increased risk of metabolic disorders and mortality from several causes. However, it is not known if the incidence of these complications in KS is different from other causes of hypogonadism.

Methods: Clinical data of 38 men with HH (19 KS and 19 hypergonadotropic hypogonadism [HH] from other etiologies [trauma, infection, cancer, radiation, idiopathic]) followed at the Endocrinology Outpatient Clinic of HCFMUSP were retrospectively collected.

Results: Among SK, the karyotype was 47XXY in 13 patients, 46XY/47XXY in five and 48XXY in one. Median height was 176 cm in SK and 168 cm in HH. Median body mass index was 27.7 kg/m^2 in SK and 24.5 kg/m^2 in HH. Gynecomastia was observed in 36.8% of SK and 26.3% of HH. Cryptorchidism was present in 10.5% of KS and 21% of HH.66.6% of all patients evaluated before treatment had micropenis (median penile length: 10 cm in SK and 9 cm in HH). Median testicular size was 2.1 cm in SK and 3.3 cm in HH. Median hormonal levels were: testosterone,128 ng/dL and 117 ng/dL, LH,18 U/L and 27.1 U/L and FSH, 29.5 U/L and 47 U/L in SK and HH, respectively. Diabetes mellitus or impaired fasting glucose was diagnosed in 31.5% of SK and 36.8% of HH and dyslipidemia in 36.8% of SK and 63.1% of HH. Psychiatric disorders were very prevalent in SK (52.6%), including depression, mental delay and schizophrenia, whereas in the HH group only 15.7% were diagnosed with depression. 38.4% of SK and 42.8% of HH had osteoporosis or osteopenia.

Conclusions: The clinical presentation was similar in both groups except for psychiatric disorders, which were more prevalent in the SK group.

P-69

Descriptive Study of Disorders of Sex Development (DSD): Clinical Series in a Public Hospital

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Introduction: DSD is defined as a congenital condition in which the development of chromosomal, gonadal or anatomical sex is atypical. The incidence is 1/5000 newborn, with a complex diagnosis and treatment, which requires a multidisciplinary comprehensive approach to achieve the best result. There is no national data in our country.

Study Design: Retrospective and descriptive.

Methods: Clinical charts review of DSD patients attended in Endocrinology Clinic of Public Hospital between 1998 and 2016.

Results: 43 patients were included, of which 23 were 46XX DSD (53.5%), 17 were 46XY DSD (39.5%) and 3 sex chromosome abnormalities (7%). Of the 46XX DSD, 22 (96%) corresponded to salt wasting Congenital Adrenal Hyperplasia (CAH) and 1 ovotestis. Prader classification CAH patients were III: 7 patients, IV: 9 patients, V: 3 patients, not register: 3 patients. The diagnostic was done at 21 days (3–120) on average. Adrenal hormone study and ultrasound were performed in all patients to confirm the diagnosis. In the 46XY DSD, clinical presentations were micropenis (M) hypospadias (H) and cryptorchidism (C) with the following combination: 3 M/H/C, 7 M/C, 4 M/H, 1 H/C and 2 bilateral C. They were studied with gonadotropins, androgens, adrenal hormones, SRY, HCG test and testosterone challenge, final diagnosis was done in 5 cases (resistance to androgens, hypogonadotropic hypogonadism, gonadal dysgenesis, bilateral cryptorchidism and bilateral anorchia). The diagnostic was done at 194 days (3–850) on average. In 2 cases feminine sex was assigned. The chromosome abnormalities DSD was 45XO/47XXY in 1 case, presented with M/H/C and müllerian remnants and 45XO/46XY in 2 cases, presented with H/C and laparoscopic biopsy confirm unilateral ovotestis and contralateral inguinal testis, with unicorn uterus and the other case presented with M/H/C without müllerian remnants.

Conclusions: Our results are comparable with international data, with a predominance of 46XX DSD, in which more than 95% were CAH. In contrast, 46XY DSD cases the etiologic diagnosis was achieved in less than 25%, thereby genetic study in this group is desirable. To our knowledge this is the first clinical series report in our country.

P-70

A Case of 46,XY DSD Due to a Novel Mutation in the HSD17B3 Gene

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Introduction: The 17β-hydroxysteroid dehydrogenase type 3 deficiency due mutations in HSD17B3 gene is a rare disorder of sex development (DSD). Molecular analyses of HSD17B3 gene, including structural and functional studies of the HSD17B3 mutant protein may confirm clinical diagnosis in cases of 46,XY DSD.

Purpose: We investigated molecular variants on HSD17B3 gene in a 9 months-old child that was referred to us due to genital ambiguity. The patient had been registered as a boy. He was the second child of a consanguineous couple without familial history of DSD. Laboratorial data and clinical features suggested HSD17B3 deficiency.

Methods: DNA was obtained by proteinase K digestion and phenol/chloroform extraction from peripheral blood leukocytes. HSD17B3 sequence investigation was performed by PCR and Sanger sequencing. Sequence variants have been identified by comparing with the reference sequence. SIFT, PolyPhen-2 and Mutation Taster were used as protein-function prediction tools. The effect of the mutation on protein stability was assessed at DUET web server. Molecular modeling was performed using MODELLER web server program. The 17-beta-hydroxysteroid dehydrogenase X-ray crystal structure available at PDB (ID: 5FYD) was used as template. The modeled image was examined and edited using PyMOL® and Millennium STING (CNPTIA-Embrapa, Brazil) programs. The conservation of the mutated residue was examined by comparison with different mammalian HSD17B3 using ClustalW.

Results: The 46,XY DSD patient was homozygous for the novel p.Gly262Val mutation. The parents were heterozygous. The Gly262 is a highly conserved residue. SIFT, PolyPhen-2 and Mutation Taster scores were compatible with a damaging missense mutation. DUET prediction indicated that Val262 destabilizes the protein structure. No differences in internal contacts between wild-type and mutant protein were observed due to the superficial location of this residue.

Conclusion: The c.785G>T nucleotide change identified in exon 10 of the HSD17B3 gene leads to the p.Gly262Val novel mutation. In silico analysis performed to estimate the severity of this missense mutation confirmed it as deleterious for HSD17B3 enzyme activity. The structural analysis of mutant HSD17B3 can be used to correlate genotypes to phenotypes of HSD17B3 deficiency. However it is necessary to investigate in vitro biochemical abnormalities caused by mutation to confirm functional predictions.

P-71

Two-Year Experience in the Treatment of Gender Dysphoria in a Reference Center in Pediatrics Endocrinology in São Paulo – Brazil

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Introduction: Over the past decade, there has been an increase in the number of gender variant children and adolescents seeking care at gender clinics and centers around the world. For most youth, the natal gender is consistent with their gender identity. However, in a small minority, there is a discrepancy between assigned (or natal) gender and gender identity. The distress that is caused by this discrepancy is called gender dysphoria (GD). For a complete care of these patients, a multidisciplinary team is necessary.

Objective: Describe the experience in gender dysphoria in children and adolescents in a Pediatric Endocrinology Unit of a reference health center in the last two years.

Methods: Retrospective analysis of medical records.

Results: We evaluated 17 patients followed-up in our unit. They represent 18.4% of the group of gender dysphoria followed by psychiatrist clinic. Eighteen percent of them are children and 82% percent are adolescents. The mean age at which patients had their first appointment was 16.25 years, 43.7% were transsexual men (FTM) and 56.2% were transsexual women (MTF). Self-medication was seen in 40% of the patients. The cross-sex hormone treatment used in most of the patientswas Testosterone 200 mg/month for FTM and conjugated estrogen 1.25 mg/day and cyproterone 50 mg/day for MTF with satisfactory results.

Conclusion: As there has been an increase in the number of patients seeking treatment for gender dysphoria, it is important to have more specialized health to improve the care of these patients.

P-72

48,XXYY Syndrome Associated to the Father's Radioactive Contamination during the Cesium Accident in Goiânia – Goiás, Brazil

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Background: 48,XXYY Syndrome occurs in 1:20.000–1:50.000 male births. It used to be considered as a variant of Klinefelter syndrome, but now it is considered as a distinct clinical and genetic entity with increased risks for congenital malformations, additional medical problems and more complex psychological and neurodevelopmental involvement.

48,XXYY Syndrome results from the fertilization of a normal female oocyte (Xm), with an aneuploid sperm (XpYpYp) produced through nondisjunction events in both meiosis I and meiosis II of spermatogenesis. Literature shows that 100% of the triploid gamete is from paternal origin.

We report a case of 48 XXYY Syndrome, whose father was contaminated by radioactive Cesium 3 years before the proband's conception. Since abnormal chromosome segregation during mitotic division has been inducted experimentally by in vitro exposure of human cells to radiation, we hypothesis that the father's cesium contamination might be responsible for this rare occurrence.

Case Report: SFAD, male, second child of a non-consanguineous young couple. His father was contaminated with radioactive cesium 3 years before his conception. At 12 years of age, he was referred to genetic testing due to agenesis of hart palate and nasal septum. At 13 years of age he was referred to the Pediatric Endocrinologist Service. At that moment he presented with: tall stature, eunuchoid body habitus, ocular hypertelorism, epicanthal folds, prominent elbows, cubitus varus, single malformed kidney, bilateral inguinal hernia, pes planus, thoracic vertebrae fusion, bilateral femur-patellar arthrosis, hypergonadotrophic hypogonadism, mild intellectual disability, emotional immaturity, anxiety, impulsivity and obsessive-compulsive behavior. He evolved withosteoporosis (14 y), hypertension, insulin resistance, obesity and dyslipidemia, (18 y), pre-diabetes (23 y), testicular volume of 5 ml as an adult, infertility due to azoospermy. He died at age 24 due to pulmonary embolism.

Conclusion: The recognition of medical, developmental and psychological problems that are more common in sex chromosome tetrasomy and pentasomy conditions, and are associated to 48 XXYY Syndrome is important for early diagnosis and interventions, as a way to reach best outcomes. This is the first reported case of 48 XXYY associated to the Cesium Accident.

P-73

Hyperandrogenism in Adolescent Girls: Relationship with the Somatotrophic Axis

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Objective: To investigate whether ovarian androgen secretion in young postmenarchal girls is related to the function of their somatotropic axis.

Design: Cross-sectional study of adolescent girls.

Patients: We studied non-obese adolescent girls with hyperandrogenism (HA; n = 21) that were matched with control girls (C; n = 25) for chronological age, age at menarche and body mass index.

Methods: We obtained a fasting blood sample for the measurement of serum glucose, insulin, 17-hydroxyprogesterone, dehydroepiandrosterone sulfate, androstenedione, SHBG, total testosterone, IGF-I, IGF-II, IGFBP-I, IGFBP-III Ghrelin, leptin, AMH, LH and FSH during the follicular phase of the menstrual period. In addition, we performed an OGTT to determine blood glucose, ghrelin and insulin levels, and we collected urine samples to measure urinary GH levels.

Results: As expected, the hyperandrogenic girls had higher Ferriman scores (13 ± 4 in HA vs. 1 ± 2 in C p = 0.001) and basal total testosterone (nmol/l) (2.4 ± 0.7 in HA vs. 1.0 ± 0.3 in C, p < 0.001), FAI (FAI 9.2 ± 5.7 in HA vs. 2.4 ± 1.3 in C, p < 0.001), androstenedione (nmol/l) (12.9 ± 4.5 in HA vs. 8.7 ± 2.8 in C, p < 0.001), AMH (nmol/l) (44.0 ± 24.1 in HA vs. 27.7 ± 14.2 in C, p = 0.005), and basal LH levelsmUI/ml) (9.6 ± 7.2 in HA vs. 4.3 ± 3.4 in C, p = 0.001) compared with controls. Serum IGF-I, IGF-II, IGFBP-III and urinary GH did not differ between HA and C. There was a correlation between urinary GH and FAI in the whole group of girls (r 0.29, p < 0.05). In addition, in HA girls FAI correlated with insulin, HOMA and ghrelin.

Discussion: We observed a correlation between urinary GH and FAI in the hyperandrogenic and control girls, suggesting that the function of the somatotrophic axis may influence the secretion of androgens in adolescent girls.

P-74

Hyperandrogenism Secondary to Bilateral Ovarian Stromal Hyperplasia in a Transgender Adolescent

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Among the etiologies of peripubertal ovarian hyperandrogenism, polycystic disease predominates, with a low incidence of androgen-secreting tumors, and other causes of functional hyperandrogenism occurring very rarely. We report the case of a 17-year-old patient who presented with a request to undergo a sex reassignment.

History: Male behaviour since childhood; the administration of exogenous androgens was ruled out in the interview, thelarche at 13 years old, increased body hair since peripuberty, primary amenorrhea (sporadic bleeding under oral contraceptives), hyperinsulinism (65.1 μIU/mL) and hypertension. Legal gender change and bilateral mastectomy one year earlier. Gynecological ultrasound: enlarged ovaries. Normal abdominal and pelvic MRI scan.

Physical Examination: BMI 32.9, male hair distribution pattern (Score Ferriman-Gallwey:31), female genital organs (clitoris 1x0.5 cm). Karyotype 46XX, high total, free and bioavailable testosterone levels: 1.5 ng/mL, 41.5 pg/mL and 0.96 ng/mL respectively. Androstenodione 3.4 ng/mL, DHEAS 1705 ng/mL; SHBG: 15 nmol/L and 17OHProgesterone: 6.0 ng/mL. Normal 17OHP and cortisol response to ACTH test. Bilateral oophorectomy and hysterectomy was performed at the patient's request (Pathology findings: bilateral ovarian stromal hyperplasia). Immunolocalization of 3β HSD showed diffuse positive reaction in the ovarian stromal hiperplasia, confirming androgenic production. Post-surgery (3 months): testosterone normalization (total: 0.19 ng/mL) and 17OHP (0.55 ng/mL), elevated gonadotropins and persistent hyperinsulinism (71 μIU/mL). Therapy with transdermal androgens was initiated at the patient's request.

Discussion: This case is particularly interesting not only for being a rare cause of hyperandrogenism in adolescence but also because bilateral ovarian stromal hyperplasia has been mainly reported in postmenopausal women, who undergo oophorectomy as a treatment of secondary hyperandrogenism. Undoubtedly, surgery is not an option for adolescents, but the fact that this was a transgender patient requesting internal genitalia removal enabled us to make a histopathological diagnosis. The potential role of hyperinsulinism in the development of the hystopathological findings observed in the patient remains controversial. Different series show 5–10% prevalence of 'idiopathic hyperandrogenism' in adolescents and young females; however, an ovarian biopsy that may rule out a condition as the one reported in this case is very rarely performed in this population. Therefore, this condition might be underdiagnosed in adolescent patients.

P-75

Assessment of Insulin Resistance (IR) by Oral Glucose Tolerance Test (OGTT) in Adolescents with PCOS

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Background: Prevalence rates of IR in adults PCOS women have been reported from 44–70%, mostly in obese patients and using surrogate markers of fasting insulin concentration instead of dynamic tests. Information about the frequency of IR in adolescent cohorts measured by OGTT is limited.

Objectives: To evaluate IR frequency in adolescents with PCOS by OGTT. To determine differences in androgenic and metabolic profiles in the presence or absence of IR and obesity. To determine diagnostic efficiency (DE) of HOMA-IR and fasting glucose/insulin index (G/I) in comparison to OGTT to diagnose IR.

Patients and Methods: Prospective cross-sectional study. PCOS adolescents diagnosed according to AES criteria underwent a standard 75-g OGTT where glucose and insulin were measured every 30 min during 2 hs. At baseline, androgens (total and free testosterone, androstenedione, SHBG), lipids (TC, HDL, LDL, triglycerides) and high sensitive CRP (hs-CRP) were measured. IR was defined as a peak insulin >150 μU/mL and/or 2-hour insulin level of >75 μU/mL. Normal cutoffs of HOMA-IR <2.5 and G/I >7 were obtained from 20 normal cycling adolescents. ANOVA analyses was used to compare the results between groups. Data are expressed by mean±SEM.

Results: Twenty three PCOS, chronological age (CA): 16.8 ± 0.40 years with gynaecological age >2.5 years were included. IR diagnosed by OGTT was found in 74% of patients (6/12, 50% with normal BMI and 100% with higher BMI). PCOS were subdivided according to IR and BMI into 3 groups: GA: n = 6, normal BMI without IR; GB: n = 6, normal BMI with IR and GC: n = 11, high BMI with IR. There were no differences in CA, hirsutism, menstrual cycle abnormalities and in the grade of hyperandrogenemia. As expected, GC showed the highest proportion of abnormal values in lipid profiles. GC showed higher hs-CRP (2.1 ± 0.68 mg/L, $p < 0.005$) than GA: 0.56 ± 0.10 and GB: 0.44 ± 0.03 mg/L. HOMA-IR presented DE of 83% and G/I of 82% to diagnose IR defined by OGTT.

Conclusion: High frequency of IR was observed in PCOS adolescents including in 50% of patients with normal BMI. Insulin surrogate cutoffs used could efficiently demonstrate IR. The coexistence of IR and obesity substantially modifies metabolic and inflammatory profiles.

P-76

Proliferative Struma Ovarii in a 12 Year-Old Patient with Recurring Abdominal Pain

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Struma ovarii is an infrequent ovarian tumor that features predominantly thyroid tissue (>50%) in the resected specimen. It is a monodermal teratoma. The maximum incidence is during the 5th and 6th decades of life. Presentation during infancy or youth is exceptional. They represent 0.3–2.5% of ovarían teratomas, and about 0.3% of all ovarian tumors. Risk of malignancy is low. 5–12% may secrete thyroid hormones. We present a 12 year-old postmenarcheal patient with recurrent abdominal pain. Throughout the clinical observation, she was hospitalized four times, one of them due to a flegmonous appendicitis that underwent an appendectomy. Ultrasound and laparoscopic visualization showed what seemed to be a 3.5 x 3.2 cm simple cyst. During her fourth admission due to abdominal pain, a new ultrasound image shows a 9 x 7.7 x 6.3 cm right juxtauterine anaechoic mass, with septa and solid component, with no evidence of vascularization. An ovarian cystectomy was carried out and the pathology report informed Struma ovarii. Microscopy showed ovarían tissue almost totally replaced by thyroid follicles, somedilated with colloid content. A solid follicle area showed cell nuclei of larger size, with increased mitoses (3/10 in high power field). No vascular nor capsular invasion was observed. Literature describes these lesions as potentially malignant. Our patient had normal pre and post surgical thyroid function tests. Although the initial resection preserved the remaining ovarían tissue, when the pathology report was received, the case was discussed at a multidisciplinary meeting to decide whether an oophorectomy should be carried out. The torsion of the remaining ovarían tissue prompted an emergency resection of that ovary 45 days later. It is noteworthy that our patient is younger than previously published cases.

P-77

Ovarian Juvenile Granulosa Cell Tumour in a 14 Year-Old Premenarchial Patient with Galactorrhoea

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Granulosa cell tumour (GCT) is a rare low grade malignant neoplasia representing 1% of ovarían tumours. Two forms have been described: the juvenile and the adult form; the first composes

a 5% of all GCTs. Its maximal incidence occurs during the first two decades of life. Though its most frequent presentation is as isosexual precocious pseudopuberty, it may display abdominal pain, a palpable mass, menstrual cycle alterations, virilization, and amenorrhea, usually of secondary type. Our patient presented with primary amenorrhea (pre-menarchial) and galacthorrhea, at age 14 years and 2 months, to her gynecologist. Her initial blood prolactin levels were 75.8 ng/ml, and after a 20 minutes' rest 67 ng/ml. A gynaecology ultrasound image displayed an hypoechoic mass of 16.5 x 15.4 x 7.5 cm. A right side anexectomy was performed. The pathological report was that of an ovarían tumour of 950 g with evidence of a juvenile granulosa cell tumour exhibiting up to 6 mitoses in 10 high power fields. Various immunohistochemical analyses, including for prolactin, were reported as negative. The majority of GCTs are localized, and may manifest recurrencies within 3 years from the diagnosis, this being related to the extra-ovarian extension, positive peritoneal cytology and rupture of the tumour. Our patient manifested no clinical evidence of hyperestrogenism. Shortly after surgery, the patient had her menarche and the prolactin level became normal. Post-surgical follow-up for 14 months, clinically, by ultrasound and inhibin B levels showed nornal values, with no evidence of tumoral recurrence. Though galactorrhea has been described in some patients with GCT, very few reports mention hyperprolactinaemia. Our patient displayed no clinical evidence of hyperstrogenism (we had no estrogen level before surgery) but we presume that this may have been the stimulus for the hyperprolactinaemia. The immediate menarche after surgery could have been an indirect evidence, as a hormonal deprivation following removal of the tumour.

P-78

The Prevalence of Premature Birth in a City in Southern Brazil during the Period of 2000–2011 and Correlative Factors

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Premature births are those which gestational age is between the 22 and the 36 week and 6 days. In 2011, Brazil had 9.8% of premature births, reaching the top ten countries with the highest rates in the world. This study avaliated the prevalence of premature births in the city of Blumenau (SC, Brazil), in the years between 2000 and 2011. This is a cross-sectional study, conducted on the basis of secondary data available in DATASUS (Brazilian Health System Department of Informatics), which came from the SINASC (Born Alive Information System). Live births with gestational age below than 22 weeks have been excluded from this selective. The variables were the same available in DNV (Born Alive Declaration): mother's age, type of delivery, gestational age, type of pregnancy, child's gender and number of prenatal visits.

Results: It was found that the prevalence of premature births in Blumenau has increased between 2000 and 2011, from 7.24% to 12.22%. There was a significant correlation ($p < 0.001$) when considering the smaller number of prenatal visits (less than 6), double or more pregnancies and cesarean type of delivery. Maternal age with higher prevalence of premature births was 10–18 years and 35–45 years, and no positive correlation with preterm birth ($p > 0.05$) was showed. We conclude that, despite advances in medicine, the prevalence of premature infants is increasing worldwide, in Brazil and even in Blumenau. The availability of treatments such as assisted fertilization may have been promoting the increasing multiple gestations, besides the large number of surgical deliveries, must be considered as risk factors for preterm birth. Besides, the improvement in prenatal care may be considered a protective factor for premature births.

P-79

Parenting Styles and Coping Strategies in Congenital Hypothyroid Children

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Introduction: Congenital hypothyroidism detected early and treated properly does not lead to mental impairment, but requires prolonged treatment, care, and control. As a chronic disease it requires long life treatment and this may influence the bonding between parents and child. This link also influences on the resources of the child to deal with conflictive situations.

Objectives: To describe predominant perceived parenting styles in congenital hypothyroid children from the perception of the child (son) and to identify their coping strategies.

Patients and Methods: An intentional sample of 60 congenital hypothyroid children, detected through neonatal screening and adequately treated since the first month of life, aged 9 to 10 years, was selected and compared with 60 healthy children of the same age that were recruited as a control group. Inclusion criteria were: absence of other concurrent diseases, half day school, parents with a complete high school educational level.

The evaluation was performed with the Argentine coping questionnaire for children aged 9–12 years, Argentina Scale perception of the relationship with Parents and Test Wisc III: comprehension subtest.

MANOVAs were carried out as statistical analysis, with a significance level of $p < 0.002$.

Results: Congenital hypothyroid children perceived the relationship with their mother as democratic based on tight control while the perception of the relationship with their father was based on acceptation.

Regarding to coping strategies the CH children showed a tendency to seek greater support and a tendency to paralyze facing problems.

Conclusion: The tendency to seek greater support and to paralyze while facing conflictive situations could be linked to the greater maternal control. This could be expressed as a psychological and behavioral trait of greater dependence and paralysis that must be taken into account in the monitoring of the CH children's development.

P-80

Thyroid Hormone Resistance: Case Report after 10 Years of Follow-Up

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The resistance to thyroid hormone (RTH) is a rare disease with autosomal dominant transmission, resulting from mutations in genes and THRβ and THRα of thyroid hormones, which commits 80 to 85% of individuals. Affected patients exhibit variable phenotype, depending on the severity of the mutation and diversity of specific response for each tissue and other factors unrelated to the mutation. Some individuals manifest symptoms suggestive of HT deprivation as growth stunting, reduced cognitive abilities and hypercholesterolemia, while other symptoms of excess HT as tachycardia, bone age advance or hyperactivity may also occur. The main clinical data are found to be goiter and tachycardia. We report a female patient, APP, with 10 years of follow-up and treatment, referred at 1 year of age because of low weight gain and low growth rate, tachycardia and irritability. On physical examination presented with normal thyroid, without evidence of goiter. Weight below the 5th percentile and height in the 10th percentile. Laboratory tests, TSH: 3.5 μUI/ml (0.3–5.0) and T4 L: 2.66 ng/dL (0.8–1.4). Molecular study performed through DNA genomic., DNA was submitted to polymerase chain reaction (PCR), sequencing reaction and analyzes using BioEdit software v7.0.9, for TRβ exons 8 9, 10 and 11, the hot spot mutation region of TRβ. The mutation is p.R320G. Different treatments were tried, such as propylthiouracil, metimazole and tri iodine acetic acid (TRIAC). Currently after 11 years she has no clinical symptoms, but has a goiter, with no palpable nodules. Menarche ocurred by the age of 10.8 years. Weight between the 50th percentile and 75 percentile and height at the 50th percentile. Complementary tests showed TSH: 8.05 μUI/ml (0.27 to 4.2), FT4: 2.47 ng/dL (0.93 to 1.7), and bone age of 12 years. Over time there was an improvement of symptoms, and the development was within normal parameters for height and weight. Many aspects of this disease are still open and need to be better understood.

P-81

Total Thyroidectomy in an 11-Month-Old Patient with Family History of MEN2A: A Case Report

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Introduction: Multiple endocrine neoplasia type 2A (MEN2A) is characterized by medullary thyroid carcinoma (MTC) associated with pheochromocytoma (40–60%) and/or primary hyperparathyroidism (20–40%). It is related to activating mutation of the RET proto-oncogene with autosomal-dominant inheritance pattern. MTC is a malignant tumor originally from thyroid parafollicular cells rare in childhood. It is associated with mutation of the RET gene in this age group. In these patients, surgical treatment is the only possibility of cure. We report a case of an 11-month-old patient with a family history of MEN2A mutated identifying the RET gene, treated with total thyroidectomy.

Case Report: DPC, male, referred to the Pediatric Endocrinology service with 5 months old because of family history of MEN2A (father and sister). Father was diagnosed with pheochromocytoma and MTC at 18 years old and identified mutation in the RET gene. Sister, also had mutated RET gene and evolved with increased calcitonin. She underwent thyroidectomy at 2.2 years old, with medullary thyroid microcarcinoma identified in clinical pathology. The patient was asymptomatic, laboratory screening with the following results: Calcitonin 18.5 pg/mL (VR <8.4), thyroglobulin 50.3 ng/mL (VR <35), free T4 1.48 ng/dL, TSH 1 22 μIU/mL and exon 11 sequencing showed RET gene mutation c.1900T>C (p.Cys634Arg). Total thyroidectomy was indicated at 11 months. Pathologic examination showed medullary thyroid microcarcinoma with two focuses in the left lobe and one in right lobe without angiolymphatic invasion. Calcitriol and levothyroxine were introduced, and has been followed up without significant changes.

Conclusion: MTC is the most common finding of MEN2A. Molecular analysis of the RET proto-oncogene in first-degree relatives allows diagnostic advance and is superior to the lab work-up. Depending on the mutation, prophylactic thyroidectomy is indicated early. In the case reported total thyroidectomy was indicated by the presence of the mutation in the RET gene. Despite the absence of significant laboratory, pathology showed the neoplastic changes. This finding reinforces the importance of molecular assessment and its impact on diagnostic anticipation and therefore the improved prognosis.

P-82

Myofibroblastic Tumor of Repetition with Infiltration to Thyroid

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Myifibroblastic tumor, subset of clone mesenchymal neoplasms, known as inflammatory pseudotumor or plasma cell granuloma. Involves a broad spectrum of benign (pseudosarcomas, fibromas, fibromatoses), intermediate (locally aggressive or rarely metastasizing), and malignant (sarcomas). Infrequent in children, incidence 12% of pediatric soft-tissue tumors. Unspecific symptoms and are derived from the affected site. Histological features infiltration of inflammatory infiltrate of plasma cells (lymphocytes, histiocytes, and eosinophils); associated with expression of ALK-1 and IgG4 indirectly. Infiltration of thyroid is exceptionally rare, predominantly in adults. Early diagnosis is essential, for complications, prognosis and different management.

Case Report: Female 16 years old, Oaxaca original, Mexico, background mother DM2, G4 product, normoevolutivo pregnancy, obtained caesarean section, 40 wga, menarche 12 years, regular cycles. Since 11 years old with difficulty breathing and nasal obstruction, external management of INP: 14/03/2013 Biopsy turbinate, nasal septum wall and right, granulomatous histopathologic acute and chronic inflammation. 20/04/2013 right nasal surgery permeabilization, reporting respiratory epithelium tissue and fibrous connective tissue with chronic inflammatory changes. 15/08/2013: FNA submandibular ganglion, report reactive hyperplasia. It comes to INP in September 2013 for rhabdomyosarcoma suspected in hemiface right submandibular region and hepatomegaly. 08/11/2013 and 17/12/2013 tumor resection, histopathological sinus tumor nasofibroblastico with extension bone. March 2016 is valued in Endocrinology service by tumor in neck, at the expense of thyroid gland, normal thyroid function, physical examination: goiter, enlarged thyroid, stone, regular, lymphadenopathy 1 cm left cervical lymphadenopathy chain and 0.5 cm in cervical right. CT scan: thyroid lesion predominantly right and takes the isthmus¸ hypodense, increase ganglionic jugular anterior right chain. 4/07/16 total thyroidectomy, report: myofibroblastic tumor of origin hyoid bone infiltrating thyroid; hormone replacement.

Myofibroblastic tumor is rare in children, with varying symptoms. In this case manifested by increased size and stony consistency of thyroid; with complete resection, considering intermediate tumor, treatment is surgical, to assess chemotherapy or radiotherapy as risk of metastasis. IgG4 elevation favors appearance of systemic fibro-inflammatory in association with ALK-1, however, is not clear association with this tumors, because is most prevalent psudo-inflammatory tumors.

P-83

Characterization of Pediatrics Patients with Thyroid Cancer, Follow-Up to 11 Years

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Introduction: Thyroid tumors are infrequent pediatric malignancies (1.5–3.4%). They are more frequent in females between 7–12 years old. Papillary Carcinoma of the thyroid is the most frequent variation (70%), followed by follicular (20–25%), medullary (5%), and anaplastic or undifferentiated (<1%) being extremely rare pediatric malignancies. Compared to adult thyroid tumors they are more aggressive, with local invasion to cervical ganglions and distant metastasis (lung metastasis). The rate of survival is between 90–100%. The management consists of thyroidectomy followed by radioactive iodine that is indicated to ablate any remnant of the tumor.

Methods: Characterize 7 patients with thyroid nodules and thyroid cancer during endocrine consult between 2000–2015.

Results: We found 7 patients, 5 females, and 2 males, with average age of 10 and 7 years respectively (RIQ 9-12.2). These patients consulted with endocrine for thyroid nodule. 58% of the nodules were found on the left side. Histopathological studies demonstrated papillary carcinoma follicular type in all cases. Average size was 2 cm in diameter, capsular invasion was identified in all patients. 85.7% had lymph node metastasis, and 71% had lung metastasis. All patients had total thyroidectomy with ablation followed by radioactive iodine with average140 mci. Patients were followed for 11 years average 5.7 ± 4.9) years.

Conclusion: Thyroid cancer is not a frequent disease in pediatrics. Ultrasound guided fine needle aspiration gives more sensitive results. The management with total thyroidectomy and ablation with radioactive iodine is recommended. In the last decade we have seen a rise in thyroid malignancies in pediatrics, possible cause include easy diagnostic test or more exposure to radiation.

P-84

Euthyroid Sick Syndrome in Term Newborns with Late Onset Neonatal Sepsis

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The term Euthyroid Sick Syndrome (ESS) refers to the pattern of hormonal changes in the pituitary thyroid axis in patients without thyroid disease. The Late Onset Neonatal Sepsis is defined by the clinical syndrome of systemic involvement, caused by a bacterium, after the third day of life. In sepsis, thyroid dysfunction is determined by the ESS.

Objective: To evaluate the frequency of the ESS in term newborns with Late Onset Neonatal Sepsis.

Study in term newborns diagnosed with Late Onset Neonatal Sepsis (positive culture in the presence of clinical signs and symptoms of infection). Variables: Sex, age, identified germ, plasmatic levels of TSH, T4 and T3, between the third and fifth day of sepsis and after antibiotic therapy.

ESS Diagnosis: Low serum levels of T3 and T4 occasionally.

Exclusion Criteria: Congenital malformations, perinatal asphyxia, intrauterine growth restriction, newborns of mothers with thyroid disease.

63 neonates were studied; 36 men, 27 women. Age: 6–18 days.

Germs Identified: Staphylococcus aureus (21 cases), Streptococcus pyogenes (18), Escherichia coli (15), Streptococcus pneumoniae (9).

Values:

* 3°–5° day sepsis: TSH, 8.4 ± 2.9 mIU/mL; T4, 5.9 ± 2.6 ug/dL; T3, 128 ± 74.3 ng/dL.

* Post-treatment: TSH, 8.1 ± 2.6 mIU/mL; T4, 8.4 ± 1.8 ug/dL; T3, 195 ± 86.4 ng/dL.

* ESS (52% of total): Low serum levels of T3 (21 cases); T3 and T4 (12 newborns).

The ESS is probably presented as adaptive metabolic response. Thyroid disorders are transient and do not represent a true thyroid disease.

P-85

An Uncommon Cause of Hypophosphatemic Rickets

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Introduction: Tyrosinemia I is a metabolic disorder characterized by fumarylacetotacetate deficiency. This is the last enzyme in the tyrosine metabolism causing accumulation of toxic metabolites. Neonatal screening has prevented the appearance of severe manifestations. In Chile, neonatal screening is not available in the public health system so only clinical manifestations may lead us to the diagnosis.

We present a severe case of tyrosinemia I.

Case Description: A 1-year-old baby girl, born to a non-consanguineous couple, without problems in the neonatal period. Diagnosed with VII factor deficiency because of recurrent nose bleeding. Was hospitalized due to a upper urinary tract infection. During her hospitalization she was found anaemic with a haemoglobin of 5 g/dl;

Concomitantly, her liver enzymes were found to be high showing a cholestatic pattern with a big hepatomegaly and an abdominal ultrasonography showed multiple heterogeneous nodules 1.5 cm in diameter and splenomegaly, suggesting chronic liver failure. Exams discarded common liver failure aetiologies and tyrosinemia was diagnosed using tandem mass spectrometry.

During her hospital admission, metaphyseal widening was found in long bones so routine exams were made showing a serum phosphate of 1.06 mg/dl calcium 9.1 mg/dl, bicarbonate 19.7 mg/dl, alkaline phosphatases of 760, PTH 47 pg/ml and 25 oh vitamin d 60 ng/ml, urinary phosphate 51 mg/dl, urinary creatinine 37 mg/dl, calciuria 0.6 mg/d. No micro albuminuria no glycosuria. Long bone x rays showed signs of rickets. Treatment was initiated with phosphate 50 mg/kg in 5 doses, calcitriol 20 ng/kg/day and bicarbonate was indicated by the nephrology group. For her tyrosinemia NTBC 1.1 mg/kg day was indicated and tyrosine and phenylalanine were eliminated fromthe diet. Clinical, radiological and laboratory examsshowed progressive improvement.

Discussion: Tyrosinemia is a known cause of liver failure and kidney damage secondary to the accumulation of the metabolites that can't be degraded by the defective enzyme.

Response to NTBC is variable and there are cases that ameliorate renal loses while some don't respond and some completely recover. Our patient recovered completely after initiation of treatment.

P-86

PWS in Brazil: 6 Months Follow-Up in a Reference Center

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Background: Prader-Willi Syndrome (PWS) patients have been followed in our country in different ways but we do not have a society or a reference center to spread adequate information about the disease.

In January 2015, we started a PWS reference center in Sao Paulo University to promote a better care for patients and families and to support them with a multidisciplinary team.

Methods: Forty two patients, between 2 and 21 years old, were followed for a 6 month period in our PWS clinic. Body mass index-SDS (BMI-SDS) was evaluated at the beginning and after 6 months and these data were compared. The following items were analyzed: 1) use of growth-hormone 2) metabolic profile: LDL, triglycerides, glycated hemoglobin (HbA1c), fasting glucose and insulin levels. 3) polysomnography. All patients received orientation in diet (900 calories/day independent of wheight), physical activity and behavior. Our team is composed by pediatric endocrinologist, dietician, nurses; neurologist specialized in sleep disorders and otorhinolaringologist.

Results: The mean age was 9.8 ± 5.2 DP. BMI-SDS at the first visit was 2.8 ± 1.9 DP and after 6 months 2.41 ± 1.8 DP. Metabolic profile showed that 21.6% patients had high LDL-c level (LDL-c >130 mg/dL), 48.6% had low HDL-c level (<40 mg/dL), 18.6% had hypertriglyceridemia (>150 mg/dL), 23.5% had high A1c (≥5.8%) and 44.8% had insulin resistance. Only 12 patients used rhGH at the first visit and at the latest we had 29 (69%) patients on rhGH use. The reason that thirteen patients were not in use of rhGH is due to polysomnography alterations and patients were waiting for surgery or CPAP. Polysomnography revealed that 47.8% patients had an apnoea-hypopnoea index (AHI) >5

events/hour, 20.8% had O2 saturations under 92% and 56.5% had reduced sleep efficacy.

Conclusions: Most of our patients could lose weight with the correct approach in diet, behavior and physical activity. The use of rhGH was increased after the beginning of the clinic and the benefit of this therapy is well known in the literature. Alterations in polysomnography were a major problem revealed in the follow up and the correct approach of the multidisciplinary team is essential to support this disorder.

P-87

Homozygous Familial Hypercholesterolemia in Childhood: A Therapeutic Challenge (Case Report)

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The homozygous familial hypercholesterolemia is an autosomal co-dominant disease predominantly caused by mutations in LDLR (low-density lipoprotein receptor). In addition, mutations in Apo B-100, PCSK9 and ARH can cause similar phenotypes with varying severity. The xanthomas occurrence at an early age and a known family history of hypercholesterolemia, suggests the diagnosis. Several studies have reported an increased cardiovascular risk and mortality at early age related with the illness. The wide distribution and size of the xanthomas in the first decade of life plus family history of hypercholesterolemia often indicate severe forms of homozygote dominance.

We report the case of a 10 year old boy with total cholesterol of 694 mg/dL and LDL of 631 mg/dL and a 9 year old girl with total cholesterol of 996 mg/dL and LDL of 948 mg/dL, both with normal triglyceride levels, with no history of consanguinity, both in follow up by Pediatric Endocrinology consultation, with xanthomas in joints and buttocks with apparition since 2 years old, corneal arcus and increase in LDL. The genetic study in Case # 1 reported homozygous non-sense mutation in LDLR and in the Case # 2 missense mutation, with double heterozygosity, in LDLR and Apo B-100 genes.

During evolution, suitable control despite treatment with cholestyramine, atorvastatin/rosuvastatin and ezetimibe was not achieved, requiring start of lomitapide, obtaining a decrease in LDL levels of 40% in the Case # 1 and 53% in the case # 2, and decreased volume of xanthomas.

The treatment of homozygous familial hypercholesterolemia is a challenge for the pediatric endocrinologist. Its approach implies early diagnosis, the use of non-pharmacological measures and the combination of lipid-lowering medicines, including New Therapies. These strategies reduce LDL cholesterol and could decrease the high risk of mortality that can arise from the first decade of life.

P-88

Comparison of Two Automated Chemiluminescence Immunoassays for 25-Hydroxy Vitamin D Measurement

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Vitamin D is a lipid-soluble steroid hormone that is essential to the maintenance of overall bone health because of its key role in maintaining calcium and phosphorus homeostasis. In infants and children, vitamin D deficiency can cause the bone deformation known as rickets.

Serum concentration of 25-hydroxy vitamin D is considered the standard clinical measure of vitamin D status.

The aim of this study is to compare the results of 25-hydroxy vitamin D in patient samples using two different automated chemiluminescent immunoassay methods: Architect® and Access®, the latter of recent development, and to analyze the correlation and agreement between both methods.25-hydroxy vitamin D was measured by both methods in 50 patient samples (F: 19, M: 31), with a median age of 8.4 (0.75–16.0) years, collected from July to September 2015. The dosages were performed by the two analyzers on the same day, making the entire study in 5 days. In both the results corresponded to the same calibration.

For statistical analysis, the distribution of values was studied using a frequency histogram and normality test Kolmogorov – Smirnov, a Deming regression (Alternate Method Comparison EP Evaluator®) to evaluate the correlation and Bland – Altman graph for agreement.

Both methods showed a normal distribution, as evidenced by mean and median values, asymmetry and kurtosis close to zero, the bell-shaped histogram frequency and significance of Kolmogorov-Smirnov greater than 0.05. Deming's analysis showed a correlation coefficient of 0.914.

Regression Analysis Results are showed in table 1.

At medical decision points (20 and 30 ng/ml) percent bias were 5 and 5.3 respectively. The mean difference by Bland-Altman graph was 0.87. The agreement between methods was evidenced by the fact that 95% of the differences fall within the limits (–4.13 to 5.87).

Both methods have correlation and agreement. They don't show significant difference at medical decision levels and are suitable for use.

Table 1. Regression Analysis (for Abstract P-88)

		95% CI
Slope	1.065	0.937 to 1.193
Intercept	–0.35	–2.84 to 2.15

P-89

Cortisol Plasmatic Levels of Term Newborns Medicated with Fluconazole

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Fluconazole, azole antifungal inhibiting ergosterol synthesis in the fungal cell membrane, usually not inhibit steroidogenesis in the patient; however they have been reported some cases of reversible adrenal suppression, especially in critically ill patients.

Objective: To evaluate the plasmatic levels of cortisol in term newborns medicated with fluconazole.

Study in term neonates medicated with fluconazole, 12 mg/kg/dose, twice a week. Variables: Sex, age of the patient, identified fungus, cortisol plasmatic levels (ug/dL) before treatment with fluconazole (C-I), seven to ten days of therapy (C-II) and two to three weeks after treatment (C-III).

Exclusion criteria: Macrosomy, small for gestational age, major congenital malformations, glucocorticoid treatment, use of vasopressors.

48 neonates were studied; 27 men and 21 women. Age: 5 to 19 days.

Diagnosis: Candidiasis by C. albicans (45 cases), C. parapsilosis (3).

Cortisol plasmatic levels (ug/dL):

* Basal: C-I: 17.1 (15.2–19.3). C-II: 14.4 (12.9–18.1). C-III: 17.6 (15.7–21.8).

* Post ACTH: C-I: 28.3 (25.2–31.6). C-II: 23.5 (21.5–29.5). C-III: 28.9 (26.2–33.6).

* Increase: C-I: 11.2 (10.0–12.3). C-II: 9.1 (8.6–11.4). C-III: 11.3 (10.5–11.8).

Fungal infections in neonates are caused mainly by Candida albicans.

Fluconazole can inhibit steroidogenesis in the neonate.

It is recommended to evaluate the possible signs of adrenal suppression in patients receiving fluconazole.

P-90

DHEA-S in Girls with Idiopathic Precocious Pubarche (IPP): Inter and Intra Tanner Stage Variability

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Objective: Precocious maturation of cortical adrenal reticular zone is observed in IPP patients resulting in elevation of DHEA and DHEA-S. Usually, it is recognized a positive correlation between DHEA-S concentration and the progression of pubertal stage. The aim of this study is to determine the intra-stage variation of DHEA-S as a potential marker of androgen sensitivity.

Methods: This is a retrospective transversal and observational study, with measurement of DHEA-S (chemiluminescent assay) in 60 IPP girls (Age at diagnosis: 7.3 ± 1.2; Age at pubarche: 5.8 ± 1.3) from Tanner stage P2 to P5.

Results: DHEA-S values are shown in table. As expected, there was a significant progressive elevation of DHEA-S in stages from P2 to P4 (ANOVA, $p < 0.05$), with only a tendency to increase from P4 to P5. The overlap of DHEA-S values between pubic hair stages was relatively small (25%), but with wild variability into the same pubertal stage (>100%).

Conclusion: With the progression of pubic hair stage, IPP girls present an elevation in DHEA-S, with small overlap between stages, but wild variability into each stage. These finding suggest significant differences in individual secretion, metabolism and androgen sensitivity in hair follicles.

Table 1. DHEA-S values according to pubertal stage (for Abstract P-90)

	Tanner 2 (n = 61) (CA: 7.4±1.2)	Tanner 3 (n = 57) (CA: 8.8±1.3)	Tanner 4 (n = 23) (CA: 11.1±1.4)	Tanner 5 (n = 19) (CA: 13.5±1.3)
Mean (SD) (p25–75)	553.0 (309.4)* (328.7–707.5)	872.9 (348.8)* (628.5–1,092.5)	1,442.5 (639.3)* (975.2–1,832.2)	1,933.2 (839.6) (1,397.5–2,250.0)

* Kruskal–Wallis: $p < 0.001$ between P2, P3 and P4.

P-91

Frequency and Clinical Characteristics of Patients with Diabetes Induced by Means of Glucocorticoids during the Period of Remission Induction Therapy of Acute Lymphoblastic Leukemia

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Introduction: Acute leukemias are the most common cause of malignancy in the pediatric population. The aim is to induce remission using a combination of chemotherapeutic agents. One of them, the glucocorticoids, produce resistance to insulin action and increased hepatic gluconeogenesis, thus, appearing as a common complication of hyperglycemia. Diabetes in the pediatric population induced by drugs during the period of remission induction has had a significant variation in the literature (9.7–15.6%). The Mexican population has increased predisposition to DM development.

Objective: To determine the frequency of secondary diabetes to the use of glucocorticoids as well as clinical characteristics of pediatric patients with acute lymphoblastic leukemia treated at the INP between January 1st, 2000 and December 31, 2015.

Design: Transversal, observational and descriptive study.

Results: 41 (18.2%) out of 225 patients were diagnosed with Steroid Diabetes when studied. The mean age at diagnosis was 10.5 years. 18 (43.9%) men and 23 (56.1%) women with a ratio of 0.78:1. The characteristics of leukemias diagnosed with Diabetes Steroid were 37 (90%) Pre B ALL and 4 (10%) T-cel ALL. CNS Infiltration, 4 patients (9.7%). Testicular infiltration, 5 patients (27.7%). Hypodiploidy 32 patients (78%). The treatment used was dexamethasone 6 mgm^2 d in 16 patients (39%) and prednisone 40 mgm^2 d in 32 patients (78%). Patients diagnosed with steroid diabetes had a family history of diabetes in 28 patients (68.2%), Down syndrome in 1 patient (2.4%). In the nutritional status, 22 patients (53.6%) with normal weight, 2 patients (4.8%) malnourished, 3 patients (7.3%) with overweight and 14 patients (34.1%) with obesity. The duration of hyperglycemia was transient in 27 patients (65.8%) and permanent in 14 patients (34.1%).

Conclusions: The frequency reported in this study is greater than in all the series of patients found in the literature. The results were as expected due to the increased predisposition to DM among the Hispanic population. This is an important finding for the start of hygienic dietary measures in patients with ALL since the period of remission induction.

P-92

Association between Type 1 Diabetes and Nephrotic Syndrome

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Objective: To report a case of association between Type 1 Diabetes and Nephrotic Syndrome.

Design: Case report.

Introduction: The incidence of Type 1 Diabetes is variable among different countries and it is related to the presence of HLA genes associated to susceptivity among general population. One of the complications of Type 1 Diabetes is Diabetic Kidney Disease but there are also other affectations to the glomeruli such as Nephrotic Syndrome. There is a lack of reported cases.

Case Report: A 4 years old male patient with Type 1 Diabetes diagnosed at age 2 and 6 months, GAD antibody positive, C Peptide 0.31 ng/ml. Subcutaneous insulin therapy with Rapid-acting and Long-acting insulin was started which did not achieve metabolic control. Currently, on insulin microinfusion therapy leading to better metabolic control. The patient presented to Emergency with 2 weeks of progressive edema, weight gain, upper respiratory tract symptoms and late development of oliguria.

Leukocytes 4500, Neutrophils 60%, Lymphocytes 34%, Haemoglobin 12.7 g/dl, Haematocrit 36.5%, Platelets 166000. Creatinine 0.28 mg/dl, Blood Urea Nitrogen BUN 35 mg/dl, Na 137, K 5, Cl 114, P 7.4, Mg 2.5, Ca 7.8, Total Proteins 3.5 g/dl, Albumin 1.3 g/dl, Triglycerides 210 mg/dl, Total Cholesterol 304 mg/dl, and Proteinuria.

The medical condition was compatible with Nephrotic Syndrome. Medical management was initiated by Nephrology department. Thyroid and adrenal autoimmune diseases were ruled out. Celiac disease screening was negative. Chronic complications of Diabetes were ruled out. Microalbuminuria was negative 9 months previous to the admission.

Conclusions: Diabetic Kidney Disease is characterized by important proteinuria and its onset generally occurs after 10 years of progression of Diabetes Mellitus. In a patient with a 5 years course of Diabetes Mellitus and absence of retinopathy and neuropathy, the presence of a Non-Diabetic Kidney Disease is highly suspicious. As Diabetes Mellitus and Chronic Kidney Disease have both an immune basis their association with HLA as genetic predictor has been investigated. The main histopathologic feature in those cases is the Minimal Change Disease with an adequate response to steroids.

P-93

The Human Factor Associated to the Use of a Blood Glucose Meter with a Built-In Bolus Calculator in Children and Adolescents with Type 1 Diabetes in Real Life

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All our patients with type 1 diabetes (T1D) are trained in multiple daily insulin injections and carbohydrate count. In order to help with insulin dosage, our hospital provides a blood glucose (BG) meter with a built-in bolus calculator (BC) (FreeStyle InsuLinx, Abbott) to all affiliates since 2014.

Our aim is to evaluate the human factor associated to the use of this technology in real life, among subjects who did not choose to have this meter and are not being paid in a study to use the devise.

We review the medical records and meter downloads of 84 children with T1D. Only 42% used the bolus calculator properly calculating insulin doses for every meal. Results are shown in the table. Those who do not use the BC were older at DM onset 8.4 ± 2.7 v/s 9.5 ± 3.3 years $p < 0.05$, had diabetes for a longer period 5.6 ± 3.6 v/s 4.3 ± 3.0 years $p < 0.05$ and had more pubertal subjects 71% v/s 94% $p < 0.05$. We found no differences in gender.

The use of a meter with a BC takes 30 to 40 seconds longer than a regular meter since it is necessary to enter the amount of carbohydrates and to accept or modify the dose proposed by the software; 58% of our patients are not available to spend this extra time or to check their blood glucose at least 3 times per day.

Subjects who do not use the BC show a worse metabolic control and are different in many aspects. Human factors as mental health disorders (depression and anxiety), older age during adolescence and longer duration of the chronic disease seem to impair the adoption of this technology. In real life 42% of children and adolescents with T1D seem to benefit from a meter with a BC.

P-94

Experience of the Change of Therapy from Multiple Daily Insulin Injections to Continuous Subcutaneous Insulin Infusion Pump in Children and Teenagers with Type 1 Diabetes

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Therapy with continuous subcutaneous insulin infusion currently offers the most physiological way to contribute to this hormone. Despite the strong evidence described demonstrating its efficacy and safety, experience in the population with social security it is still very limited. International consensus indicate that all children with diabetes can be considered as potential candidates for treatment with insulin pump; however extensive knowledge of the disease and commitment to treat it are key determinants for selecting the patient. The purpose of this paper is to describe the experience generated with the use of micro infusers in pediatric patients carriers of DM1 with social security.

An observational, descriptive and prospective study was designed, which included five pediatric patients with DM1 (2 to 5 years of evolution) previously treated with basal and bolus insulin regimen.

After 19 months: BMI was not affected in any case. HbA1c decreased in 3 cases (0.1 to 5.3%) and increased in 2 cases (0.4 to 2.7%). Insulin requirement decreased in all cases (23% to 43%). No DKA or severe hypoglycemic events were recorded. Patients: 1) 15 years old female with trisomy 21, excellent metabolic control and attachment to treatment, which continued with the insulin pump. 2) 9 year old female persists with poor glycemic control due to altered family dynamics. 3) 10 years old male, pump therapy was able to improve hard to control glycemic control. 4) 13 year old female without benefit of therapy because of self-injurious behavior. 5) 13 year old male was excluded from the study for not attending trainings.

Successful education in diabetes control is the basis for any therapy. Bad habits by the patient in case of not being eradicated can turn the insulin pump into an instrument to potentiate them. The pump generated more interaction from the patient with his disease because it reduce by 80% the number of injections. To involve an adult responsible for the care of the child with diabetes requires a functional family dynamics to the success of therapy. A multidisciplinary team remains indispensable for the treatment of diabetes assisted by technology.

Table 1. Characteristics of subjects who use and do not use the bolus calculator (BC) properly/Mental Health Disorders (MHD) (for Abstract P-93)

USE of BC (%)	Age (year)	HbA1c (%)	MHD (%)	BG per day (n)
Yes 42	12.6±3.6	8.1±1.8	11%	3.5±1.0
No 58	15.1±3.2**	9.8±2.5**	63%**	2.8±1.6*
Total 100	14.0±3.6	9.0±2.4	42%	3.1±1.4

* $p < 0.05$; ** $p < 0.001$.

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P-95

Temporal Trend of More Newly Diagnosed Type 1 Diabetes Children and Adolescents Identified in a 35-Year Period in a Brazilian Institution

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Introduction: The incidence of type 1 diabetes mellitus has been increasing worldwide, and it appears to have been particularly pronounced among children younger than 5 years of age. However, in a previous study we showed an increased frequency of DM1 in the age group older than 10 years old in a Brazilian pediatric hospital.

Objective: The aim of this study was to confirm the temporal trend of newly diagnosed DM1 cases in a Brazilian endocrinology service by evaluating a larger group of children and its distribution according to age.

Materials and Methods: Data was obtained from the Pediatric Diabetes Group of the University Hospital. Information about: age and year at diagnosis were obtained through medical charts and a standardized questionnaire.

Results: Since 1969, 663 children and adolescents diagnosed with DM1 were identified in the hospital records. Temporal trends were analyzed between 1980 and 2014 with 642 children, who were divided into three groups according to age at diagnosis (≤4 y, 5–9 y and ≥10 y). The studied period was divided in 5-year intervals: 1980–1984, 1985–1989, 1990–1994, 1995–1999, 2000–2004, 2005–2009 and 2010–2014. There was a progressive decrease in the proportion of children diagnosed between 0 and 4 years old (47% in 1990–1994 to 20% in 2010–2014; $p = 0.01$), and an increase in the proportion of children diagnosed after 10 years old (13% in 1990–1994 to 54% in 2010–2014; $p = 0.01$). There was no statistical difference between the proportion of children having 5 to 9 years of age through the studied time. The analyses including the 21 patients diagnosed between 1969 and 1979 and 2015, didn't modify this trend.

Conclusions: Analyzing a larger time period and a higher number of cases, we found the same results observed in our previous study that analyzed the temporal trend between 1990 and 2014. In both studies there was decreased frequency of DM1 in children younger than 5 years old and an increased frequency in children 10 years or older through the time period, in this particular population. We suggest more studies should be performed to confirm this trend mainly in other regions of Brazil.

P-96

Overweight Adolescents with Type 1 Diabetes May Decrease Body Mass Index, Insulin Dose and Glucose Variability on Dapagliflozin, a SGLT2 Inhibitor

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Dapagliflozin, an insulin-independent sodium-glucose cotransporter 2 inhibitor (SGLT2-I), increases glucosuria and reduces hyperglycemia but it is not approved in T1D nor in adolescents.

The objective was to describe the effect of Dapagliflozin (10 mg/day during 12 months) on body mass index (BMI) in 3 overweight female adolescents with T1D, acne, hypertrichosis and normal androgen levels. The insulin dose was adjusted based on blood glucose levels.

Patients were 15 ± 2 years old, 3 ± 1 years post menarche and had attained near final height. Weekly capillary beta-hydroxybutyrate was low or undetectable (range 0.0–0.5) and none of the patients showed electrolyte disturbances or urinary tract infections.

Polydipsia, polyuria and dry mouth were reported. One patient exhibited hand tremor but refused to discontinue the SGLT2-I. After 11.6 months on Dapaglifozin, one girl who had showed a progressive reduction of HbA1c (8.3% to 7.5%) and BMI SDS (0.85 to –0.05) developed an euglycemic diabetic ketosis and treatment was stopped. After 6 months, all subjects reduced their body weight (3.9; 6.7 and 6.8 kg respectively) and 2 girls showed a reduction in body acne. After 12 months, two subjects exhibited a partial rebound on BMI SDS.

Interestingly blood glucose levels and variability (Glucose SD) were reduced but HbA1c did not improved in 2 out of 3 subjects.

Insulin dose and body weight were reduced after 6 months on Dapagliflozin without metabolic deterioration in 3 adolescents with T1D; whereas a partial rebound on both parameters was seen after 12 months on treatment. Adverse drug side effects as euglycemic ketosis and hand tremor may appear. Randomized controlled trials are needed. Our findings provide hope that SGLT2 inhibition might be an effective adjuvant to insulin treatment in overweight adolescents with T1D.

Table 1. Results are shown in the table as mean ± SD, glucose variability is expressed as glucose SD (for Abstract P-96)

Time (month)	BMI (SDS)	HbA1c (%)	Insulin dose (U/day)	Blood glucose	
				mean (mg/dl)	SD
0	1.42±0.7	8.1±0.7	58±16	191±24	92±7
6	0.75±0.8	8.1±0.8	36±7	171±34	85±4
12	0.86±0.9	8.1±0.8	51±6	177±22	74±5

P-97

Adrenal Hemorrhage in a Newborn with Salt-Losing Form of Congenital Adrenal Hyperplasia and Craniofacial Dimorphisms – Case Report

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Adrenal hemorrhage (AH) is a rare event and term male infants vaginally delivered are mostly affected. Incidence of AH has been estimated as about 1.7 per 1,000 births and main differential diagnoses include congenital adrenocortical tumor, congenital neuroblastoma, lung sequestration, mesoblastic nephroma and duplication of the urinary or intestinal tracts. The most common clinical signs of AH are persistent jaundice and flank mass. Scrotal hematoma, anemia, adrenal insufficiency or shock may be present, although adrenal insufficiency is rare, even when bilateral, due to the presence of residual functioning adrenal tissue in the subcapsular region. How long to observe such an adrenal lesion and when to indicate a surgical intervention remain controversial.

Case Report: Term male newborn, 3rd child of a 35-yr-old mother was born after vaginal delivery, with 3,598 g and 50 cm. Physical examination revealed the following dimorphisms: microcephaly, long nasal filter, high nasal bridge, oblique eyelid slot, low-set ears. Enlarged penis and hyperpigmentation of the scrotum were noted. He presented protracted jaundice that required phototherapy. On day 11th, he developed low sodium (128 mEq/L), high potassium (6.7 mEq/L) and signs of moderate dehydration. Screening 17-OHP value (190 ng/mL) was positive for Congenital Adrenal Hyperplasia (Ref. values <30). Laboratory profile showed: 17OHP >2,000 ng/dL (70–250), androstenedione >10 ng/mL (0.6–3.7), dehydroepiandrosterone 8.5 ng/mL (<3.5), and ACTH 84 pg/mL (7.2–63.3). In virtue of stigmata and protracted jaundice an abdominal ultrasound was performed which revealed a mass in the topography of the left adrenal gland; subsequently, an abdominal CT scan was suggestive of neuroblastoma. On laparotomy, the adrenal mass was totally removed and histopathology revealed massive hemorrhage. After 48 days of hospitalization patient was discharged, under hydrocortisone and fludrocortisone, in good clinical conditions and with normal electrolytes and plasma androgens. To our knowledge, this is the first case of the association of adrenal hemorrhage in a patient with salt-wasting form of 21-hydroxilase deficiency and craniofacial dimorphisms. Molecular studies are mandatory to elucidate the association of these two latter conditions.

P-98

DNA Extraction Method from Neonatal Dried Blood Spots Samples and 11 Most-Common Mutations Screening in CYP21A2 Gene

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Background: Neonatal dried blood spots (DBS) represent an inexpensive method for long-term biobanking. Congenital adrenal hyperplasia (CAH) neonatal screening has a low positive predictive value (about 1%), which leads to many follow-up evaluations that have negative results. The positive predictive value might be improved by second-tier screening using DNA-based methods. Besides, genotyping using DBS samples is very useful for sample transportation from different geographical regions especially when it is difficult for the patient to travel for a suitable blood extraction and also allow for a retrospective study of the disease.

Objective: To evaluate DNA extraction method and 11 most-common mutations screening in CYP21A2 gene from DBS samples as another tool in CAH neonatal screening.

Methods: Twelve neonatal dried blood spots (DBS) from 5 different NS laboratories conserved at room temperature between 2010 and 2015 which were presumably pathological for CAH in neonatal screening were analyzed. DNA extraction was performed with a commercial extraction kit (QIAamp DNA Mini Kit, Qiagen). DNA quality was assessed based on spectrophotometric measurements, DNA detectability by PCR and DNA integrity by gel electrophoresis. Eleven most-common mutations described in CYP21A2 gene were analyzed by automated sequencing and MLPA analysis.

Results: 260/280 ratio was found to be 1.72 ± 0.11. DNA integrity was fairly satisfactory and detectability by PCR and sequencing was successful in all the samples. In 10 from 12 samples, CAH diagnosis was confirmed while 2 patients turned out to be false positive cases, in coincidence with molecular studies performed in DNA extracted from blood samples.

Conclusion: Early confirmation of the diagnosis by molecular studies is very important to improve the clinical management of the patient, preventing SW crisis and incorrect sex assignment, especially in those cases where the patient is difficult to access. In this study we could prove that DNA extracted from DBS is a useful tool for 21-hidroxylase deficiency diagnostic confirmation for newborn screening programs. Moreover, DBS represent an inexpensive method for long term biobanking and for a posible use in restrospective studies.

P-99

Clinical, Biochemical and Genetic Characteristics of Patients with Congenital Adrenal Hyperplasia by 21OHasa Deficiency. Experience of Ten Years

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Congenital adrenal hyperplasia (CAH) is an inherited disorder of the adrenal steroid genesis, involving the enzymes involved in the biosynthesis of cortisol. It is the most common adrenal disorder in childhood, and the most common cause of ambiguous genitalia.

Objectives: To characterize clinical, biochemical and genetically patients with CAH. Material and Methods: A descriptive study including phenotypic characterization was performed biochemical evolution and identification of point mutations in patients with CAH assisted in the last ten years in our institution.

Results: We studied 45 patients, of which 36 (80%) they belong to female social sex, with an average age of 10.05 years. The prevailing color white skin 30 patients (66.7%). A higher frequency of the classical clinical forms 30 patients (66.7%), of which 15 (33.3%) were virilising simple, 15 looser salt (33.3%), 14 (31.1%) was found no classical forms, 1 (2.2%) cryptica. The biochemical study showed a decrease of 17 OHP evolutionary according to therapeutic scheme used and testosterone presented with normal levels in most patients. Point mutations were identified in 44.5% (20/45) of the patients studied, with classical forms 17/30 and 3/14 in the NC, in 16 of the 22 surveyed parents and a sister of one of the patients.

Conclusions: The clinical spectrum of presentation of this condition is necessary to perform biochemical and genetic tests to make a diagnosis. The genetic study of the family makes it possible to detect carriers and provides the opportunity for genetic counseling.

P-100

A Novel CYP21A2 Mutation Identified a Patient with Classical 21-Hydroxylase Deficiency

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Introduction: Congenital adrenal hyperplasia (CAH) is one of the most common inborn endocrine disorders and is caused by defects in one of the steroidogenic enzymes involved in the adrenal steroids biosynthesis from cholesterol to cortisol. Approximately 95% of CAH cases are caused by CYP21A2 deficiency. This deficiency is classified in classic and non-classic forms depending on the clinical manifestations. In general, CYP21A2 deficiency leads to consequences of androgen excess such as virilization and rapid somatic growth with accelerated skeletal maturation. The variability of phenotypes observed in patients with CYP21A2 deficiency is attributed to different mutations occurring in the gene and depends on how each mutation affects the protein production or the enzyme activity. Generally, there is a good correlation between genotypes and the clinical form of the disease. The aim of this study was to investigate CYP21A2 mutations in a family with a girl with classic form of CYP21A2 deficiency whose older brother had died of dehydration at 5 months old.

Methods: CYP21A2 mutations were investigated in the girl and her parents by gene amplification and Sanger sequencing.

Results: The novel c.901T>C nucleotide change was identified. The putative consequence of this change is the mutation p.Ser301Pro. The girl is homozygous for the mutation and her mother and father are heterozygous. The whole gene sequence of the girl did not show any heterozygosis indicating identical alleles inherited from each parents as they are second cousins. She was diagnosed with salt wasting form of CAH after birth and her older brother deceased at 5 months old without diagnosis, his symptoms were vomiting and inadequate weight gain.

In silico studies indicated that the change of serine to proline within the α-helix may introduce kinks into it because proline is unable to adopt a normal helical conformation. Although using PyMol Viewer we did not observe the α-helix disruption, prediction algorithms such as PolyPhen-2, Align GVGD, and SNPs&GO indicated p.Ser301Pro as probably damaging.

Conclusion: Based on data presented here, the novel variation is compatible with classical form of CAH, however in vitro studies on protein functional activity shall be performed to validate in silico data.

P-101

Testicular Adrenal Rest Tumors in Patients with Congenital Adrenal Hyperplasia: Outcome after 6 Years of Follow-Up

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Aim: Adrenal rest testicular tumors (TART) leading to primary gonadal failure are the main etiology of infertility in men with Congenital Adrenal Hyperplasia (CAH). We aimed at evaluating related findings and the evolution of TART in young patients with CAH after a 6 years of follow-up.

Patients and Methods: We included 12 male patients with 21-hydroxilase deficiency, 3 to 23 years old, followed-up each trimester from 2009 to 2015 in the same service. They were treated with oral Hydrocortisone or Prednisone. The clinical and laboratory data were retrieved from medical records. Testicular ultrasonography (US) was performed in two different moments (between 2009–2011 and in 2015) by a single specialist in diagnostic imaging to evaluate the presence and the characteristics of TART. Tumor progression was classified according to RECIST criteria. Hormon-

al control was evaluated by serum 17OHP and androstenedione concentrations during the whole period of follow-up. The hormonal and therapeutic variables were compared to the presence of TART by Logistic regression with repeated measures. The study was approved by the local Research Ethics Committee.

Results: Prevalence of TART was 41.6% (n = 5) in initial evaluation and 66.6% (n = 8) in the follow-up. Tumor progression was detected in 4 of the 5 patients previously diagnosed with TART. All of them showed inadequate hormonal control. Other 3 patients, who also had inadequate hormonal control, showed new lesions in the second evaluation and were classified as having tumor progression. One of the patients presented stable tumor. In 2015 most of the patients (n = 11) were pubertal, and two of them were currently diagnosed with precocious puberty. The youngest child diagnosed with TART was 7 years old. Patients with inadequate hormonal control presented a 16x higher risk of TART occurrence (p = 0.004). Patients presenting TART used higher glucocorticoid daily doses (med = 18 mg/m^2), when compared to non-TART patients (med = 12.3 mg/m^2; p = 0.048).

Conclusions: We found high prevalence of progressive TART in those young individuals. US testicular screening should be included in routine evaluation of CAH male patients since childhood. As well as therapeutic optimization, the routine US evaluation would contribute to prevent future implications of these tumors in fertility.

P-102

Frequency of CYP21A2 Gene Mutations in Peruvian Patients with Congenital Adrenal Hyperplasia

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Congenital adrenal hyperplasia (CAH) is one of the most frequent errors of metabolism with autosomal recessive inheritance mainly caused by the complete or partial inactivation of the 21-hydroxylase enzyme, coded by CYP21A2 gene. Many mutations had been described disrupting 21-hydroxylase activity, but only a few are frequent in most populations studied. Detection of these mutations helps in diagnostics, treatment decision and genetic counseling. Peru has only a few experiences about that, so for proper clinical applications more studies are needed in Peruvian population. This is a preliminary study to determine the frequency of 10 common CYP21A2 mutations in pediatric peruvian patients diagnosed with CAH from the National Institute of Child Health (Lima-Perú). This is a descriptive study. We worked with peripheral blood samples of n = 23 individuals with levels of 17-OH progesterone higher than normal reference value (0.4–3.3 ng/ml). To avoid the pseudogene CYP21A1P an 8 bp deletion in exon 3 was evaluated. CYP21A2 gene were amplified by PCR in two fragments only when 8 bp mutation was present in heterozygous state or was absent. The fragments were amplified using primers CYP48 and P1 (exons 1 to 3) and P4 and CYP55 (exons 3 to 10). In second round of PCR we performed a ASO-PCR to detect 655 A/C> G in intron 2, 999T>A (I172N), 1380T>A; 1383T>A and 1389T>A (I236N; V237E; M239K), 1683G>T (V281L), 1994C>T (Q318X), 2108C>T (R356W), 1762_1763insT (L307insT) mutations and PCR-ACRS for 89C>T (P30L) and 2578C>T (P453S) mutations. 6 mutations of the 10 were detected, the most frequent was deletion of 8 bp in exon 3 (19.6%), followed by Q318X and R356W (15.2% each), 659A/C> G in intron 2 (13%), I172N (6.5%) and Cluster 6 (4.3%). These preliminary results indicate that 8 pb deletion is the most common in our population, which is associated with the salt wasting phenotype that is the most severe disease because completely inactive 21-hidroxylase activity.

P-103

The Easypod Connect Observational Study (ECOS): Descriptive Analysis of Adherence to Treatment of Growth Hormone Deficient and Small for Gestational Age Naïve to Easypod Patients in Mexico 2012–2015

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The Easypod™ electronic auto-injector device is designed to make daily administration of recombinant human growth hormone (r-hGH), comfortable and easier for the patient. Easypod also provides accurate, real-world records of patients' adherence to r-hGH therapy, which can be shared with a healthcare practitioner. This work aimed to assess adherence to r-hGH therapy delivered via easypod device in patients naïve to easypod, with growth hormone deficiency (GHD) and born small for gestational age (SGA), and correlate the adherence with growth outcomes. ECOS is a phase IV, prospective, multicenter, longitudinal observational, open-label study, started in 2010. Data from Mexico included a total of 193 patients of whom 131 were naïve to Easypod. 107 patients were GHD and 24 were SGA. Mean age (years) at treatment start was 9.44 ± 3.46 and 9.54 ± 2.70 in the GHD and SGA groups, respectively. Mean treatment duration (years) was 1.85 ± 0.80 and 1.99 ± 0.66 in the GHD and SGA groups. In both groups, most patients made more than 2 adjustments to dose. The main reasons for change were adjustment to body weight, efficacy and puberty. The mean starting doses were similar (0.040 GHD and 0.042 SGA). Mean % adherence after 1 year of treatment was 87.01 ± 17.73 and 89.92 ± 11.24 in the GHD and SGA groups. Adherence was maintained over four years of treatment. For the first year, change in height velocity (HV) in cm/year was similar in both groups (GHD

8.92 ± 2.18 vs. SGA 8.90 ± 1.71). The changes in height velocity SDS in the first year were 0.59 ± 0.36 and 0.54 ± 0.29 in the GHD and SGA groups. Although the number of patients was small, the correlation (Spearman coefficient) between adherence and HV cm/year and HV SDS in the GHD group was 0.146 and 0.175, respectively, but it was higher in the SGA group (0.538 and 0.170) in HV. The correlations between adherence and change in height (cm/year and SDS) were higher in the SGA group (0.51 and 0.35) than the GHD group (0.24 and 0.22). Overall, adherence rates with the easypod device are high and maintained over time in GHD and SGA naïve patients. High adherence rates were associated with clinically meaningful growth outcomes.

P-104

Use of the Aromatase Inhibitor Anastrazole in Male Adolescents with Short Predicted Adult Height with and Without Associated GH Therapy: First Year Data

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Estrogen is an essential regulator of bone maturation, growth plate fusion, and cessation of longitudinal growth. Aromatase inhibitors (AI) block the conversion of androgens to estrogens, and can be used to delay bone maturation in males.

We sought to determine whether the blockage of estrogen biosynthesis due to the use of the AI Anastrazole increases the Predicted Adult Height (PAH) in boys with short stature, with and without associated GH therapy.

28 boys (13.6 years), used oral Anastrazole 1 mg/day for 1 year. 18 received GH therapy ('GH' group) and 10 did not ('ØGH' group). PAH was calculated based on Bayley/Pinneau formula.

The Basal PAH was statistically below the TH (–2.9 cm, $p = 0.008$), and after one year of treatment with Anastrazole it was above the TH (+3.4 cm, $p = 0.008$) and above the Basal PAH (+6.3 cm, $p < 0.001$). For the 'GH' group the increase in PAH after 1 year was +3.6 cm comparing to TH ($p = 0.01$) and +6.3 cm for Basal PAH ($p < 0.001$). For the 'ØGH' group, the increase in PAH after 1 year was +3.1 cm comparing to TH ($p = 0.06$) and +6.2 cm for Basal PAH ($p < 0.002$).

One year use of anatrazole in boys with short PAH can improve PAH in 'GH' and 'ØGH' groups. The complete follow up until adulthood will determine if this increase in PAH will reflect in better final adult height.

P-105

Factors Associated with Bad Response in the First Year of Growth Hormone Therapy in Girls with Turner Syndrome

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Background: Turner síndrome (ST) is a disorder caused by the loss of genetic material from one of the sex chromosomes. Therapy with growth hormone (GH) is the standard of care, and if appropiate treatment is not given, the final height is much shorter than the general population.

Design: Nested case-control study, observational, analytical, retrospective, longitudinal.

Objective: To assess factors associated with poor response during the first year's GH-therapy in ST girls. MATERIALS AND METHODS: We analyzed files of patients with ST under 11 years of age, in the first year of the GH-therapy, in the period from January 2012 to April 2015. We excluded those who had previously received sex steroids. We define 'poor response' when the growth rate was less than 5 cm/year. Each patient was measured before and after the 1st year of therapy. The measures included heigh, weight, BMI, karyotype, bone age, growth velocity, Somatomedin-C levels, comorbidities, and the dose at the start of therapy. We used abolute frequencies and percentages for qualitative variables, and mean or median standard deviation or limits for quantitatives variables. It was considered as significant a value of $p < 0.05$.

Results: 31 girls under 11 years with ST receiving GH during the first year, with an average of 7 ± 1.9 years were included. The growth rate in the group of bad and good response was 3.8 ± 0.75 cm/year versus 6.74 ± 1.15 cm/year ($p = 0.001$). The group of poor response had 8 patients and 23 the good response group, with more than 9 years 62.5% and 13% respectively ($p = 0.013$). Based on a bad or good response, girls who had karyotype 45X0 were 8/8 and 21/23, respectively ($p = 0.389$). None of the patients classified as poor response were obese ($p = 0.389$). The most common comorbidity in both groups was the aortic coarctation with 56%.

Conclusions: The patients in whom GH therapy was started after 9 years had a bad response to GH-therapy in the first year of therapy.

Table 1. Comparison of TH with basal and one year PAH (cm) (for Abstract P-104)

Group	TH (cm)	Basal PAH (cm)	1 year PAH (cm)	p*
0GH	173.70±4.39	170.62±3.90	176.80±3.89	0.003
GH	171.48±4.48	168.77±4.10	175.11±4.46	<0.001
Total	172.28±4.50	169.43±4.06	175.71±4.27	<0.001

* Fiedman test.

P-106

Clinical Response and Growth Prediction in a Large Cohort of Latin-American Patients with Growth Disorders Treated with rhGH: Results from Pfizer International Growth Database (KIGS)

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Background: Idiopathic Growth Hormone Deficiency (IGHD), Turner Syndrome (TS), Idiopathic Short Stature (ISS) and Small for Gestational Age (SGA) are the most common indications for rhGH therapy in childhood. However, sparse clinical response data are available for Latin-American patients treated with rhGH and no growth prediction data are available to date.

Aim: To evaluate the clinical response and growth prediction of Latin-American patients enrolled in KIGS.

Patients and Methods: A retrospective analysis of patients enrolled in KIGS from Argentina, Brazil, Colombia, Mexico, Peru and Venezuela with at least one year rhGH treatment follow up data were studied: children with IGHD (n = 560), ISS (n = 159), TS (n = 286), and SGA (n = 170). Descriptive statistics are presented as mean (SD). Studentized Residuals (SR) were used to determine if the groups grew as predicted (1).

Results: Patients characteristics at start of rhGH and at last visit are shown in the Table. SGA gestational age: 38.2 wk (2.9) and BW –2.25 SDS. Mean GH peak to provocative test in IGHD: 4.3 ng/ml (2.7) and 1st year prepubertal growth SR.

Conclusion: Overall patients had a good response to rhGH therapy, although slightly lower than predicted. Possible explanations, for the lower than predicted response, are the relative late onset of therapy, in some cases suboptimal rhGH dose and possible poor adherence to therapy.

Reference

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P-107

Use of Growth Hormone in a Girl with Cleidocranial Dysplasia

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Introduction: Cleidocranial dysplasia (CCD) is an autosomal dominant heritable disorder caused by mutations in the runt-related transcription factor 2 gene (RUNX2), main regulatory gene of the skeletal development and morphogenesis in vertebrates. CCD is present at a frequency of one in 1,000,000 individuals worldwide. Characteristic features include several dental and skeletal abnormalities such as hypoplasia of clavicles and delayed closure of fontanelles. Individuals with CCD are shorter than their unaffected sibs.

Case Report: An 8 year-old girl was sent to our Endocrinology Unit when she was 5 months old because of growth failure. She had been a full term newborn appropriate for gestational age. Birth weight: 3290 g (+0.13 SD) and length: 50 cm (+0.33 SD), no consanguineous parents. She had normal psychomotor development. During follow up delayed closure of fontanelles and mild disproportional growth impairment became evident. Laboratory biochemistry was normal except for low IGF1 (33 ng/mL) (55–327 ng/mL) (–2 SD). Karyotype was 46, XX and skeletal radiological study was consistent with cleidocranial dysplasia. Molecular study for RUNX2 described an unclassified variant c.560T> A in one of the

Table 1. Patients clinical characteristics at start of rhGH and at last visit (for Abstract P-106)

At GH start/last visit	IGHD (n = 560) males (62%)	TS (n = 286)	ISS (n = 159) males (62%)	SGA (n = 170) males (46%)
Age (yrs)	9.5 (3.7)/13.5 (3.8)	9.6 (3.6)/13.5 (3.9)	10.3 (2.7)/13.2 (3.1)	8.9 (3.5)/11.7 (3.5)
Height SDS prader	–3.2 (1.5)/–1.9 (1.3)	–3.7 (1.1)/–2.9 (1.1)	–2.4 (1.0)/–1.6 (1.0)	–2.6 (1.2)/–1.7 (1.3)
rhGH dose (mg/kg/wk)	0.22 (0.08)/0.22 (0.07)	0.32 (0.06)/0.33 (0.06)	0.26 (0.07)/0.26 (0.06)	0.30 (0.10)/0.30 (0.08)
Years on rhGH	3.7 (3.1)	3.6 (2.3)	2.6 (1.9)	2.5 (1.8)
1st year on GH (prepub)	n = 88	n = 115	n = 42	n = 47
Predict/actual HV (cm/y)	9.2/8.7	8.0/7.4	8.4/8.2	9.0/8.5
SR (prepubertal)	–0.27 (1.26)	–0.51 (1.27)	–0.16 (1.20)	–0.37 (1.18)

two copies of the patient, absent in her parents. She had normal Otolaryngology and Odontopediatric evaluation.

Because of low IGF1 and slow growth according to parent's target, we started treatment with growth hormone (GH) which was successful showing a growth rate of 9.6 cm/year (+0.26 SD) during the first year of treatment without adverse effects. We found this barely described in the literature.

Conclusions: CCD is a rare syndrome characterized by dental and skeletal abnormalities in addition to growth impairment in some cases. Our case illustrates that GH therapy could be a good therapeutic alternative in these cases.

P-108

A Case of Tall Stature: Weaver Syndrome

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The biological process that controls the human growth is diverse, complex and poorly understood. Genetic factors controlling growth are polygenic. There are common variants as well as rare genetic variants. The overgrowth syndromes are rare and caused by multiple genetic conditions of importance, so a high index of suspicion is required in order to make a correct diagnosis and prevent complications.

Weaver syndrome is a condition characterized by overgrowth, dysmorphic craniofacial features, learning disorder, advanced bone age and other variables characteristics. The cause of this condition has been recently described and is due to a mutation in the oncogene, histone methyltransferase EZH2.

We report a child 2 ½ years with Weaver syndrome. He was a macrosomic newborn baby with some mild dysmorphic craniofacial features. He evolves with tall stature, macrocephaly and mild psychomotor retardation. Recently he developed a lymphoblastic leukemia. His hight is 104 cm (>4.0 SDS), weigth 21 kg (W/H >2.2 SDS) and head circumference of 53 cm (>3.5 DSD). His bone age is 6 years.

The EZH2 sequence analysis from peripheral blood and nails, demonstrated three variants of the coding region. One of them, a heterozygous variant in exon 20, c2233G> A, which causes a substitution p.Glu745Lys, it is probably a pathogenic variant. His parents did not have this variant, so it is a novo mutation.

It is well recognized the association between overgrowth syndromes and tumors. In this condition, the mechanism of tumorigenesis is unknown. It has been described only one patient with the same genetic mutation, who developed a leukemia, so it is difficult to establish a causal relationship in our case.

In children with features of an overgrowth syndrome, macrocephaly, craniofacial dysmorphism and mild developmental delay, Weaver syndrome should be suspected and tumor surveillance should be initiated.

P-109

Assessment of Ovarian Function in Girls Cancer Survivors

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The development of new therapeutic regimens increased the cure rate in patients with childhood cancer, as well as the aftermath. Ovarian toxicity is a frequent adverse effect, so the use of GnRH analog (GnRHa) could have a protective effect. Objective to evaluate ovarian function 2 years after finishing cancer treatment in children with or without use of GnRHa.

We review electronic medical records (2006–2016) of oncological patients referred to a Pediatric Endocrinology Service in a general University Hospital. Ovarian Failure was defined as amenorrhea after two years of treatment or lack of development or progression of puberty with FSH levels >40 mIU/ml. Data from 34 patients were recruited. Mean age at cancer diagnosis was 11.4 years (1–18 years), 35% were at Tanner I stage and 56% at V. 62% were hematopoietic tumors, and 38% solid and central nervous system tumors. 15 patients received GnRH (44%). They were all postmenarchal.

41% of the population developed Ovarian Failure and 59% had normal function when evaluated. 15/34 patients received concomitant treatment with GnRHa. ⅓ of these presented ovarian failure, but coinciding with relapse of underlying disease and requirement of new cancer treatments. Ovarian failure: 42.8% were prepubertal at diagnosis (RR 1, 46) 36% had recurrence of the disease and required radiotherapy 78.5% (11/14) and/or bone marrow transplant (BMT) 64% (9/14) RR 2.26 and 4.5 respectively. Only 28% received GnRHa. No ovarian failure: 60% had completed puberty at diagnosis. GnRHa was indicated in 55%, 10% presented relapse of his illness and only 1 patient received BMT.

Ovarian failure is related to aggressive cancer treatment. Prepubertal status may not protect ovarian function. The benefits of GnRH analog are not clear. Large, prospective, double-blind studies are required.

P-110

Gene Expression Profile of Granulosa Cells Modulated by Human FSH: Role of Oligosaccharide Structure

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FSH plays an essential regulatory role on ovarian folliculogenesis, particularly on granulosa cell function; its actions have important implications in fertility. The aim of this study was to analyse

the response to different human FSH preparations in terms of gene expression at whole-genome scale in human granulosa-like tumor cell line, KGN, and to correlate transcriptional changes with specific biological functions. Preparative isoelectrofocusing was used to characterise the gonadotropins and to isolate uhFSH glycosylation variants according to their sialylation degree. Two preparations, more (uhFSH-AC) and less sialylated (uhFSH-BA) were obtained from urinary FSH by combining pH <4.10 and pH >4.40 fractions, respectively. Native rh and uhFSH were applied to a Concanavalin-A column to characterize FSH glycosylation variants according to glycan complexity: unbound and weakly bound glycoforms (UB and WB) bearing complex type and firmly bound glycoforms (FB) bearing hybrid type oligosaccharides. The predominant proportion of rhFSH charge analogues was isolated within a 4.40–4.69 pH interval and those from uhFSH within 4.10–4.39. Three groups of glycoforms disclosed by lectin were detected in native rh and uhFSH preparations. A predominance of glycoforms bearing hybrid-type oligosaccharides was found in rhFSH (FB: 70% vs. UB+WB: 30%) whereas glycoforms bearing complex carbohydrates were predominant in uhFSH (UB+WB: 83% vs. FB: 17%). A microarray approach was used to explore gene expression pattern induced by recombinant (rhFSH) and highly purified urinary human FSH (uhFSH). Global gene expression profile changed according to the FSH oligosaccharide structure. Hormone sialylation degree differentially affected stimulated vs. inhibited gene expression ratio; uhFSH-AC: 1.35 vs. uhFSH-BA: 0.66. Set enrichment analysis revealed that hormone sialylation and oligosaccharide complexity differentially affected the expression of genes involved in cell essential biological processes; i.e.: inflammatory response and metabolic processes were affected by rhFSH; prostaglandin metabolic and lipid catabolic processes were affected by uhFSH; triglyceride homeostasis was affected by uhFSH-AC and mitotic cell cycle interphase was affected uhFSH-BA. These results indicate that a close relationship between the biological responses in terms of gene expression and the oligosaccharide structure present in the FSH molecule is evidenced by different transcriptomes.

P-111

Time Course of Central Precocious Puberty Development Caused by an MKRN3 Gene Mutation: A Prismatic Case

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Introduction: Loss-of-function mutations in the imprinted gene MKRN3 represent the most common known genetic defects associated with central precocious puberty (CPP). The penetrance of these mutations remains to be established. To date, all reported individuals with MKRN3 mutations were already in puberty or postpubertal and were identified retrospectively. Herein, we report the first case of a prepubertal child with an MKRN3 mutation who was followed prospectively and developed CPP.

Method: We describe the complete clinical and laboratory features of a female patient carrying an MKRN3 mutation, detected in childhood, followed until the development of pubertal signs.

Results: The patient was screened at the age of 4 years because of positive family history – her sister developed CPP at the age of 6 years and was found to harbor the MKRN3 p.Pro161Argfs*16 mutation, inherited from their asymptomatic father. During close follow-up, this young girl initially developed increased growth velocity at age 6 years (9 cm/year), followed by a slightly increased basal LH level (0.4 mIU/mL) and, ultimately, clinical thelarche, with rapid progression (Tanner stage 1 to 3) between the ages of 6.3 and 6.7 years, when the LH level became clearly pubertal (0.9 mIU/mL). In the context of a loss-of-function MKRN3 mutation and a positive family history, these features established the diagnosis of CPP and supported the initiation of treatment with GnRH analog, with complete regression of the thelarche after 6 months of therapy. The absence of significant bone age advancement, of pubic or axillary hair, or of behavioral or social problems at the diagnosis could be ascribed to the early diagnosis.

Conclusion: The identification of carriers of MKRN3 mutations may contribute to early diagnosis of CPP, facilitating treatment decisions and guiding genetic counseling and prompt intervention in familial cases. This case deepens the available information on the penetrance and clinical characteristics of MKRN3 mutations, and illustrates how genetic testing can be useful in the clinical setting.

P-112

Endocrinopathies in the Follow-Up of Pediatric Leukemia Survivors of Posadas Hospital

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The survival rate in children treated for cancer is approximately 80%. About 40% may develop endocrine disease years later. The aim of this study was to evaluate the frequency of endocrinopathies in leukemia survivors during 10 years of follow up. We conducted a descriptive, retrospective and observational study. We analyzed the medical records of patients referred with leukemia. Inclusion criteria: Patients who have had acute lymphoblastic leukemia (ALL), with 2 or more years free of disease. Exclusion criteria: presence of relapse or death. Clinical examination was performed according to the Children's Oncology Group Long-Term Follow-Up Guidelines. The frequency of occurrence of the different types of endocrinopathy (obesity, hypothyroidism, dyslipidemia, hyperinsulinism, vitamine D deficiency, osteopenia, precocious puberty, growth hormone deficiency and hypogonadism) was evaluated at 2; 5 and 10 years free of disease. Statistical analysis: Categorical data were expressed as number of cases and percentage. The continuous data are expressed as median and range. The medical records of 281 patients diagnosed with leukemia were selected from June 1, 2007 to May 31, 2015. Of the 143 patients (51% male) who met the inclusion criteria of 2 years free of disease, 39 (27.3%) presented endocrine disorders. The median age at diagnosis of ALL was 6.19 years (r: 0.3–14.8). Of the 95 patients with 5 years free of disease, 31 (33%) had endocrinopathies and of the 39 patients with 10 years free of disease, 15 (38%) presented endocrinopathies. The frequency of obesity from 2 to 10 years free of disease increased from 10.5 to 28.2%, of hypothyroidism and dyslipidemia from 8.4 to 23.1%, of hyperinsulinism from 2.8 to 23.1%, of vitamine D deficiency from 7 to 23.1%, of osteopenia from 4.2 to 23.1%, of precocious puberty from 2.8 to 5.1%, of growth hormone deficiency from 0.7% to 2.6% and of hypogonadism from 0 to 5.2%. Conclusions: Endocrinopathies in leukemia survivors tend to increase over time, as is reported. These data should be confirmed with an analytical study.

P-113

Mosaic Turner Syndrome: Study of Five Cases

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Introduction: Turner Syndrome is the most common chromosome anomaly in girls and its diagnosis is difficult. Mosaic (MTS) is challenge diagnostic.

Materials and Methods: The present case study reports on five patients ranging in age from eight (8) to twenty-five (25). The main reasons for consultation included short stature, delayed puberty and primary amenorrhea. In two cases, cúbitus valgus and excessive pigmented nevi were observed and in one case Horseshoe kidney, with urinary infection was noted. Gonadotropins were high relative to ovarian failure and ovarian ultrasound scans showed a volume of less than 1 cc with an infant uterus. Varied mosaicism karyotype was observed. Karyotype 45X/46XY with SRY positive has made gonadectomy.

Discussion: MTS patients display pronounced variability of phenotypic abnormalities, which leads to delayed diagnosis as reported by diverse studies. Major alterations are not common in these patients since in comparison with other studies, cardiac alterations occur at the same rate as they do with the general population.

Conclusion: MTS diagnosis usually goes unnoticed in pediatric age children. Suspicion and high resolution karyotyping are necessary for diagnosis and an interdisciplinary approach. Stature in MTS could be normal.

P-114

Histidine Decarboxylase as a Novel Therapeutic Target for the Treatment of Leydig Cell Tumors in Prepubertal Boys

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Leydig cell tumors (LCTs) account for 1–3% of all testicular tumors in adults and 4% in prepubertal children. While usually benign, approximately 10% of LCTs in adult patients exhibit a malignant phenotype and respond poorly to chemotherapy or radiation. LCT incidence has been increasing worldwide. Although the etiology of LCTs is still unknown, several studies indicate that overexpression of CYP19 aromatase (CYP19) and excessive estrogen (E2) production play a significant role in sustaining Leydig cell tumorigenesis. Also, IGF-1 has been reported to elicit proliferative

effects in rat Leydig tumor cells (LTCs) through an autocrine mechanism. Previously, we described the proliferative effect of histamine (HA) and the overexpression of histidine descarboxylase (HDC) in MA-10 LTCs. Considering that MA-10 LTCs lack 17α-hidroxylase and produce progesterone (P4) as the major steroid in response to trophic hormone and cAMP analogs, we decided to complement our former studies by evaluating the potential role of HDC in regulating the proliferation of R2C LTCs, which show constitutive CYP19 overexpression, as well as elevated E2 and IGF-1 synthesis. Furthermore, we studied HDC expression in human LCT versus normal human testis (NHT). The expression of HDC in R2C LTCs was evaluated by Western Blot and immunocytochemistry. P4 and E2 levels were determined by radioimmunoassay, and CYP19 mRNA expression was evaluated by RT-qPCR. Cell proliferation was assessed as a function of 3H-Thymidine incorporation. HDC immunoexpression was also studied in 9 NHT samples of four age groups (G): G1 (neonatal, n = 2), G2 (infantile, n = 1), G3 (juvenile, n = 3) and G4 (pubertal, n = 3), and in 3 LCT samples. We observed high HDC expression in R2C LTCs, and it significantly increased after a 24 h-treatment with 100 ng/ml IGF-1 ($p < 0.001$). Also, HA stimulated cell proliferation ($p < 0.001$; HA 1 nM vs. Control). Moreover, HDC inhibitors α-methyl-DL-histidinedihydroclorure and epigallocatechin gallate decreased cell proliferation in R2C LTCs, as well as CYP19 expression and P4 and E2 synthesis. Finally, we detected HDC in all the LCT, but only in Leydig cells and germ cells of two NHT, corresponding to G4. In conclusion, our results suggest that HDC may constitute a potential therapeutic target for the treatment of LCTs, at least in infant and juvenile patients.

P-115

Evaluation Index Triglycerides and Glucose as a Marker of Insulin Resistance and Its Comparison with Other Markers of Insulin Resistance in Obese Children

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Introduction: The aim of this study is to evaluate the glycemic index and triglyceride levels as a marker of insulin resistance and its comparison with other indicators is the same as insulin, HOMA index and triglyceride/HDL.

Material and Methods: They were studied in a population of children with obesity, different rates of insulin resistance. The index triglycerides and glucose (TGC and Glucose Index) was evaluated using the formula: natural logarithm Ln (TG [mg/dL] x glucose [mg/dL]/2) (cutoff level ≥8.15), insulin levels (≥20), HOMA (glycemia x Insulinemia/405) (≥3) and triglycerides/HDL ratio (TGC/HDL) (cutoff value: ≥2.05). The relationship between them is also analyzed.

Results: The index triglycerides and glucose is analyzed in 96 children with obesity was found high (≥8.15) in 58 of them (60.41%) (average: 8.65 (range 8.15 to 10.02)) and normal 38 (39.59%) (mean: 7.76), insulin (cutoff level: ≥20) (n = 94 children) was elevated in 32 of them (34.04%, mean 33.5, range: 20–82) and normal in 62 (65.96% average: 11.98); HOMA index is analyzed in 91 children being high (≥3) in 56 (60.21%; average: 5.86) and normal in 38 children (39.79%, average: 1.35); and finally the TGC/HDL (≥2.05) index was evaluated in 83 of them (average: 2.77) is finding increased by 42 (50.60%, average: 4.18) and normal in 49.4% remaining.

Conclusions: The triglycerides and glucose index turned out to be a good marker of insulin resistance and in similar manner correlated with the HOMA index. It is suggested to consider this index as a marker of insulin resistance more in children and adolescents with obesity.

P-116

Obesity and the Use of Probiotics and Prebiotics: Review Systematic

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The increasing prevalence of childhood obesity is a problem worldwide.

It is associate with a increased risk of chronicdisease and mortality, before more prevalent in adultlife, but now on the rise in pediatric patients. For thisreason it is important to study the involvement, development and progression of obesity not yetcompletely clear.

The human intestinal microbiota has being studiedfor over a century. It has importance in bodyhomeostasis, trough the transport of essentialmetabolites, protective, structural and histologicalfeatures. Recent studies point to the use ofprobiotics, live microorganisms administered in adequate amounts that promote health benefits, between the complementary measures for theprevention and management of obesity as dysbiosisprocesses, that is, a disruption in the normal balance of intestinal microbiota and host, have beenassociated to obesity, malnutrition, inflammatorybowel disease, neurological disorders and câncer.

It was made a literature review of science articles, using a database, Pubmed and ELSEVIER. The inclusion criteria for the studies found was the use of prebiotic and probiotic strains in all age groups withoutcomes in body weight, body mass index, waistcircumference and other parameters of adiposity. The microorganisms used were predominantlyLactobacillus genus, Bifidobacterium and othergram-positive bacilli. The strains used were veryheterogeneous between studies and most used a single strain in intervention. The main strain withantiobesity potencial are specially Lactobacillusgasseri SBT2055 and Lactobacillus rhamnosus-CGMCC 1.3724.

Recent studies show the relation between intestinal microbiota and obesity. Currently it is known theimportance of probiotics and prebiotics as adjuvanttreatment in various diseases. However arenecessary new studies that identify the preparationmethod, Initial doses, types of probiotics andprebiotics to be used, biosecurity,

intervention time and characteristics of the population, since theresults are controversial, which hinders theformulation of recommendations to be adopted in professional practice.

P-117

Prevalence of Metabolic Syndrome in Children and Adolecents with Obesity and Overweight in a Childhood Obesity Clinic in Mexico

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Mexico ranks first in childhood obesity being an important health problem for its increasing prevalence and relationship to cardiovascular disease, type 2 diabetes and hypertension. Metabolic syndrome (MS) was proposed to define this connection. Actually, MS is poorly studied in children and adolescents and the limited data available do not allow to do inferences about the magnitude of the problem.

The aim of this was to determine the prevalence of metabolic syndrome in obese children and adolescents in our population.

A retrospective descriptive study was conducted in 752 healthy children and adolescents aged 2–16 years from childhood obesity clinic during October 2013 to April 2016. The studied variables were sex, age, weight, height, body mass index (BMI), waist circumference (CC), basal glucose, insulin, insulin resistance (IR) by HOMA index, triglycerides (TG), HDL and blood pressure (BP). The definition of MS was established according to the ATP III adapted for children, when patients meet 3 to 5 criteria.

The analyzed data after elimination included 630 patients: 323 men (51.2%) and 307 women (48.7%). Average age was 10.7 years. According to BMI, 34 patients (5.3%) have overweight and 596 (94.6%) were obese. The frequency observed of MS clinical parameters was as follows: 77% CC> p90 for age and sex; HTA ≥p95 1.6% for age and sex; 49.5% HDL ≤40 mg/dl; 51.9% triglycerides ≥110 mg/dl; 20.6% glucose ≥100 mg/dl; HOMA ≥2.5 77.7%. MS diagnosis was performed in 355 children and adolescents (56%), 175 men (54%) and 180 women (58.6%). In children distributed by age: from 2 to 5 years were 12 (26%); from 6 to 11 years, 204 (57.9%) and from 12 to 16 years, 139 (59.9%) of the total.

According to MS criteria, we observed high prevalence of MS at early stages of life, being children and adolescents from 6 to 16 years the most affected group, so it is important a prompt and early diagnosis and intervention to prevent and delay cardiovascular diseases, type 2 diabetes and other cardiometabolic diseases.

P-118

Pseudotumor Cerebri: Differential Diagnosis of Headache in Obese Patients

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Introduction: Pseudotumor cerebri (PTC) is a syndrome characterized by headache (75%), papilledema (95%), blurred vision (70%), nausea and vomiting; often associated with obesity. Isolated increased cerebrospinal fluid (CSF) pressure make the diagnosis.

Cases Report: Four patients followed-up in our Obesity Clinic in the Pediatric Endocrinology Department were diagnosed with PTC. Their median age was 13 years (range 11–16), three females and one male, BMI 32–44.8 kg/m^2.

They presented with daily mild to moderate headache associated with nausea, vomiting, blurred vision. One patient developed seizure. All patients were submitted to a complete lab evaluation which was normal. They underwent CT scan and MRI of the head which were also normal. Only one patient had a previous diagnosis of central venous thrombosis. CSF pressure was elevated, with values ranging from 32 to 40 cmH_20 (normal below 20 cmH_2O) with normal biochemical tests and culture. Neurologic evaluation was normal and fundoscopic exam showed papilledema in three of the patients.

Diagnosis of PTC and atypical PTC (patient with no papilledema) was made due to severe obesity. Treatment with acetazolamide was initiated in all the four patients. After on average of six months of treatment all patients presented clinical improvement and since they were also being treated for obesity, reduction in their BMI allowed gradual dose decrease in acetazolamide until total suspension in three patients. The one male patient who had only partial clinical improvement did not lose weight and had laparoscopy sleeve gastrectomy indicated. After the surgical procedure he had significant weight loss (37.4% of the weight) and showed full recovery of PTC.

Conclusion: Although it is a rare condition, in our casuistic four of 400 patients had diagnosed. PTC has to be investigated in obese children with headache using complementary exams and ophthalmological evaluation The severe obesity is a challenge for the pediatrician because the management includes life style modification, pharmacological intervention, and eventually surgery.

P-119

Chylomicronemia in Infants: A Case Report

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Chylomicronemia syndrome is characterized by the presence of pathologic fasting chylomicrons associated with fasting triglyceride levels >10 mmol/l (875 mg/dl), and the presence of at least one accompanying clinical feature, such as eruptive xanthomas on the trunk and extremities, lipaemia retinalis, recurrent abdominal pain, acute and/or recurrent pancreatitis and hepatosplenomegaly.

The genetic basis for chylomicronemia is heterogeneous, but is often caused by mutations in the genes LPL, APOC2, APOA5, GPIHBP1 and LMF1.

We report a case of a one month old boy, with history of consanguinity. A blood sample was taken by a respiratory infection and was incidentally found a 'creamy' appearance. Lipid profile revealed fasting triglycerides of 18856 mg/dl, Total Cholesterol 939 mg/dl, LDL 701 mg/dl and HDL <5 mg/dl. He had eruptive xanthomas on the face and lipaemia retinalis. Echocardiography reported non-obstructive left ventricular hypertrophy and hepatobiliary ultrasound was normal. Further laboratory investigations showed normal glucose, liver, and kidney function.

The first therapeutic measure was an exclusive milk feeding with medium-chain triglyceride-based formula (MCT) (Monogen®). With this treatment plasma lipid levels weresignificantly lower (triglycerides of 265 mg/dl, total cholesterol 258 mg/dl, LDL 159 mg/dl and HDL 8 mg/dl).

During follow-up for 3 years he received treatment with diet without saturated fat, supplemented with MCT formula and high dosis of omega-3 fatty acids capsules. Further elevation of triglyceride levels was noted again once he started the complementary feeding. It has been difficult tomaintainadherence to this extremediet, keeping triglycerides from 2000 to 5000 mg/dl.

The sequencing of the genes LPL and APOC2 did not showed genetic variants.

The mainstay of therapy for patients with primary chylomicronaemia is a diet very low in fat. The improvement of the lipid profile in these patients is a challenge for the endocrinologist. In our patient, the best control was achieved when he received exclusive milk feeding with MCT formula.

Given the severity of the case, the difficulties in nutritional adherence and lack of evidence, other treatments described in case reports and emerging therapiescould be considered in order to avoid life-threatening complications such as pancreatitis.

P-120

Nutritional Quality of Diets of Children from One Area of the Basque Country (Spain)

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Objectives: Good nutrition is essential to healthy childhood. Because there is no previous analysis of diet of children from the province of Gipuzkoa, in the Basque Country, we evaluated intake from children at scholar age to ascertain whether their diet fulfil nutrient intake recommendations.

Material and Methods: Data were collected during 2012–2013 as part of a program to determine vitamin D status in children from Goierri-Alto Urola shire in the province of Gipuzkoa (Spain). Data on children's dietary intakes were collected through 24-hour dietary recalls. SUBJECTS: The analysis is based on a representative sample of 249 children (51.8% girls, 8.2% boys) at an average age of 8.7 ± 3.2 years who attended Hospital of Zumarraga (Gipuzkoa). Mineral and vitamin adequacy was assessed by comparing usual nutrient intake distributions to Estimated Average Requirements (EAR) and Recommended Dietary Allowances (RDA) when EAR was not available (Institute of Medicine, 2005). According to the objectives proposed by the Spanish Society of Community Nutrition, the prevalence of inadequate and excessive intakes of proteins, carbohydrates, fats, dietary fibre and cholesterol were evaluated.

Results: Most of the children presented an excessive intake of protein (girls consumed 17.6 ± 3.8% of total energy intake as protein and boys 17.1 ± 3.2%), total fat (girls: 39.4 ± 7.2% of total energy intake and boys 38.8 ± 6.7%) and saturated fat (girls: 11.8 ± 3.3% of total energy intake and boys: 11.7 ± 3.3%). In general, noncompliance with nutrient recommendations was high for both sexes with no statistical differences (with the exception of monounsaturated and polyunsaturated fat). With regard of micronutrients intake, a high prevalence of inadequate intake of calcium, potassium, vitamin D, vitamin E and folates was detected.

Conclusions: According to a previous nutrition study in the Basque Country (2005), no changes in consumption of carbohydrate, protein and total fat were observed. It has been showed that there were several intake deficiencies such as calcium, potassium, vitamin D, vitamin E and folates, which could have an important role in children growth. We would suggest to Public Health Government and institutions to make an effort to improve this pattern.

P-121

Recurrent Bacterial Thyroiditis Secondary to Pyriform Sinus Fistula. A Case Report

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Introduction: Acute suppurative thyroiditis is one of the rare causes of neck mass in children and manifests with recurrent thyroid abscess, signs of systemic inflammatory response and local pain. When this condition is suspected it should be discarded as remnants of branchial congenital anomalies apparatus.

Case Presentation: Preschool female 3 years with no history of previous thyroid disease that manifested as recurrent thyroid mass with local inflammatory changes, suppurative fistulae drainage, fever and sore throat; Ultrasonography reported abscessed collection in left thyroid lobe. She received antibiotics and surgical management where the remnants of brachial apparatus is evidence piriform sinus fistula. Histopathology confirmed bacterial infection and remnants of pyriform sinus fistula. She presented as a complication hypothyroidism requiring levothyroxine substitution.

Discussion: Acute suppurative thyroiditis is a rare condition in children that when presented should be discarded remnants of brachial apparatus that predispose to its presentation, taking into account the anatomical features of the thyroid gland that make it resistant to infections. The germs can be gram positive and less commonly gram negative and anaerobes in the context of polymicrobial infections. The diagnosis is made by ultrasonography and to identify the piriform sinus fistula is used telescopic pharyngoscopy. Treatment is antibiotic and surgical after resolution of the inflammatory process; It should make long-term monitoring because there may be recurrence, surgical complications and hypothyroidism.

P-122

Etiology and Evolution of Newborns with Congenital Hypothyroidism and Eutopic Thyroid Gland

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Introduction: In Neonatal Screening Programs, recent studies have reported an increase in the detection of infants with congenital hypothyroidism (CH) associated with eutopic thyroid gland. It is controversial to be exclusively attributable to changes in TSH cutoff.

Objectives: To describe clinical, biochemical, and complementary studies features at diagnosis.

To analyze the evolution of the patients who met criteria for the re-evaluation.

Patients and Methods: We retrospectively analized medical records of 237 patients with CH detected by neonatal screening in Córdoba, Argentina from 1996 to 2015 with an incidence of 1/2146.

81 patients (34%) F35/M46 had eutopic thyroid gland; 10 patients with associated genetic syndromes were excluded.

TT4, FT4, T3, TSH, TPOAb, TgAb and Thyroglobulin (RV:>15 days: 6–83 ng/ml; <15 days: 29–173 ng/ml) (ECLIA ROCHE), thyroid ultrasonography and ^{99}Tc scan were assessed.

TSH cutoff for diagnostic confirmation was ≥10 mUI/ml.

Genetic analysis were performed in selected cases.

Those who had no goiter, normal thyroglobulin, and had not required increases in L-T4 dose underwent re-evaluation after the age of 3 years.

Results: 50% of the patients (36/71) showed glandular hyperplasia.

In 84% (60/71) TSH cutoff for diagnostic confirmation was ≥20 mUI/ml (20–1186).

TgAb and TPOAb were positive n: 1.

Tg levels were: normal in 29% (21/71), elevated in 56% (39/71) and low in 14% (10/71).

Gene mutations were found in 18 patients (25%): TPO n:7, Tg: n:6, NIS n:2, DUOX2 n:2 and T3 TRβ n:1.

Congenital anomalies were reported in 11% (8/71) patients 11% (8/71) were re-evaluated resulting in: 5 Transient CH, 2 Permanent CH and 1 with Resistance to Thyroid Hormone.

The incidence of infants with HC and eutopic gland remained constant along 19 years of the Program.

Conclusions: Our results show that the incidence of CH with eutopic gland was stable, with permanent forms characterized by phenotypes of moderate to severe intensity.

Other genetic and environmental factors should be investigated to help determine possible associated risk factors.

P-123

Phenotypic Characteristics of Permanent Congenital Hypothyroidism with Topical Thyroid in Children Screened by the Newborn Screening Program

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Objective: To determine the phenotypic characteristics of congenital hypothyroidism (CH) in children with topical thyroid screened by a Newborn Screening Program.

Patients and Methods: During the 1997–2007 period, 2,915,592 children were screened by the Newborn Screening Program. CH was diagnosed (TSH >10 microUI/mL) in 865 patients and they were followed-up at the University Hospital. At three years of age 680 of them underwent thyroid ultrasound and nuclear medicine tests (thyroid scan and perchlorate discharge test) for

the etiologic diagnosis of CH. The exams were performed by a single specialist in radiology and diagnostic imaging. Out of 680 patients, 118 presented absent or ectopic gland, transient hypothyroidism or inconclusive etiologic evaluation and were excluded. The study was approved by the Institutional Review Board of the University.

Results: Among the 562 patients with topic thyroid, 34 presented with hemiagenesis (6%) and 80 with hypoplasia (14.3%). In 143 children it was observed a goiter (25.4%) and 305 presented a thyroid of normal volume for the children's height (54.3%). The perchlorate test was positive in 116 children (21%).

Conclusion: In this study we found a higher prevalence of children with CH, topic thyroid and synthesis defects (positive perchlorate discharge test) than other studies conducted in Brazil, that reported rates ranging from 10 to 15%. This find suggests the local population may have higher incidence of mutations of genes involved in the steps of the synthesis of thyroid hormones. However, molecular biology studies are necessary to confirm this hypothesis.

P-124

Usefullness of Levotiroxine Dose for Earlier Recognition of Transient and Permanent Congenital Hypothyroidism in Children with Eutopic Gland

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Introduction: The prevalence of congenital hypothyroidism (CH) has been raising. The reason could be the lower cut-off in screening programs which could increase the diagnosis of transient CH (TCH). This study aimed to identify factors that would allow earlier discrimination between TCH and permanent CH (PCH) in patients with eutopic thyroid gland (ETG).

Study Design: We analyzed every newborn with positive screening results for CH referred to our confirmation center between 1995 and 2013. CH was confirmed with TSH ≥25 uUI/ml and T4<10 ug/dl. Median Levotiroxine dose (LTd) was 12.13 (10.29–13.33) mcg/kg/day at start of treatment. At three years of age 675 children were reevaluated to distinguish between PCH and TCH. Median TSH, T4, LTd at start, at first and second year, and at reevaluation were compared between PCH and TCH patients with ETG. Statistical analysis: R (Project for Statistical Computing) version 3.2. Mann-Whitney test was used to compare differences between TCH and PCH children.

Results: One hundred and thirty (19.2%) patients had ETG. TCH forms were found in 28 (21.5%) cases. No significant differences were found in TSH and T4 levels between TCH and PCH during follow-up. Median LTd are showed in Table 1.

LTd at second year was the only variable that showed significant differences between PCH and TCH patients (p = 0.00068). ROC curves analysis showed that the best LTd cut-off point at to second year was 2.92 mcg/kg/day, with a specificity of 78% and sensitivity of 58%.

Conclusions: Patients did not show significant differences in both TSH and T4 serum levels during follow-up.

– Although LTd was significantly different at 2 years, the ROC curves could not identify specific cut-off values between PCH and TCH patients.

P-125

TSHR and NKX2-1 Germline Mutations Are Not a Frequent Cause of Congenital Hypothyroidism Due to Thyroid Dysgenesis in Mexican Population

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Mexico is globally ranked as one of the countries with the highest incidence of congenital hypothyroidism (CH). There are no studies in Mexico that have searched for germinal mutations in candidate genes such as TSHR and NKX2-1 in patients with CH.

This is an observational, descriptive, cross-sectional and ambispective study. We included 95 Mexican patients between 5 and 120 days old, with an abnormal thyroid function test as well as scintigraphy or ultrasound imaging findings compatible with CH due to thyroid dysgenesis (TD): ectopia (n = 19), agenesis (n = 61) or hypoplasia (n = 15). Both, TSHR and NKX2-1 genes were analyzed in 15 cases with thyroid agenesis, NKX2-1 gene was analyzed in 19 patients with ectopic thyroid gland and TSHR gene in 61 patients (46 with thyroid agenesis and 15 with thyroid hypoplasia).

Mutations were searched in the three coding exons of the NKX2-1 gene and in the 10th exon of TSHR gene by polymerase chain reaction, single-strand conformation polymorphism (SSCP) and by Sanger automated sequencing. We found 3 genetic variants related to TSHR gene, one synonymous and two non synonymous: c.1377G>A (p.Ala459Ala) in one heterozygous patient; c.2181G>C (p.Glu727Asp) 11 heterozygous and 65 homozygous for C allele,

Table 1. Median LTd (mcg/kg/day) in PCH and TCH children (for Abstract P-124)

	Start	First year	Second year	Reevaluation
PCH	12.29 (10.12–13.43)	3.88 (3.51–4.49)	3.45 (2.97–4.12)*	3.16 (2.69–3.85)
TCH	11.55 (10.72–12.94)	3.64 (3.09–4.16)	2.89 (2.31–3.38)*	2.32 (2.09–2.86)

and c.1264T>C (p.Trp422Arg) in one heterozygous patient. No mutations or polymorphisms were found related to NKX2-1 gene.

In this study, the high predominance of CH in Mexican population is not explained by mutations in the TSHR or NKX2-1 genes. The three variants in TSHR have been previously described at international databases as polymorphisms, but we consider that c.1264T>C (p.Trp422Arg) should be mentioned as a genetic variant of uncertain clinical significance because it has not been reported in any homozygous individual, there are 12 different species with highly conserved tryptophan, which suggests that a change on it would be poorly tolerated, with the possibility of altering protein function and it was considered pathological by SIFT, Mutation Taster and PolyPhen when in silico analysis was performed. We will look for this variant in 100 healthy controls in order to ascertain or discharge a pathogenic relation with CH.

Table 1. Thyroid function tests (for Abstract P-126)

	TSH (μUI/ml)	TT4 (μg/dl)	FreeT4 (ng/dl)	FreeT3 (pg/ml)
Index case (20 days)	11.30	20.70	2.63	198.9
Index case (23 month)	13.63	20.06	3.06	303.38
Mother	3.66	18.6	2.46	–
Father	2.11	7.0	1.06	–
Maternal grandmother	1.75	7.25	0.94	–

Reference values adults: TSH: 0.35–5.0 μIU/ml; Free T4: 0.71–1.85 ng/dl; Total T4: 4.5–12.0 μg/dl. Over 30 days of age: 0.49–4.67 μIU/ml; Free T4: 0.71–1.85 ng/dl; Free T3: 2.7–4.6 pg/ml; Total T4: 6–12 μg/dl.

P-126

Thyroid Hormone Resistance: A Case Report Detected by Neonatal Screening

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Resistance to thyroid hormone (RTH), an inherited syndrome of reduced sensitivity to thyroid hormone, is characterized by high serum thyroid hormones together with inappropriately normal TSH. Phenotype of RTH is variable; most patients present mild to moderate symptoms. About 85% of cases result from an autosomal dominant mutation in the gene coding for thyroid hormone receptor β (THRβ). This report describes a 20 days old female with RTH detected through neonatal screening. Clinical evaluation and biochemical analyses of the patient, mother, maternal grandmother and father were made. Preterm newborn with a gestational age of 36 weeks, birth weight 2565 grams and length of 47 cm, presented feeding difficulty and neonatal jaundice. Mother presented preeclampsia, cardiac arrhythmia, suppressed level of TSH with elevated thyroid hormones and presence of goiter on ultrasound. TSH screening test performed on 3rd day of life was 20.0 μU/mL (cut-off = 10 μU/mL). Further investigations revealed elevated serum free thyroid hormones (FT4 and FT3) in the presence of unsuppressed TSH (table 1), negative thyroid antibodies and absence of symptoms. Electrocardiogram and cardiac ultrasonography tested normal; thyroid ultrasonography at 23 month demonstrated goiter in index case. RTH was confirmed by positive hotspot mutation p.Met313Val (c.937A>G) in THRβ gene in mother and patient. At the age of 23 months patient was symptomless without pharmacological treatment. This is the first case of RTH detected by the neonatal screening program of our state, which has screened over 4 million newbornssince 1991. Abnormal TSH on neonatal screening associated with elevated thyroid hormones values and absence of clinical symptoms should encourage physicians to consider RTH syndrome, therefore avoiding iatrogenic treatment.

P-127

Evaluation of the Response to the Oral Glucose Tolerance Test (oGTT) in Overweight and Obese Adolescents

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Patients with overweight and obesity may have carbohydrate metabolism disturbances such as insulin resistance, hyperinsulinism, impaired fasting glucose, glucose intolerance and diabetes. These abnormalities can be evaluated with fasting glucose and insulin dosages or after oral glucose test. The aim of this study was to evaluated the response profile to oGTT in adolescents with overweight and obesity. Methods: retrospective study, a survey of medical records of 147 adolescents with overweight accompanied on an endocrinopediatrics ambulatory. The following data were collected at the time of the oGTT: chronological age (CA), gender, weight, and height to calculate body mass index (expresses as SDS – WHO, 2007), puberal stage. The test was carried out with 1.75 g/kg, po, glucose with serum glucose and insulin dosages in basal,30, 60, 90 and 120 minutes. Results: we evaluated 147 adolescents of both genders (54 boys and 129 girls), all in puberty, mean (SD) CA of 12.9 (2.2) years. These patients underwent a total of 183 oGTT. No patients had type2 diabetes. There were no differences between genders in relation to CA or BMI SDS, but boys had insulin sum at oGTT greater than girls (457.3 x 360, $p = 0.043$). We divided the patients into two groups according to the sum of insulin at oGTT (25 and 75 percentile). Patients at p75 of sum of insulin were younger than those at p25 (12.3 (2.2) x 13.4 (1.9), $p < 0.05$, respectively) and have higher BMI SDS. Fasting insulin levels were different in both groups, with higher values in p75 group, but with overlapping values (median 27 (22–35) x 11 (8–18), $p < 0.05$). Con-

clusion: boys have insulin sum higher in oGTT than girls. Fasting insulin values may not reflect the insulin response to the stimulus of oral glucose challenge.

P-128

Improved Clinical and Laboratory Changes after 12 Months of Use of Metformin in Obese Children and Adolescents

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Background: Childhood obesity is one of the most prevalent and challenging health care concerns. In this context, insulin resistance (IR) is an important disorder with strong association with metabolic (type 2 diabetes, hypercholesterolemia) and cardiovascular (hypertension, atherosclerosis) outcomes. Clinical trials have been showing Metformin as an effective drug on reducing the IR and body mass index (BMI). However, there's little data on use of metformin in children.

Objective and Hypotheses: The aim of this study is to evaluate our experience on use of metformin in obese children and adolescents with IR, and determine the benefits in weight loss after 12 months of treatment. Other clinical and biochemical variables were described.

Method: Retrospective study of 50 children and adolescents followed in the Pediatric Endocrinology Clinic ICR-FMUSP, due to obesity and IR, at baseline and after a year of use of metformin. Exclusion criteria: T2DM, Neurological disorders with or without mental impairments and use of other weight related medications. Clinical (age, gender, weight, height, waist circumference, BMI, pubertal stage) and biochemical (fasting glucose, insulin, lipid profile) data were analyzed. IR was measured by HOMA-IR.

Results: Mean age 12.4 ± 2.2 (8–17 years), without gender predominance. At baseline and 12 months after metformin's introduction, statistical analyses of the studied variables were respectively: HOMA-IR: 4.7 ± 2.5, 3.56 ± 1.8 ($p = 0.005$); Fasting insulin 23 ± 9.5, 17.3 ± 9.1 ($p < 0.001$); BMI score Z 3.2 ± 0.67, 2.9 ± 0.58 ($p < 0.001$). There was a statistical improvement in fasting glycemia ($p = 0.002$) and cholesterol ($p = 0.041$). There were no significant differences in outcomes between others variables.

Conclusion: Metformin increased insulin sensitivity, and provided a statistically significant, but very modest reduction in BMI. This poor alteration in BMI makes our results arguable. Further researches are needed to prove if there is a substantial clinical benefit on using metformin in children and adolescents.

P-129

Beta Cell Function and Clinical Evaluation in Adolescents with Cystic Fibrosis: The Havana Multicenter Study

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Background: The impaired nutritional status and decreased pulmonary function preceding Cystic Fibrosis-Related Diabetes (CFRD) may be the consequences of insulin deficiency and insulin resistance. The progression of both process triggered by puberty may be responsible for clinical deterioration and eventual CFRD.

Aim: To estimate β cell function in Cystic fibrosis adolescents and it relationship with clinical evaluation.

Methodology: Nutritional and pulmonary condition of 22 Cystic fibrosis patients between 10 and 19 years old (mean 14.2 (±2.8)) attended in pediatric hospitals of Havana was evaluated by Shwachman score. Fasting plasma glucose and insulin were determined to estimate β cell function on the basis of Homeostasis Model Assessment (HOMA). HOMA-β and HOMA-IR equations were calculated, and QUICKI index was also used to measure insulin resistance. Frequencies obtained were compared through Cohen's kappa index.

Results: Impaired fasting glucose was demonstrated in 5 adolescents and only 1 patient had insulin resistance by HOMA-IR. 17 patients (77.3%) showed an Excellent (86 to 100 points) or Good (71 to 85 points) Shwachman score and 5 (22.7%) showed Medium or Bad scores (lower than 70 points). There were no differences between groups according to fasting plasma insulin, HOMA-IR or QUICKI means. Mean of fasting serum glucose was significantly higher (6.04 ± 0.58) in adolescents with worst clinical condition in comparison with the other group (4.82 ± 0.73) ($p = 0.003$), and 4 of the 5 adolescents with impaired plasma glucose (80.0%) had clinical deterioration ($p = 0.003$). Patients with Medium or Bad Shwachman evaluation showed remarkable poorer HOMA-β estimation (42.49 ± 4.77) than those with Excellent or Good scores (230.96 ± 86.67) ($p = 0.001$). Agreement between Shwachman score and impaired fasting glucose was significant (0.741).

Conclusions: β cell deficiency, more than insulin resistance, was associated to impaired fasting glucose, and importantly, to nutritional and pulmonary deterioration in adolescents with Cystic fibrosis.

P-130

Impact of Insulin Therapy on Body Mass Index and Pulmonary Function in Patients with Cystic Fibrosis-Related Diabetes Mellitus in a Non-Caucasian Population

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Objective: Cystic fibrosis is the most common autosomal recessive disease among Caucasians and mortality rates are high. Recent therapeutic advances have increased survival rates, resulting in increased risk of comorbidities, such as cystic fibrosis-related diabetes (CFRD). Current guidelines recommend early diagnosis and treatment of CFRD with insulin; however, few studies have evaluated the clinical impact of therapy. Moreover, published studies have focused on Caucasian populations. The objective of this study was to evaluate the effect of insulin on BMI and pulmonary function in a non-Caucasian cohort with CFRD.

Research Design and Methods: This retrospective study analyzed the medical records of patients reviewed at the Multidisciplinary Center of Cystic Fibrosis of São Paulo School of Medicine, Brazil. BMI and pulmonary function (measured by forced vital capacity [FVC] and forced expiratory volume [FEV] in 1 second) were assessed. The relevant time interval commenced one year before (T-12) and ended one year after (T+12) the introduction of insulin (T0).

Results: The zBMI values were as follows: –0.434 ± 1.3 (T-12), –0.462 ± 1.3 (T-6), –0.547 ± 1.3 (T-3) –0.607 ± 1.3 (T0) –0.478 ± 1.3 (T+3), –0.534 ± 1.3 (T+6), –0.547 ± 1.3 (T+12). Between T-12 and T0, there was a zBMI reduction of –0172 ($p < 0.05$). Following T0, zBMI increased and then stabilized. FVC and FEV worsened between T-12 and T0 and stabilized after T0.

Conclusions: Early insulin therapy has a positive effect on BMI and pulmonary function in non-Caucasian patients with CFRD.

P-131

Utility of Complete Oral Glucose Tolerance Test to Evaluate Disorders in Carbohydrates Metabolism in Cystic Fibrosis

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Introduction: Disorders in carbohydrates metabolism are a frequent comorbidity in patients with cystic fibrosis.

Objetives: To evaluate disorders in carbohydrates metabolism, from 8 years of age, its possible clinical impact and its correlation with body mass index (BMI) and lung function (FEV1).

To study insulin secretion by Availability Index (DI) and measurement of C-peptide.

Material and Methods: In 34 patients (M23, F11) we performed C-peptide, HbA1C and complete oral glucose tolerance test (OGTT): glucose and insulin at 0, 30, 60, 90 and 120'.

We calculated DI (insulin sensitivity) x (insulin secretion). Insulin sensitivity: 1/fasting insulin.

Insulin Secretion: Δinsulin 0–30'/Δglucose 0–30'. We evaluated pancreatic exocrine function, bacteriology and molecular biology. Actual data about BMI (SDS) and FEV1 (%) were compared to previous year.

OGTT results were classified into: tolerance normal glucose (TNG) impaired fasting glucose (IFG), impaired glucose tolerance (IGT), indeterminate alteration (INDET) and cystic fibrosis related diabetes (CFRD). Patients were divided in two groups, G1 (TN-IFG) and G2 (IGT-INDET-CFRD).

Statistics: SPSS program. Mann-Whitney and Student test.

Results: Mean age was 12.71 ± 2.86 years, 67.6% were pubertal. OGTT disorders were found in 64.7% patients (n = 22): IGT 29.4% (n = 10), IFG 11.8% (n = 4), INDET 11.8% (n = 4) and CFRD 11.8% (n = 4). Three patients were pancreatic sufficient (9%), one of them had INDET. All patients younger than 10 years (20%) had normal OGTT. C-peptide was low in 85% patients.

There were significant differences in BMI between G1 –0.06 ± 1.46 and G2 –1.27 ± 1.78 ($p = 0.040$), and in DI between G1 1.65 (0.91–5.2) and G2 0.86 (0.62–1.22) ($p = 0.008$). Considering patients with impaired OGTT but excluding CFRD, significant differences were found in patients with impaired tests between actual BMI –1.22 ± 1.82 and BMI in previous year –0.59 ± 1.45 ($p = 0.005$), and between actual FEV1 77.67 ± 27.49 and FEV1 in previous year 89.92 ± 29.60 ($p = 0.013$).

Conclusions: 1) Disorders in carbohydrates metabolism in this group of patients are frequent. They were found from 10 years of age.

2) BMI and FEV1 worsened in comparison with the previous year in patients with OGTT alterations (excluding CFRD).

3) Availability Index was the only useful parameter that could demonstrate beta cell function impairment.

P-132

To Determine the Frequency of Disorders of Carbohydrate Metabolism in Patients with Cystic Fibrosis

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Objective: To determine the frequency of Disorders of Carbohydrate Metabolism in patients with Cystic Fibrosis.

Design: Observational, descriptive and cross study.

Introduction: Diabetes is a common comorbidity of Cystic Fibrosis that impairs its course due mainly to a specific Pancreatic Beta-Cell Dysfunction. The onset of Diabetes typically occurs in the second decade of life but a Prediabetes stage is frequently present and can be diagnosed.

Study Population: Patients with Cystic Fibrosis treated at Mexico National Institute of Pediatrics between February 1st 2016 and February 1st, 2018.

Main Outcome Measures: Venous blood glucose and blood insulin levels during the oral glucose tolerance test OGTT at minute 0, 30 and 120, capillary blood glucose at minute 0, 30, 60, 90 and 120.

Results: The preliminary results of the 2 years-prospective study are showed. 20 patients have been included in the study. The median age of the patients was 10.6. The results were analysed in two groups: Group 1, age <= 10; group 2, age >10. All the patients had normal fasting blood glucose level. 10% of the patients had impaired glucose tolerance IGT, 8.3% in group 1 and 12.5% in group 2. After analysing blood glucose levels at minute 30, 60 and 90, an INDET result was presented in 65% of the patients, 66.6% in group 1 and 62.5% in group 2. Insulin resistance was determined in 10% of the patients, 8.3% in group 1 and 12.5% in group 2, after analysing the insulin resistance index HOMA. None of the patients were diagnosed with diabetes.

Conclusions: The same metabolic alteration (INDET) was found in children younger than 10 years old as well as in those older than 10 years old. It is to be confirmed at the end of the study when the complete analysis of the population is carried out. However, in the meantime we recommend that even though the patient does not meet the diagnostic criteria for diabetes, each case is individualized. It is to evaluate the benefits of insulin therapy in patients with inadequate progression of weight and height and/or impaired pulmonary function whose glucose metabolism may be affected.

P-133

Congenital Hyperinsulinemic Hypoglycemia Due to a Splicing Site Mutation

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Congenital hyperinsulinemic hypoglycemia or nesidioblastosis is the most common cause of persistent severe hypoglycemia in infancy and has an incidence of 1 in 40.000 live births. Brain damage due to severe hypoglycemia must be prevented by an early diagnosis and aggressive intervention. Eleven distinct gene defects, involved in the pathways that regulate pancreatic beta-cell insulin secretion, have been associated with monogenic forms of congenital hyperinsulinism: ABCC8, KCNJ11, GLUD1, GCK, HADH1, UCP2, MCT1, HNF4A, HNF1A, HK1 and PGM1. The most common causes are recessive mutations of ABCC8 and KCNJ11. The disease is the result of an extensive formation of new Langerhans islets that can be diffuse or focal. In many cases pancreatectomy is neccesary due to imposibilities in controlling insulin secretion. A girl born at 38th week gestational age by cesarean incision due to hypertensive disease of pregnancy, weighed 4645 grams, measured 50 cm in length and presented a 7/8 Apgar, without dysmorphias. Within minutes of life installed respiratory distress syndrome, hypoglycemia 20 mg/dl requiring an intravenous support of 10%glucose. A critical blood sample was taken and shown hypoglycemia (10 mg/dl), hyperinsulinemia (90 uIU/ml) and absence of ketonemia. Persistent hypoglycemia was observed despite intravenous glucose inyection (20 mg/kg/min), diazoxide, hydrocortisone, octreotide and glucagon treatment. The genetic study of ABCC8, KCNJ11 and HNF4A genes revealed an heterozygous splicing mutation c.3991+G>A at ABCC8 gene favouring a focal lesion within the pancreas. 18F-DOPA PET-CT scanning could not be performed. This mutation affects the highly conserved splice donor site of intron 32 and is predicted to be pathogenic. Both parents were also studied and showed that the father presents the same mutation but is clinically unaffected. The patient has been partially pancreatectomized (97%) at 30 days of life, leading to a diabetic state that has been initially treated with intravenous Insulin and after with intermediate acting Insulin and rapid acting Insulin. C Peptide measurements were low. Insulin requirements were declining and currently she is not receiving it, while maintaining normal glucose levels. Prompt diagnosis and treatment is essential in these patients to avoid neurological sequelae of persistent hypoglycemia.

P-134

Glycogen Storage Disease Type I b as a Cause of Hypoglycemia

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Introduction: Glycogen storage diseases (GSD) are inborn errors of metabolism secondary to one of the glycogen synthesis or degradation pathways. Type I b is caused by a deficiency in the glucose-6-phosphate transporter (G6PT) and is characterized by hypoglycemia, neutropenia and neutrophil dysfunction. This is clinically manifested as severe hypoglycemia and repetitive bacterial infections. It is due to a mutation of the SLC37A4 gene on cromosome 11q23.

Case Report: A 4 year 6 month old female, which at two weeks old presents with repetitive bacterial skin infections, one of them evolving into septic shock, with neutropenia, a neutrophil count of less than 500 mm3, and a negative immunodeficiency study. She responds favorably to Filgrastim (granulocyte colony stimulating factor).

She evolves with severe and persistent hypoglycemia, progressive hepatomegaly and a negative autoimmune and viral hepatic study. During hypoglycemia critical sample, there was no hyperinsulinism, altered conterregulatory hormonal responses nor lactic acidosis. As liver biopsy is compatible with GSD, a special diet is started with good clinical response.

Gene sequencing of SLC37A4, found two heterozygous mutations where found:

1) c.82C>T, in exon 1, which leads to the p.Arg28Cys change.

2) c.1194_1201delGGtGGcTG, in exon 9, which leads to p.Trp398X change.

Discussion: Glycogen storage disease type I b is a vary rare disease, besides the severe hypoglycemia, it has the added gravity of an increased risk of repetitive bacterial infection.

P-135

Outcome of Patients with Congenital Hyperinsulinism. The Utility of [18F] Dihydroxyphenyl-Alanine Positron Emission Tomography Imaging (18F-DOPA-PET-CT) in Therapeutics Decisions

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Congenital hyperinsulinism (HI) results from inappropriate insulin secretion and is most commonly caused by mutations in the ABCC8 and KCNJ11 genes which encode for the pancreatic β-cells ATP-sensitive potassium channel subunits. Diagnosis of HI is based on an evidence of elevated plasma insulin levels during hypoglycemia, suppressed β-hydroxybutyrate and NEFA. Treatment with diazoxide, octreotide or sirolimus can restore euglycemia, otherwise an extensive pancreatectomy is generally required. The histopathological lesions (focal/difuse) are differentiated by ^{18}F-DOPA-PET-CT scanning. In the focal form a small resection can be curative with a low risk of diabetes.

Objective: To describe a retrospective series of cases of 6 patients with HI, and to highlight the usefulness of pancreatic resection guided by ^{18}F-DOPA-PET-CT in patients with focal disease resistant to medical treatment.

Results: Six patients without dysmorphic features born to nonconsanguineous parents presented with hypoglycemia (6–28 mg/dl), within 6–48 hours of life associated with seizures; three were macrosomic. Pregnancies were uneventful except for one who had fetal bradycardia during labor. Maximum glucose infusion rate required was: 8–21 mg/kg/minutes. Laboratory investigations during hypoglycemia showed: Insulin:5–46 uUI/l (NV‹2), βhydroxybutyrate: 0.03–0.1 mmol/l (NV: 0.03 to0.35), NEFA:0.13–0.5 mmol/l (NV0.1–0.9), GH:5.4–33.0 ng/ml (NV >20), Cortisol:10.40–33 ug/dl (NV›18), negative urinary ketone bodies. Glucose increase post glucagon:42–62 mg/dl (>30 is consistent with HI). All had normal ammonia. High insulin level during hypoglycemia with low values of β-hydroxybutyrate allowed diagnosis of HI. Genetic testing identified ABCC8 mutations in 4 patients, in the remaining two patients ABCC8 and KCNJ11 sequencing did not identify a mutation. In one patient HNF4A gene was also screened but no mutation was found. Five patients underwent a ^{18}F-DOPA-PET-CT evaluation, 3 had diffuse uptake and two had focal. Two patients with diffuse pattern were diazoxide responsive and one did not respond to diazoxide (15 ug/kg/day), octreotide (48 ug/kg/day) nor sirolimus (0.75 mg/m^2/day), this patient, required near-total pancreatectomy to achieve transient euglycemia

followed by relapse 2 month after. One patient with focal disease responded to diazoxide while the other did not response to diazoxide (15 ug/kg/day) or octreotide (24 ug/kg/day), requiring surgery to achieve normal glucose levels.

Conclusions: The ^{18}F-DOPA-PET-CT has contributed to identify patients with a focal disease and subsequent partial pancreatic resection allowing normal blood glucose homeostasis. Patients receiving medical treatment should maintain long-term surveillance.

P-136

Neonatal Morbidity in Children of Mothers with Gestational Diabetes

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Introduction: Gestational diabetes is a glucose tolerance disorder of varying severity that begins during pregnancy. The children of gestational diabetes mothers are exposed to an environment with hyperglycemia, which determines increased secretion of fetal insulin that can alter embryogenesis and growth, resulting in impaired functions as macrosomy, respiratory distress and hypoglycemia.

Objectives: To determine the frequency of neonatal morbidity in infants of diabetic gestational mothers according to Freinkel's classification and treatment; also to determine the frequency of perinatal complications by gestational age of diagnosis.

Methodology: A retrospective descriptive cross-sectional study was conducted on 66 infants of diabetic gestational mothers born between March 2015 and June 2016 at Hospital's Perinatology service whose mothers were treated by the team of gestational diabetes. They were studied: weight and height at birth, neonatal complications, type of gestational diabetes (A1, A2 and B1), gestational age at diagnosis and used treatment.

Results: According to the data table attached in gestational diabetes A1 we found these complications: macrosomy (3) (33.3%), respiratory distress (5) (55.5%), hypoglycemia (1) (11.1%) divided in insulin treated and non insulin treated mothers. With gestational diabetes A2 we found: macrosomy (4) 44.4%, respiratory distress (4) (44.4%), hypoglycemia (1) (11.1). Of the total macrosomic (8), 75% (6) had been late diagnosis after week 30 of gestation. Of those who had respiratory distress (10) the 30% (3) presented late diagnosis.

Conclusion: There were more complications in the A2, probably caused by the early hiperglycemia. The high percentage of macrosomy in mothers diagnosed late could be related to longer exposure to hyperglycemia. The early diagnosis of gestational diabetes could decrease the frecuency of macrosomy. Probably the frequency of occurrence of macrosomy and neonatal respiratory distress is related to the use or not of insulin as a treatment depending on the group.

P-137

Dumping Syndrome Causes Hypoglycemia in Children. Reports 2 Cases

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Introduction: Dumping syndrome refers to symptom complex that results from the rapid transit of food into the small bowel with secondary hyperglycemia. Symptoms occur 15 minutes after eating and are abdominal distention, pallor, diaphoresis, somnolence and syncope. Hypoglycemia may occur one to four hours later and the symptoms are similar. Dumping syndrome is rarely in children, most cases occurring after Nissen fundoplication.

Study Design: Cases report.

Methods: Reports two patients who has gastric surgery, who presents postprandial symptoms similar to the dumping syndrome.

Cases Report: Patient 1, Boy 10 months. At 3 months of age, Nissen fundoplication for gastroesophageal reflux. Postoperatively episodes of somnolence and abdominal distention are noted. In hospitalization for cyclic vomits and malnutrition, presents similar episode, blood glucose 28 mg/dl and insulin 4 uU/ml, glucagon tests positive and negative ketone bodies. Diazoxide was started (until 18 mg/k/d) with partial response. Scintigraphy gastric emptying, confirm rapid gastric emptying. With frequently alimenta-

Table 1. Results (for Abstract P-136)

Type of DBT/pathology	Macrosomy no ins.	Macrosomy ins.	RD no ins.	RD ins.
A1 (n = 34) 9 Comp (26.47%)	1 (33%)	2 (67%)	4 (80%)	1 (20%)
A2 (n = 25) 9 Comp (36%)	2 (50%)	2 (50%)	0 (0%)	4 (100%)
B1 (n = 7) 2 Comp (28.75%)	0 (0%)	1 (100%)	0 (0%)	1 (100%)

tion and gradual increase of volume, it is achieved suspend Diazoxide treatment after 2 months. Patient 2, boy 6 year, down syndrome, esophagic atresia and use yeyunostomy since first months of life. Hi was admitted for agitation episodes like seizures in EEG. His mother takes a capillary glycaemia results in 28 mg/dl. In critical sample insulin levels was 7 UuI/ml. Barium study of upper gastrointestinal tract revealed rapid emptying in to the intestinal asas. Frequent-small volume feeding resulted in normalization postprandial glucose level.

Conclusions: The pathogenesis of hypoglycemia in dumping syndrome is associated to inappropriately early release of pancreatic glucagon and exuberant early release of insulin. Neural control may also play a role. The diagnosis may be difficult and needs to be suspects in patient with gastric surgery. The treatment to be focused to slow gastric emptying and to prevent hyperglycemia. Frequent and small amount of food are recommended or continues feeding, to prevent hyperglycemia and reactive hypoglycemia.

P-138

Insulin Sensitivity in Girls with Central Precocious Puberty at Diagnosis and at 6 Months of GnRH Analogue Treatment

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Background: Puberty is associated with a physiological decline in insulin sensitivity. Overweight and obesity are common among girls with Central Precocious Puberty (CPP). CPP and early menarche have been considered as risk factors for obesity and cardiovascular diseases during adulthood. Besides, concern has been raised by the potential impact of GnRH analogues (GnRH-a) treatment on body weight and metabolic profile.

Objective and Hypotheses: To evaluate BMI and metabolic parameters in CPP girls at diagnosis and during GnRHa treatment.

Method: We performed a cross sectional and prospective longitudinal study of 15 CPP girls at diagnosis and at 6 months on GnRHa therapy with an oral glucose tolerance test (OGTT). Glucose and insulin levels were measured at 0, 30, 60, 90 and 120 minutes. Fasting lipid profile was also evaluated. Surrogates indices for fasting (SFI) insulin resistance (IR) [HOMA-IR, G/I, QUICKI] were calculated and evaluated according to own local cutoff. Matsuda Index was calculated from OGTT.

Results: At baseline median chronological age was 7.8 years (5.7–8.5). All girls were on Tanner stage 3. Eight patients had normal weight, whereas 7 were overweight (OW) or obese (Ob). No significant change in BMI was observed between baseline and on treatment. Six patients had at least 2 impaired indices for insulin sensitivity (three of them had normal weight) and 2 patients only one. During OGTT 5 patients with OW or Ob showed hyperinsulinemia. Few patients had dyslipidemia. Matsuda index was low in 3 patients at diagnosis. There were not significant changes in SFI and during OGTT between diagnosis and on GnRHa treatment.

Conclusion: Our cohort of CPP girls showed a high frequency of OW and Ob as well as high frequency of IR. BMI and metabolic profile did not show changes at six month of GnRHa treatment. Further studies will be necessary to determine long term metabolic risk in these patients.

P-139

Evaluation of Vitamin D Levels in Obese versus Non-Obese Children and According to the Seasons

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Introduction: The aim is to assess levels of vitamin D in a pediatric population according to different seasons and if there is a difference between obese versus non-obese children.

Material and Methods: The level of vitamin D is analyzed (25-OH-vitamin D) to 118 children and adolescents under 16 years who consulted the endocrinology department for different pathologies. The results are grouped on one side according to the seasons, and is also divided into obese and non-obese. Vitamin D levels were divided into sufficient (≥30 ng/ml), insufficient (20 to 30 ng/ml) and deficient (<20 ng/ml).

Results: The average vitamin D was 27.21 ng/ml (4.50 to 56.01). When the data were analyzed according to the seasons it was observed that the average of the lowest levels in spring was 23.56 ng/ml, then winter 23.80 ng/ml, summer 28.42 ng/ml and finally autumn 33, 88 ng/ml with the highest level (it was the only station that provided sufficient or desirable average levels). The percentage decline in levels between autumn and spring was 30.47%. The 41.52% of children were obese (n = 49), of which 71.42% of them had levels below 30 ng/ml of vitamin D (compared to 57.97% of children do not obese). By dividing them according to the seasons, summer was the season with the highest% of children with lower levels of 30 ng/ml in the obese group (26.53%) and spring in non-obese (21.73%). And most important was that 32.65% of obese had levels of vitamin D (<20 ng/ml) versus 20.28% of non-obese.

Conclusions: According to the results of this study was the autumn season with higher levels of vitamin D, related this with the greatest sun exposure received throughout the summer. On average one in three obese children have deficient levels of vitamin D versus one in five non-obese.

P-140

Osteopetrosis: Unusual Etiology of Pathological Multiple Fractures in Pediatrics. Case Report

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Malignant infantile osteopetrosis (MIOP) is a rare congenital disease characterized by an increase in bone mass and density due to a failure in bone resorption (abnormal osteoclast activity). Affected infants can exhibit a wide spectrum of clinical manifestations including: impaired hematopoiesis, hepatosplenomegaly, hypocalcemia, visual and hearing impairment.

We report the case of a twenty two month-old female patient with pathological multiple fracture after minor traumas. Physical examination showed macrocephaly, growth failure and delay of developmental milestones. Ophthalmic exam suggested cranial nerve compression with right convergent strabismus, showing right eye with retraction in abduction and supraduction with nystagmus in all portions of the gaze. Atrophic papillae were found at the fundus exam. No response was observed in the visual evoked potential. Only a minor commitment of the right optical path that blocked the conduction of the light stimulus was observed.

The x-ray scan showed that the skull and vertebrae presented generalized dense bone, particularly in the skull base and the vertebrae, with 'bone-in-bone' appearance and bone modeling affecting the metaphyses of long bones. Cerebral CT scan revealed narrow optic nerves.

Biochemical analysis revealed 25OH vitamin D deficiency: 7 ng/ml, high PTH levels (164 pg/ml, secondary hyperparathyroidism), and elevated lactate dehydrogenase, glutamic oxaloacetic transaminase and creatine kinase levels.

Although diagnosis of MIOP is easy and depends mainly on radiographic examination, it's often delayed due to rarity of the disease and lack of clinical suspicion. At present treatment is largely supportive, Hematopoietic Stem Cell Transplantation (HSCT) was not performed given its high morbidity and mortality.

P-141

Elevated Levels of Alkaline Phosphatase in Children

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The hyperphosphatasemia may be the first sign of benign disorders or serious disease.

Objective: To describe clinical and biochemical characteristics of patients with elevated levels of APL to used us to a guide of benign condition or disease.

Methods: A retrospective study of 10 children with elevated levels of Alcaline phosphatase (APL) derivatives to endocrinology.

Results: Patients with Bening transient hiperphosfatasemia (BTH), had a history of intercurrent infectious disease at the time of discovery, without bone and liver disease, a normalization of APL levels was observed over a period of 1–6 months without treatment; patients with osteopenia of prematurity had a history of extreme prematurity, parenteral nutrition, corticosteroid use, biochemical and radiological alteration; the patient with rickets, presented gait disturbance, short stature, clinical, biochemical and radiological sign of active rickets.

Conclusion: Hyperphosphatasemia is a sign, which added to the history, physical exam and laboratory results should guide us to a benign picture to a pathological condition that requires treatment.

P-142

Symptomatic Hypercalcemia Due to Parathyroid Adenoma: A Case Report

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A female patient, 14 years old, was hospitalized for acute pancreatitis, and severe hypercalcemia.

On physical examination she presented an enlarged thyroid gland with increased left lobe consistency. A café au lait spot with Maine Coast borders was observed in the left tibial region.

Laboratory tests shoed hypokalemia, hypomagnesaemia, hypophosphatemia, hypercalcemia and high urine calcium.

Because of refractory hypercalcemia (maximum value of 19.73 mg%), with an electrocardiogram repolarization disorder, she required treatment in the Intensive Care Unit (ICU) with isotonic solution at an infusion rate of 4000 ml/m^2, intravenous magnesium sulphate, potassium chloride, furosemide 2 mg/kg/hour, pamidronate 90 mg, hydrocortisone 4 mg/kg/day and calcitonin 200 IU/day with doses up to 400 IU/day until normal values of calcemia were obtained.

Neck ultrasound and PET were made, and a solid image was observed in the left inferior parathyroid gland. Plasmatic intact PTH molecule level was 4641 pg/ml (normal range: 12–95 pg/ml).

Total tumor resection was performed. Histopathology and histochemistry both confirmed a parathyroid adenoma. It is still pending the result of GNAs mutation, because of the suspicion of the McCune Albright Syndrome.

In the short-term postoperative period, she presented severe vitamin D deficiency and a hungry bone syndrome, requiring high calcium, magnesium and calcitriol supplies.

In conclusion, we present a unique case of primary hyperparathyroidism due to an isolated parathyroid adenoma, with a severe life-threatening hypercalcemia requiring several treatments until total resection could be performed, with a favourable evolution.

P-143

Benign Transient Hyperphosphatasemia of Infancy and Childhood: Case Report

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Benign transient hyperphosphatasemia of Infancy (BTHI) is characterized by sudden transient elevation of serum alkaline phosphatase (AP), about 2 to 50 times higher them the reference value, affects children under 5 without any trace of liverwort disease, bone or kidney. It has as triggers viral intestinal infections, protozoa or bacteria and upper respiratory tract infections. Usually is a laboratory finding and does not require further development in research, unless the age is atypical, the laboratory normalization be over four months or there is a systemic disease symptoms. A.T.D, 10 months, male, without pathological history, personal and family. Developed well. Admitted with a history of fever for 3 days and flu-like symptoms associated with dyspnea. In good condition, respiratory auscultation with diffuse snores without signs of respiratory distress. Laboratory examination and image without signficant changes (Hb9.66 Ht30.6 platelets 282000 Leuco 18.5 sec 47 lympho 42 mono 11). Discharged from hospital and it was oriented outpatient treatment. After two months had the same symptoms. Routine exams showed elevation of AP (3707 U/l), being oriented to the hospitalization sector to elucidate the case. On the same day he was admitted, where it remained for three days. The main pathologies related to the metabolism of AP were discarded, and oriented to the Pediatric endocrinology. In a consult with the endocrinologist, before one week of the discharge, the AP remained high (2246 U/l). The research continues for further 4 weeks, showing drecreasing levels AP (673 U/l –370 U/l), and not being evidenced association withbone diseases, liver and endocrine or use ofmedications. Was confirmed the diagnoses of BTHI remaining asymptomatic and unchanged physical examination. The BTHI despite being a relatively common entity in childhood, it has unknown prevalence. Persists the lack of literature studies evaluating the value of AP for each specific pediatric age. It's important to consider this pathology as a differential diagnosis of hyperphosphatasemiawithout an apparent cause, in order to avoid unnecessary expenditure on further investigation, as it has transient and benign condition.

P-144

Familial Pseudohypoparathyroidism

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Pseudohypoparathyroidism type Ia (PHP Ia) is an inherited disease characterized by resistance to Parathyroid Hormone (PTH) due to a mutation in GNAS gene on the maternal allele. This mutation results in loss of function of the alpha-stimulatory subunit (Gs) of the intracellular G protein of the GNAS gene and the expression of the normal Gs-alpha protein only from the paternal allele.

Pseudohypoparathyroidism manifest as hypocalcaemia, hyperphosphatemia and elevated plasma levels of PTH. PHP Ia is associated with Albright hereditary osteodystrophy (AHO), which includes short stature, obesity, round facies, subcutaneous ossifications, brachydactylic, and other skeletal anomalies. Some patients have mental retardation.

We have studied 7 members of a family with 3 sisters aged 13, 8 and 6 years old (case 1, 2 and 3, respectively) that have consulted due to obesity since the first year of life, subcutaneous calcifications, rounded facies and sunken nasal root. Laboratory evaluation showed normal calcaemia, hyperphosphatemia, increased PTH levels and subclinical hypothyroidism. In the evolution they added shortening of the fourth and fifth metacarpal toes in hands and feet, cubitus valgus, mild mental retardation. Acute hypocalcaemia was not detected. Case 1 height is normal but presented a rapidly progressive early puberty. Case 2 and 3 have normal height with increased bone age. GNAS gene mutations were studied for the 3 sisters, both parents, maternal aunt and maternal grandmother. It was detected the presence of pathogenic heterozygous deletion c.563_566delCTGA, frameshift mutation. Ala188AlafsX203 in the GNAS gene of the 3 sisters and mother (asymptomatic). The other relatives studied showed no mutation. This deletion results in a truncated protein, causing a loss of 52% of the amino acids of the protein. This is consistent with the presentation of PHP-1a phenotype in the offspring due to inactivating mutations of the maternal allele (imprinting) inherited by them. It was not possible to study the maternal grandfather to confirm the mode of inheritance but the mother of the girls could have inherited the mutation from her father presenting a pseudopseudohypoparathyroidism phenotype with no hormonal resistance, could present a germline mosaicism or a de novo mutation.

HORMONE
RESEARCH IN
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Author Index

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