Idiopathic central *diabetes insipidus*: the challenge remains

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Central *diabetes insipidus* (CDI) is a heterogeneous hypothalamus-pituitary disease due to the deficiency of arginine vasopressin (AVP), and is characterized by polyuria and polydipsia. CDI is caused by the destruction or degeneration of the AVP-secreting magnocellular neurons in the hypothalamic supraoptic and paraventricular nuclei. The etiology of CDI can be familial or secondary to malformations, autoimmune, infiltrative (e.g. neoplastic or histiocytsis) or traumatic processes (1). Genetic defects in the synthesis of vasopressin are typically inherited as an autosomal dominant trait and caused by mutations in the *AVP-NPII* gene, but autosomal recessive defects have also been described (2-4). Autosomal dominant familial neurohypophyseal *diabetes insipidus* accounts for ~1% of all cases of CDI and its clinical features usually begin between 1 and 6 years of age (2). Familial CDI is often accompanied by the loss of the posterior pituitary bright spot on T1 magnetic resonance imaging (MRI) (1).

The *AVP-NPII* gene, which is located on chromosome 20p13, consists of 3 exons and encodes the preproAVP. Exon 1 encodes the signal peptide, AVP, and the aminoterminal region of neurophysin II (NPII). Exon 2 gives rise to the central region of NPII, and exon 3 contains the carboxyterminal region of NPII and glycoprotein. PreproAVP is converted to proAVP by removal of its signal peptide and the addition of carbohydrate side chains. Additional posttranslational processing occurs within neurosecretory vesicles during transport to axon terminals in the posterior pituitary, yielding AVP, NPII and glycoprotein (5). To date, more than 50 mutations in the *AVP-NPII* gene have been reported (5). Most *AVP-NPII* mutations are located in the coding sequence of NPII and promote conformational changes in protein structure which disrupt the normal cellular folding and processing of the preproAVP and lead to neuronal damage. In consequence, the mutant precursor cannot be folded and dimerized and is retained in the endoplasmic reticulum, where it accumulates and promotes cell toxicity (2,3).

The etiology of CDI remains unknown in 15%-50% of the patients, classified as idiopathic CDI (1). In this issue of ABE&M, Batista and cols. (6) describe the clinical features and investigated *AVP-NPII* sequencing variants in 7 patients with idiopathic CDI and a long-term follow-up. The diagnosis of CDI was confirmed by fluid deprivation test and vasopressin analog response in all cases. No history of autoimmunity was identified in any patients. A mild infundibulum thickness was identified in only one patient and disappeared during follow-up. The sequencing analysis of the *AVP-NPII* gene revealed no mutation in the coding region. A homozygous guanine insertion in intron 2 (IVS2 +28 InsG) was identified in 4 of 7 patients, but also in the controls.

Considering the early onset of the clinical features and the absence of autoimmune disease and stalk thickening in the patients described by Batista and cols. (6), it

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was reasonable and clinically relevant to investigate the association between *AVP-NPII* gene mutations and idiopathic CDI in this cohort. A *de novo AVP-NPII* gene mutation was previously described in a patient with early onset of CDI and no family history (7). Since CDI can be associated with growth retardation and bone delay in children, the diagnosis of *de novo* mutations has important implications for genetic counseling and a subsequent precocious diagnosis.

Circulating vasopressin-cell autoantibodies (AVPc-Abs) have been detected in 23%-75% of young patients with CDI, indicating that autoimmune CDI might account for a significant number of the idiopathic cases (8,9). The history of autoimmune disease and the presence of stalk thickening strongly support the hypothesis of autoimmune CDI. However, circulating AVPc-Abs were also frequently measured in patients with non-idiopathic CDI, demonstrating that AVPc-Abs are not reliable markers of an autoimmune etiology (8,9). Thus, the diagnosis of autoimmune CDI may be suspected by examining clinical characteristics and past history of the patients and by MRI evaluation.

Abnormal blood supply to the posterior pituitary gland was also evidenced in patients with idiopathic CDI, suggesting that selective vascular damage affecting the inferior hypophyseal arteries can be associated with the pathogenesis of CDI (10). However, the etiology of a significant subset of young patients with CDI remains to be characterized and explored. Therefore, continuing clinical and genetic studies are necessary to further investigate the etiological variability of what, until now, has been considered idiopathic CDI.

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