Neuroendocrinology and Pituitary CASE REPORTS IN SECRETORY PITUITARY PATHOLOGIES, THEIR TREATMENTS AND OUTCOMES

Pregnancy in Acromegaly: Report of Five Cases

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SAT-267

Introduction: In acromegaly, there are changes in growth hormone (GH), insulin-like growth factor-1 (IGF-1) and insulin, hormones very important in pregnancy as well. Despite novel treatments, pregnancy in acromegaly is uncommon, remaining a challenge for clinicians.

We report seven pregnancies in five women with acromegaly.

Clinical Cases: Five acromegalic patients (17 – 35 years-old) underwent seven pregnancies. All patients had macroadenoma: four were submitted to non-curative neurosurgery and two of them had gamma-knife radiosurgery. One patient had medical treatment prior to curative transsphenoidal surgery (TSS).

One patient being treated with estroprogestative for hypo-gonadism had a spontaneous pregnancy; three others had pregnancy just before biochemical diagnosis of acromegaly, one of them had also a spontaneous abortion and another successful pregnancy during treatment with somatostatin receptor ligand (SRL); the last patient become pregnant during treatment with SRL, prior to TSS.

Monitoring was made with IGF-1, GH (assay with no distinction of pituitary GH versus placental GH), prolactin (PRL) and visual field; pituitary imaging was performed after pregnancies in all.

All women conceived naturally, two being on treatment with SRL (discontinued after confirmation of pregnancy). No treatment for acromegaly was administered before delivery. All patients had physiologic pregnancies, delivered full-term healthy babies, no malformations or metabolic disruptions; one did not breast-feed; another one had a spontaneous abortion 2 days after confirmation of pregnancy.

No patient developed either hypertension, pre-eclampsia or gestational diabetes.

In three cases, the clinical suspicion of acromegaly had risen during pregnancy and the diagnosis was made 1 year after delivery. The one with three pregnancies had controlled secretion of GH on Lanreotide and GH and IGF-1 levels remained stable during pregnancy.

The woman with gonadotroph deficiency after TSS and GK and substitutive therapy had a decrease in IGF-1 during pregnancy (45 %), which after delivery returned pathologically to before pregnancy values; GH levels remained stable.

The last patient, who became pregnant with uncontrolled acromegaly on Pasireotide, had increased, but stable GH and IGF-1 (2 X upper limit of normal) before, during and after pregnancy. TSS performed 3 years after delivery cured the disease.

Conclusion: From our experience, patients with acromegaly may have normal babies, even in patients with uncontrolled hypersecretion and lack of medical treatment during pregnancy. The consensus is, however, that there is no indication to use medication to control GH hypersecretion or tumor size in acromegaly patients during pregnancy (1).

Reference: (1) Muhammad A, Neggers SJ, van der Lely AJ. Pregnancy and acromegaly. Pituitary. 2017;20(1):179–184. doi:10.1007/s11102-016-0740-3

Neuroendocrinology and Pituitary HYPOTHALAMIC-PITUITARY DEVELOPMENT AND FUNCTION

An Extremely Rare Novel Missense Variant C.912G≫A; P.M304I in SOX3 Gene Is Responsible for X-Linked GH Deficiency in a Brazilian Boy Without Mental Retardation

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SAT-295

SOX3 (SRY-related HMG-box gene 3), located in the X chromosome, spans only one exon and is expressed in the infundibulum, diencephalon and hypothalamus. Alterations in SOX3, mainly deletions or insertions in the polyalanine tract, were associated with mental retardation, isolated GH deficiency (IGHD) or combined pituitary hormone deficiencies (CPHD). Missense variants are rare and only two were reported. Our aim was to find a molecular cause in patients with pituitary hormone deficiency and determine genotype-phenotype correlation.

Twenty-eight patients (15F:13M) 24 CPHD:4 IGHD were selected for the study. Whole blood DNA was extracted using the Salting Out method. Library preparation was performed following Agilent’s SureSelectXT customized gene panel protocol containing 654 genes known to cause endocrine diseases. Illumina NextSeq 500 platform was used for sequencing at SELA. Alignment to genome reference hg19 was performed using BWA-MEM. Variants were called with FreeBayes and annotated by Annovar. Allele frequency ≤1% for exonic regions was considered in 1000 Genomes, gnomAD, ABrAOõ and SELA populational databases for variant filtering. Family segregation was done using Sanger sequencing. RNA and protein analysis were performed using mfold and YASARA, respectively. Protein models were made by I-Tasser. SOX3 missense variant (c.912G>A/p.M304I) was found in one male patient, without mental retardation, diagnosed with IGHD...
at the age of 7 years. After GH replacement, he reached final height at the age of 18 within family target height. Pituitary image showed an ectopic posterior pituitary, hypoplastic anterior pituitary and thin pituitary stalk. SOX3 (c.912G>A;p.M304I) variant in hemizygous state was absent in populational data banks. In silico prediction algorithms SIFT, PolyPhen, and Mutation Assessor were predicted as damaging. Family segregation showed normal mother and sister carriers of the variant, while father, brother and uncle (from mother’s side), all phenotypically normal, did not harbor the variant. RNA In silico analysis pointed that the variant causes mRNA structure change. Protein stability dropped from 677.46 kcal/mol in wild type to 666.69 kcal/mol in p.M304I, making it less stable. Protein Interaction analysis with DNA binding motif (PDB 2LE4) required two times less energy in mutant (376.19 kcal/mol) than wild type protein (646.77 kcal/mol), leading to a less stable interaction. We conclude that one among 28 patients presented a rare novel variant in SOX2 associated to IGHD in a patient without mental retardation and compatible with an X-linked inheritance pattern.

**Pediatric Endocrinology**

**PEDIATRIC ENDOCRINE CASE REPORTS II**

**WF51 Related Disorder in A 4-Month Old Girl**

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**MON-078**

WF51 related disorder in a 4-month old girl

**Background:** Idiopathic early-onset central diabetes insipidus (CDI) may be due to mutations of arginine vasopressin-neurophysin II (AVP-NPII (AVP)) or wolframin (WF51/2) genes (1).

**Clinical Case:** A 4-month old girl presented to our pediatric endocrinology clinic due to severe polydipsia-polyphagia compatible with partial central DI: at 5-hrs weight loss 5%, plasma osmolality 155 from 111 at 0 hrs and 355 mOsm/kg 2hrs after DDAVP administration. Pituitary MRI was normal with presence of posterior pituitary and WFS1 related disorder. The conclusion was that the variant causes mRNA structure change. Protein stability dropped from 677.46 kcal/mol in wild type to 666.69 kcal/mol in p.M304I, making it less stable. Protein Interaction analysis with DNA binding motif (PDB 2LE4) required two times less energy in mutant (376.19 kcal/mol) than wild type protein (646.77 kcal/mol), leading to a less stable interaction. We conclude that one among 28 patients presented a rare novel variant in SOX2 associated to IGHD in a patient without mental retardation and compatible with an X-linked inheritance pattern.

**Thyroid**

**THYROID DISORDERS CASE REPORTS III**

**A Case of Resistance to Thyroid Hormone with Concurrent Hashimoto’s Thyroiditis and Postsurgical Hypothyroidism**

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**MON-472**

Introduction: Resistance to thyroid hormone (RTH) is a rare defect that results in impaired sensitivity to thyroid hormone. While most commonly caused by mutations in the thyroid hormone receptor beta (THRβ) gene, in 15% of patients with the RTH phenotype, no mutation is identified.1 This entity is known as non-thyroid hormone receptor RTH (nonTR-RTH). Patients with RTH have an increased risk of autoimmune thyroid disease with a reported odds ratio of 2.36.2 Hashimoto’s thyroiditis or other etiologies of hypothyroidism add a layer of complexity to RTH as such individuals may require high doses of levothyroxine to overcome hormone resistance.

Clinical Case: A 36-year-old male was referred for abnormal thyroid function tests. He denied symptoms of thyroid dysfunction. Physical examination was notable for a goiter. Weight was 83 kg. Initial labs revealed TSH 6.8 mcIU/mL (0.3-4.7 mcIU/mL), free T4 2.0 ng/dL (0.8-1.7 ng/dL), free T3 491 pg/dL (222-383 pg/dL), and thyroid peroxidase antibody >600 IU/mL (≤20 IU/mL). Additional work-up demonstrated elevated free T4 by equilibrium dialysis 2.5ng/dL (0.9-2.2 ng/dL) and elevated TSH with ruling out familial dysalbuminemic hyperthyroxinemia and HAMA interference. Alpha-subunit of 0.30 ng/mL (<0.55 ng/mL) and normal pituitary MRI did not support a TSH-secreting adenoma. Quest Diagnostics RTH Gene Sequencing was negative for a mutation in the THRβ gene. The patient was subsequently diagnosed with nonTR-RTH.

Thyroid ultrasound showed multiple thyroid nodules,