

autoimmune thyroiditis. **Objectives:** To evaluate the association between thyroid function, antithyroid antibodies levels, insulin resistance and markers of cardiovascular risk in patients with autoimmune thyroiditis. **Methods:** We evaluated 228 patients with autoimmune thyroiditis, 93.9 % female, with a mean age of 47.06 ± 15.35 years. We analyzed thyroid function, anti-thyroglobulin antibodies (anti-Tg), anti-thyroid peroxidase antibodies (anti-TPO), HOMA-IR, HOMA-B, QUICKI, HISI (Hepatic Insulin Sensitivity Index), WBISI (Whole-Body Insulin Sensitivity Index), the levels of lipid profile, high-sensitivity C-reactive protein (hs-CRP), homocysteine, folic acid, and vitamin B12. We defined 3 groups based on TSH levels: TSH between 0.35-2.49 $\mu\text{UI/ml}$, ($n = 166$), TSH between 2.50-4.94 $\mu\text{UI/ml}$, ($n = 43$) and TSH over 4.95 $\mu\text{UI/ml}$, ($n = 19$), and normal levels of free T4 and free T3. A 75-g OGTT was performed in the morning and blood samples were obtained every 30 min for 120 min for measurements of plasma glucose, insulin, and C-peptide. For the statistical analysis we used the Mann-Whitney test and Spearman correlations. Results are expressed as means \pm SD or percentages. A two-tailed $p < 0.05$ was considered statistically significant. **Results:** There were no significant differences regarding median age or median BMI between groups. We did not find any significant differences comparing group with TSH 0.35-2.49 and group with TSH 2.50-4.94, in all parameters evaluated. Group with TSH 2.50-4.94 had higher indexes of QUICKI (0.69 ± 0.39 vs 0.48 ± 0.13 ; $p = 0.02$) and HISI (79.83 ± 63.72 vs 41.73 ± 29.02 ; $p = 0.01$) than group with TSH over 4.95. The group with TSH over 4.95 demonstrated a higher index of HOMA-IR than group with TSH 2.50-4.94 (3.77 ± 2.93 vs 1.95 ± 1.24 ; $p = 0.01$). In the TSH 0.35-2.49 group we found significant correlations between TSH and HOMA-IR ($r = 0.18$; $p = 0.01$), total cholesterol and anti-TPO ($r = 0.23$; $p = 0.002$), anti-Tg and HDL-cholesterol ($r = -0.17$; $p = 0.002$), anti-Tg and triglycerides ($r = 0.34$; $p < 0.001$), and anti-Tg and LDL-cholesterol ($r = 0.16$; $p = 0.03$). In the TSH 2.50-4.94 group we observed positive correlation between Apo A1 and HOMA-B ($r = 0.58$; $p < 0.001$), HOMA-IR and LDL-cholesterol ($r = 0.34$; $p = 0.02$) and WBISI and HDL-cholesterol ($r = 0.34$; $p = 0.02$). In the TSH over 4.95 group we observed a correlation between TSH and triglycerides ($r = 0.70$; $p < 0.001$) and between anti-Tg and hs-CRP ($r = 0.64$; $p = 0.004$). **Conclusions:** The association among TSH, lipid profile, insulin resistance, hs-CRP and antithyroid antibodies in patients with autoimmune thyroiditis may contribute to an increased cardiovascular risk, not only in patients with subclinical hypothyroidism but also in those classified as euthyroid.

Pediatric Endocrinology

PEDIATRIC ENDOCRINE CASE REPORTS II

Unusual Association Between Congenital Hyperinsulinism and Neurofibromatosis Type 1

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Background: Neurofibromatosis type 1 (NF1) is an autosomal dominant multisystemic disorder characterized by

an increased risk of benign and malignant tumor formation affecting skin, bone and nervous system. In children with NF1, endocrine manifestations include central precocious puberty, growth hormone deficiency and growth hormone hypersecretion, resulting from complications of optic pathway gliomas involving the hypothalamic and sellar region. A few reports of adults with NF1 have been described to have hypoglycemia due to insulinoma. However, hypoglycemia due to hyperinsulinism has not been described in children with NF1. We present a case of NF1 diagnosed during neonatal period associated with congenital hyperinsulinism.

Case: Patient was delivered at 36 weeks by C- section with birthweight of 2780 grams which was appropriate for her gestational age. There was no maternal history of diabetes. Pertinent exam findings included microcephaly and multiple café-au-lait spots. She developed hypoglycemia at DOL1 with blood glucose of 26 mg/dl which normalized with IV dextrose at a glucose infusion rate of 6 mg/kg/min. At DOL8, an attempt to wean IV dextrose failed and she developed hypoglycemia with blood glucose of 47 mg/dl. Critical sample showed insulin level 3.3 uU/ml, betahydroxybutyrate 0.08 mg/dl (0.2-2.8), cortisol 18.1 mcg/dL and GH 13.2 ng/mL. A glucagon stimulation test showed an increase in glucose of 30 mg/dl. She was diagnosed with hyperinsulinism and started on Diazoxide (8 mg/kg/day) with improvement of blood glucose with prefeed glucose of > 70 mg/dl. She had normal 8- hour fasting tolerance with all BG > 70 while on Diazoxide. Genetic test for known mutations causing hyperinsulinism was negative. Microarray confirmed a 1.42Mb interstitial deletion at chromosome 17q11.2 which encompasses NF1 gene confirming the diagnosis of NF1. Additionally, she has an Xp22.33 duplication of uncertain clinical significance.

Conclusion: Our patient presented with an unusual association between congenital hyperinsulinism and NF1. Further testing needs to be performed to determine whether this association is coincidental or whether congenital hyperinsulinism is a rare manifestation of NF1.

Thyroid

THYROID NEOPLASIA AND CANCER

Cell Adhesion Molecules mRNA Expression in Thyroid Tumors

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Thyroid cancer biology is extremely diverse. While some cases never progress clinically or do so indolently, others evolve aggressively and may even lead to death. Cell adhesion molecules are glycoproteins present in the cell membrane and play an important role in inflammatory and neoplastic diseases by recruiting immune cells to these sites. The aim of the present study was to investigate the role of mRNA expression of *SELL*, *ICAM1* and *ITGAL* in thyroid tumors and their relationship with lymphocyte infiltration. We evaluated by RT-qPCR technique 191 thyroid nodules including 97 benign (79 females, 17 males; 49.8±12.5 years old) and 94 malignant (71 females, 23 males; 48.3±15.5 years old) cases. Clinical and pathology data were obtained from 47 goiters; 50 follicular adenomas (FA); 74 papillary thyroid carcinomas (PTC), including: 29 classic papillary thyroid carcinomas (CPTC), 21 follicular variant of PTC (FVPTC), 12 oxifilic variant of PTC (OVPTC), 12 tall cell papillary thyroid carcinomas (TCPTC); and 20 follicular thyroid carcinomas (FTC). All patients were managed according to a standard protocol based on current guidelines and followed-up for 78.7±54.2 months. *SELL* was more expressed in malignant (0.85±1.54 UA) than in benign (0.54±0.71 UA, p=0.0027) nodules. The same occurred with *ICAM1* (0.99±1.41 vs. 0.46±0.85, p=0.0001), but not with *ITGAL* gene expression (1.04±1.63 vs. 0.76±1.21, p=0.2131). In addition, the expression of *SELL* was different when we compared PTC with FA (0.94±1.62 UA vs. 0.47±0.72 UA, p=0.0018) and FTC with FA (0.82±2.38 UA vs. 0.47±0.72 UA, p=0.0078). *ICAM1* expression was lower in goiters (0.46±0.90 UA) when compared with PTC (0.93±1.22 UA, p=0.0030) and FTC (1.03±3.30 UA, p=0.0207). Higher expression of *ICAM1* (1.16±3.04 UA vs. 0.52±0.96 UA, p=0.0064) and *ITGAL* (1.17±1.54 UA vs. 0.49±1.39 UA, p=0.0244) was observed in tumors with lymphocyte infiltrate. Also, *ITGAL* gene expression was higher in tumors that had distant metastasis at diagnosis (1.53±2.18 UA vs. 0.57±1.10 UA, p=0.0217). We were not able to demonstrate any association between any of the investigated molecules and patients' outcome. In conclusion, our data suggest that cell adhesion molecules may play an important role in neoplastic thyroid cells proliferation. In addition, our findings show that gene expression of *SELL* and *ICAM1* may assist in the histological characterization of follicular patterned thyroid nodules.

Reproductive Endocrinology

SEX DETERMINATION AND REPRODUCTIVE AXIS DEVELOPMENT

Discordant Serum 17-hydroxyprogesterone and Androstenedione in the Management of Congenital Adrenal Hyperplasia: Are 11-oxygenated Androgens Useful?

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Background 21-hydroxylase-deficiency (21OHD) accounts for more than 95% of CAH cases. Serum 17-hydroxyprogesterone (17OHP) and androstenedione (A4) are traditional biomarkers for monitoring therapy. While generally there is good linear correlation between 17OHP and A4, physicians are likely to encounter scenarios where 17OHP is within “acceptable range” while A4 is elevated and *vice versa*. Mildly elevated 17OHP is considered acceptable, as normalization of 17OHP is likely to result in overtreatment. 11-ketotestosterone (11KT) is a potent agonist of the androgen receptor with androgenic activity equivalent to testosterone. We hypothesized that patients with high 17OHP would be more likely than those with high A4 to be in good disease control. We speculated that A4 would correlate more strongly with 11-oxygenated C₁₉ steroids (11oxyandrogens) than 17OHP and that patients in poor clinical control would have higher median fold-elevation of 11oxyandrogens, especially 11-KT, compared to controls. **Methods** We performed retrospective analysis of patients seen at NIH from 2006 to 2019 and identified discordant 17OHP and A4 (17-OHP ≥1200 ng/dL with A4 normal for age/sex or tanner stage and *vice-versa*). Good or poor clinical control was based on abnormal growth, precocious puberty, irregular menses, hypogonadotrophic hypogonadism and A4/T. Quantitation of 15 steroids in stored peripheral sera was performed by LC-MS/MS and compared to age- and sex-matched controls. Data between groups were compared using t-tests or non-parametric Wilcoxon rank sum tests. Correlation analyses utilized the Pearson and Spearman's rho. **Results** We identified 122 of 789 (15%) discordant laboratory assessments among adults [84 with high 17OHP (69%)] and 347 of 1,949 (18%) among children [319 with high 17OHP (92%)]. Of these, 50 patients with available serum samples were identified (44 with high 17OHP). Twenty-five patients (50%) appeared to have good disease control. There was no difference in the frequency of patients in good or poor control between patients with high 17OHP or those with high A4 (p=0.7). Median fold elevation of 11KT relative to controls was higher in patients in poor control (2.87 fold, IQR 1.87-5.42, range 0.31-10.69) but with wide ranges and substantial overlap compared to those in good control (1.71 fold, IQR 1.06-2.92, range 0.35-16.59, p=0.068). 17OHP correlated with 21-deoxycortisol (r_s=0.67, p<.001) while A4 correlated strongly with 11oxyandrogens (r_s range 0.42-0.71, p<.003 for all). However, we did not find any substantial difference in the level of 11oxyandrogens between patients with high 17OHP and those with high A4. **Conclusion:** Discordance between 17OHP and A4 is common in the management of CAH and patients with elevation of either of these biomarkers are equally likely to have poor disease control. Limited evidence suggests a role for 11KT, as a discriminator for disease control.

Pediatric Endocrinology

SEXUAL AND GENDER DEVELOPMENT IN THE PEDIATRIC POPULATION

Gain in Near Adult Height Using the Combination of an LHRH Analogue and an Aromatase Inhibitor in Early Maturing Girls with Compromised Growth. The “Gail” Study ISRCTN11469487

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