AVP-NPII gene mutations and clinical characteristics of the patients with autosomal dominant familial central diabetes insipidus

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Familial central (neurohypophyseal) diabetes insipidus (DI), usually an autosomal dominant disorder, is caused by mutations in arginine vasopressin (AVP)–neurophysin II (NPII) gene that leads to aberrant preprohormone processing and gradual destruction of AVP-secreting cells. AVP-NPII gene is located on chromosome 20p13 and consists of three exons [1]. Patients with DI typically present between 1 to 6 years of age with polyuria and polydipsia, and failure to thrive may become evident over time. The present study describes clinical and molecular characteristics of patients with familial central DI from two different Turkish families. We describe a novel mutation (p.G45C), and a previously reported mutation (p.C98X) in exon 2 of AVP-NPII gene.

Patients and methods
Family A, a 7 years old boy (case A1) and his 8.5 years old sister (case A2) were referred to our pediatric endocrinology outpatient clinic because of polyuria and polydipsia existing for more than 3 years. The parents were not consanguineous. Both siblings had no symptoms of neurological or pituitary dysfunction, nor a history of head trauma. However, they had poor weight-gain. The mother (case A3) had similar complaints, and were using desmopressin. Additionally, two sisters of grandfather and his mother had a history of polyuria and polydipsia. Complete blood count, glucose and calcium levels, renal, hepatic and thyroid function tests, and anti-endomisium Ig A were all normal for both siblings (case A1, and A2). However their bone ages were delayed by 2 years. A 10-h water deprivation test (WDT) for case A1, A2 and A3 confirmed the diagnosis of DI (Table 1). After intranasal administration of desmopressin, urinary osmolarity of the three patients increased by more than 50%. With these results, diagnosis of central DI was established, and sublingual desmopressin replacement therapy was initiated. MRI studies demonstrated that both siblings had hyperintense T1 signal (bright spot) on posterior pituitary gland. However, bright spot was absent in that of their mother. At the end of 18-month follow-up period on desmopressin replacement therapy, two siblings had good weight-gain without polyuria and polydipsia. Additionally, bright spot on posterior pituitary gland has still been present on recheck pituitary MRI of both siblings.

Family B, a 7 years old girl (case B1) was referred to our clinic because of polyuria and polydipsia existing for more than 6 years. The parents were not consanguineous. She had no symptoms of neurological or pituitary dysfunction, nor a history of head trauma. However, she had severe short stature (height SDS: -3.0). Her mother (case B3) had also polyuria and polydipsia. Complete blood count, glucose and calcium levels, renal, hepatic and thyroid function tests, and anti-endomisium Ig A level were all normal for case B1. However, bone age was delayed by 3 years. A WDT with maximum toleration for case B1and B3 confirmed the diagnosis of DI (Table 1). After intranasal administration of desmopressin, urinary osmolarity of the two patients increased by more than 50%. With these results, diagnosis of central DI was established, and sublingual desmopressin replacement therapy was initiated. MRI studies demonstrated that case B1 had bright spot. However, it was absent in that of her mother. Case B1’s growth velocity and weight gain increased after 8-month follow-up period on desmopressin therapy. Her little brother (case B2) at the age of one was brought to our clinic because of polydipsia for more than 3 months. A 6-h WDT confirmed the diagnosis of DI (Table 1), and sublingual desmopressin replacement therapy was initiated. Genetic analysis for AVP-NPII gene was performed to the families’ members.

Results
We found a previously known mutation (p.C98X) in exon 2 of AVP-NPII gene in five affected members from three generations of the family A. Additionally, we described a novel mutation (p.G45C) in exon 2 of AVP-NPII gene in three affected members of the family B. In family B, a heterozygous missense mutation at codon 45, which causes the substitution of GCG (Gly) by TGG (Cys) was present. We made a prediction on mRNA structure of the mutated protein. G45C mutation is located in the first beta-sheet (residues 11-14) of the amino terminus of the protein, and affects the following beta-sheet structures (Figure 1).

Discussion
There are some hypotheses for the role of AVP-NPII gene in pathogenesis of familial central DI. Under normal circumstances, AVP precursors form homodimers in endoplasmic reticulum (ER). However, the mutant AVP precursors also bind to wild-type AVP precursors, and form heterodimers that are retained in ER [2]. It has been hypothesized that the accumulated mutant AVP heterodimers in ER are cytotoxic, causing gradual but progressive loss of neurosecretory neurons, finally leading to AVP deficiency.

The present study describes familial cases of central DI due to p.C98X and p.G45C mutations in exon 2 of AVP-NPII gene. Genetic analyses revealed that five members of family A, and three members of family B are heterozygous for the mutations as expected from autosomal dominant mode of inheritance.

In healthy people, the posterior pituitary gland typically shows a hypointense signal (bright spot) on T1-weighted images. However, the presence of a bright spot on posterior pituitary on MRI does not exclude central DI, and the absence of bright spot does not prove it. Bright spot is formed by axonal terminals of magnocellular neuronal cell bodies located in hypothalamus, and decreases with progressive neuronal cell damage in patients with familial central DI. In the present study, we found that posterior pituitary hypointense signal was present in three affected children, but absent in their affected mothers. These findings suggest a progressive neurodegradation of the posterior hypophysis in these patients.

When we compared the clinical characteristics of the two families, we noticed that age of onset of symptoms in family B is quite early (<1 yr), and growth retardation and bone age delay are more pronounced in case B1. Growth retardation and delayed bone age are commonly reported in patients with central DI with an incidence of 20% to 35%, and effectively corrected by desmopressin treatment [3]. However, some patients with unlimited and unrestricted fluid intake can thrive normally, which causes a difficulty in creating a clear genotype–phenotype correlation.

In conclusion, we describe a novel mutation (p.G45C), and a previously reported mutation (p.C98X) in exon 2 of AVP-NPII gene in two different families. Familial central DI is a progressive disease, and age of onset of symptoms can differ depending on the mutation. Bright spot on pituitary MRI might be present at onset, but become invisible over time. Genetic testing and appropriate counseling should be given in familial cases of central DI to ensure adequate treatment, and to avoid chronic water deprivation that might result in growth retardation in childhood.

References