Pediatric Endocrinology

PEDIATRIC GROWTH AND ADRENAL DISORDERS

Two Cases of Autosomal Dominant Familial Central Diabetes Insipidus: A Novel Variant in Neurophysin II Region of AVP Gene.

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Central diabetes insipidus (CDI) is a disorder of water balance characterized by polyuria and polydipsia owing to partial or complete deficiency of the antidiuretic hormone, arginine vasopressin (AVP). Although non-hereditary causes are the most frequent, Familial CDI forms, due to heterozygous mutations in the AVP gene, have also long been recognized. Inheritance occurs mostly in an autosomal dominant manner with almost complete penetrance. The *AVP* gene encodes for a 164 aminoacids preprotein: the AVP preprohormone which consists of a signal peptide, AVP hormone (9 amino acidpeptide), Neurophysin II (AVP carrier), and a glycoprotein, Copeptin. The AVP preprohormone, is produced in the hypothalamus sand is targeted to the endoplasmic reticulum (ER) by the signal peptide. After cleavage and processing, the AVP hormone is packaged within protein carrier NPII and are transported by axonal trafficking to the neurohypophysis where they can be stored and secreted.

Structural changes in NPII have been associated with intracellular accumulation of mutant AVP precursors that have been postulated to be cytotoxic and decreased cell viability of vasopressin-producing neuronsin the neurohypophysis.

In this study we describe two index cases from two families of four-generation kindred suspected to have Familial neurohypophyseal diabetes insipidus (FNDI), with absent or barely visibleposterior pituitary by MRI. A water deprivation test was performed in both cases, resulting confirmatory for DI in case 1 while it was inconclusive in case 2.

In both cases, molecular studies revealed a pathogenic variant in heterozygous state in the NPII region of the AVP gene, in case 1 we found a previously reported and well characterized variant p.Cys116Gly, cysteine at codon 116 is involved in disulfide bridge important for the secondary structure of NPII. While in case 2 we found a novel variant, p.Gly45Val, in which all in silico tools predict deletereous, whereas there are a previously reported patogenic variant at the same amino acid residueand in 3D modeling it can be observed that structural and conformational changes occur in binding bridge of NPII.

We are reporting two novel non related familial CDI cases, even though lack of functional studies, the clinical phenotype in each pedigree suggest this diagnosis, and support the genetic counseling.

Neuroendocrinology and Pituitary

PITUITARY TUMORS II

Non Functioning Pituitary Adenomas (NFPA): Sex Related Differences in Presentation, Clinical Features and Outcomes

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INTRODUCTION: NFPA are characterized as tumors without a typical hormonal hypersecretion syndrome. They are frequently diagnosed in the sixth decade, by visual field defects, hypopituitarism or incidentally. PATIENTS AND METHODS: retrospective and observational study that included 103 patients with NFPA (60 females) who were seen between 1999 and 2019 in our hospital. We compared and analyzed patients characteristics by sex: reason for consultation, hormonal status at diagnosis, invasiveness of the tumor through MRI, treatments and outcomeRESULTS: out of 103 patients, 58,2% were women (W). Men (M) were significantly older than women (56 vs. 45 yold. p=0,002). The presence of a macroadenoma was similar in both sexes (93%W vs. 94,7% M), however tumor invasiveness was more frequent in men (50% vs. 24,6%). Most men consulted for incidental finding (47,4% vs. 29,8%); most women consulted for symptoms related to the tumor(70% vs 52%): hypogonadism 31,6% W, 13% M; galactorrhea 17% W; visual field defects 21,7% W, 23,7%M, pituitary apoplexy 11,6% M. At baseline hormonal assessment hyperprolactinemia was more frequent (50,9% vs 42%) and higher in women (mean PRL levels 75 ng/ml vs. 37 ng/ml). Hypogonadism was more frequent in men (54% vs 42%) as well as hypopituitarism (15% vs. 10,5%). Surgery was the most used therapy in both sexes (69% M vs. 73%W) but males required more frequently second surgery and radiotherapy than females (15% vs. 5% and 10% vs. 5% respectively). Gonadotropin secreting adenoma was diagnosed in 62% of men and 37,5% by tumor immunohistochemistry, in the 45% of women who presented negative immunostaining the presence of a gonadotrophic lineage is not ruled out, median Ki-67 labeling was low in both sexes (2%). After surgery 66% of men and 37% of women showed tumor remnant > 1cm (p=0,001), tumor regrowth was seen in 38,4% men and 10,4% women (p=0,03). Hypogonadism was greater in men than in women (56% vs 39%). Ninety two percent of men and 60,9% of women developed some degree of pituitary deficiency after surgery (P<0,001). Men showed a higher degree of complete hypopituitarism compared to women (pretreatment 15% vs 10,5%, post treatment 32% vs 13%). CONCLUSION: NFPA in men are usually diagnosed incidentally at an older age, are more invasive at presentation with a higher incidence of pituitary dysfunction. Moreover, they presented with greater rate of tumor regrowth and hypopituitarism after surgery. NFPA in women are diagnosed earlier due to endocrine symptoms, had lower degree of invasiveness with better outcomes after treatment. Sex related differences in NFPA may be associated with the delay