Thyroid

THYROID DISORDERS CASE REPORTS III

Isolated Hyperthyroxinemia - Does Everyone Needs Treatment?

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Background: Raised free thyroxine (T4) with normal thyroid stimulating hormone (TSH) levels should be identified and interpreted with caution. Some of these conditions do not need treatment. We present three cases with similar biochemical abnormalities from three different causes.

Case 1: A 62-year-old clinically asymptomatic lady was referred to us with Free T4 34.9 pmol/L (10.0 – 24.0 pmol/L), TSH 0.81 mU/L (0.2 – 5.0 mu/L) and negative TSH receptor antibodies (<0.9 IU/L). She was trialled on antithyroid drugs for 6 months. Her Free T4 stayed elevated between 29.0 – 35.0 pmol/L with normal TSH. We worked up for assay interference by running tests on two analysers, Roche Cobas e801 and Siemens ADIVA Centaur CP, both yielded similar results. Alpha1 glycoprotein subunits and SHBG were normal with clinical euthyroid status making TSHoma less likely. Serum protein electrophoresis did not detect any abnormal albumin. We were unable to perform equilibrium dialysis due to non-availability of facility at our centre. Due to strong clinical suspicion and family history of thyroid dysfunction that never needed a treatment, we tested her genetically for familial dysalbumineic hyperthyroxinemia (FDH) using mutation surveyor and fluorescent sequence analysis showed her to be heterozygous for c.725G>A ALB variant confirming diagnosis of FDH.

Case 2: A 65-year-old clinically asymptomatic lady, was referred to us with Free T4 28.8 pmol/L (10.0 – 24.0 pmol/L) and TSH 2.50 mU/L (0.2 – 5.0 mu/L). Given inappropriately normal TSH levels, we repeated her TFTs using 3 different analysers, Roche cobas e801, Siemens ADIVA centaur CP and Abbot ARCHITECT i1000SR. Roche and Siemens assays yielded similar results, however Abbot assay showed normal thyroid function tests with TSH 1.01 mu/L (0.4-5.0 mu/L) and free T4 18.7pmol/L (9.0-19.0 pmol/L), confirming assay interference. As Siemens and Roche uses streptavidin-biotin immobilizing system while Abbot uses a magnetic bead-based capture system, the abnormal results could be due to biotin interference.

Case 3: A 65-year-old lady, clinically asymptomatic was referred to us with Free T4 29.2 pmol/L (10.0 – 24.0 pmol/L) and TSH 1.59 mU/L (0.2 – 5.0 mu/L), 3 months after stopping amiodarone, which she took for 3 weeks for atrial fibrillation. This was thought to be due to amiodarone, owing to its long half-life of 58 days. We repeated thyroid function tests in 3 months from first clinical encounter i.e. 6 months after stopping amiodarone that showed Free T4 24.2pmol/L and TSH 2.30 mU/L and repeated further 3 months later that were normal, confirming amiodarone induced abnormal biochemical profile requiring no treatment.

Conclusion: Hyperthyroxinaemia with normal TSH need to be interpreted with caution as illustrated above. Some of them do not need treatment and inappropriate interpretation can potentially cause anxiety for the patient and harm due to unnecessary treatment.

Reproductive Endocrinology

OVARIAN FUNCTION — FROM OLIGOMENORRHEA TO AMENORRHEA

Candidate Gene Variants in a Large Cohort of Women with Primary Ovarian Insufficiency

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Primary ovarian insufficiency (POI) is highly heritable. The majority of cases have no known cause. We hypothesized that mutations in previously identified genes or genes from the same pathways are the cause of POI in a recessive or dominant manner. Subjects included 294 women diagnosed with POI (amenorrhea with an elevated FSH level). All had a 46XX karyotype, and normal *FMR1* repeat number. Subjects were recruited in Boston (n=95), at the NIH and Washington University (n=98), and in Pittsburgh (n=98). Controls included subjects recruited for health in old age and disorders unrelated to reproduction or cancer, and subjects from the 1000 Genomes Project (total n=587). Variants were called using the Sentieon software package (https://www.sentieon.com). Case and control samples were stratified on ethnicity, relatedness and heterozygosity. Peddy and XPAT were used to calculate quality control metrics to detect outlier samples for removal from analysis to create a homogenous dataset. The number of cases (227) and controls (458) was adjusted for downstream analysis. XPAT imposed additional quality filters and removed variants. A second filter removed variants that did not pass a Gnomad filter of <0.001 allele frequency. VAAST was used to determine a composite likelihood ratio (CLR) as the test statistic to represent the aggregate burden of variants of affected individuals in each transcript relative to a set of 458 control genomes. The significance of each transcript's VAAST CLR score was evaluated by 1 million permutations. We screened exomes for variants in previously identified genes causing POI in humans and those demonstrating infertility in a male or female mouse model. We also used the American College of Medical Genetics and Genomics standards for interpretation of pathogenicity of a variant, with priority on null variants in genes with probability of loss of function intolerance based on the observed vs. expected rate in gnomAD, in vivo or in vitro functional evidence of a damaging effect, significantly increased prevalence compared to controls, i.e. not found in any controls or in fewer than 10 in the gnomAD database if the subject had a matching race/ethnicity. Thirty-four subjects were removed for poor quality exomes and relatedness. Fifty-three subjects had at least one variant in a previously identified POI gene or one in which there was a previously identified functional model. Two subjects carried recessive variants and 30 carried at least one novel heterozygous candidate variant for follow up. Analysis of genetic causes

of POI in this large cohort identified candidate causal gene variants in over half of the subjects. The data demonstrate that the genetic architecture is heterogeneous. Although recessive mutations have been identified in consanguineous families, the data suggest that a dominant or oligogenic pattern of inheritance may be important.

Neuroendocrinology and Pituitary

CASE REPORTS IN SECRETORY PITUITARY PATHOLOGIES, THEIR TREATMENTS AND OUTCOMES

Pregnancy in Acromegaly: Report of Five Cases

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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 hypogonadism 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 andacromegaly. *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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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, ABraOM 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