Molecular Aspects of the Pathogenesis Involved in the Development of Familial Central Diabetes Insipidus

Among the types of central diabetes insipidus, familial central diabetes insipidus (FCDI) shares approximately 1% of this disorder. It is an autosomal dominant disease; the clinical findings of polyuria and polydipsia progress slowly after birth until approximately 10 years of age as a result of mutation in the gene coding arginine vasopressin biosynthesis in the hypothalamus. The vasopressin gene resides on chromosome 20 and consists of exons A, B and C. Exons A, B and C include coding regions of three types of mRNA translating signal peptide and vasopressin, neurophysin II and glycoprotein, respectively. The pre-prohormone of vasopressin, the precursor of vasopressin during its biosynthesis pathway, consists of these three components (1). The inborn error of hypothalamic vasopressin synthesis was initially elucidated in rats with hereditary hypothalamic diabetes insipidus (2), the Brattleboro strain. In these animals the vasopressin gene has a single base deleted from vasopressin-associated neurophysin-coding region of exon B. This causes a frame shift and eliminates a stop codon, resulting in a vasopressin precursor with an altered C-terminal region. Despite the intact signal and vasopressin coding region in this gene, vasopressin or its precursor does not appear in the secretory granule of magnocellular neurons of the hypothalamo-neurohypophyseal tract. This is presumably due to defective cotranslational transport of the prohormone from the rough endoplasmic reticulum to the Golgi apparatus (2).

In humans, 23 mutations of the vasopressin gene have been hitherto reported in cases of FCDI (3), since the first report by Ito et al (4). Kawakami et al (5) report in the last month’s issue a case of FCDI with a point mutation of G-to-A at base 279 in exon A coding signal peptide. This mutation is one of the most common types among the identified mutations of the vasopressin gene in the reported cases of FCDI. It is noticeable that none of the reported mutations involve a region that codes vasopressin directly. Mutations of a coding region of signal peptide, as in the case of Kawakami et al, or neurophysin II are involved in the reported cases. In this connection, it is a remarkable clinical finding of FCDI that the symptom of vasopressin deficiency, polyuria, is not generally observed in newborns but it develops slowly at a later age. In the case reported in the present issue, the patient did not complain of marked polyuria until 18 years of age when he was incidentally found to be polyuric. This makes a striking contrast with the cases with hereditary nephrogenic diabetes insipidus that show marked hypotonic polyuria immediately after birth due to gene mutation coding V₂ vasopressin receptor or the vasopressin responsive water channel in the renal collecting duct, aquaporin 2.

The reason why the patients with FCDI show slowly progressive development of vasopressin deficiency is not fully elucidated yet. The rare autopsy cases of FCDI, however, reveal degenerative change in the magnocellular neurons in supraoptic and paraventricular nucleus of the hypothalamus. These findings may suggest the apoptotic process of these nerve cells during the development of vasopressin deficiency in the cases of FCDI. In the cases with gene mutation coding neurophysin II, proteolytic disruption of neurophysin II or intraneuronal transport of abnormal vasopressin-neurophysin II complex may be impaired. This may result in the accumulation of abnormal protein in the magnocellular neuron and cause gradual death of the cells forming the supraoptic and paraventricular nucleus (6). Although further studies are required to confirm this hypothesis, the elucidation of its pathogenetical process would provide further knowledge about the pathogenesis during the development of other degenerative nerve diseases.

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References