Hyperintensity of Posterior Pituitary on MR T1WI in a Boy with Central Diabetes Insipidus Caused by Missense Mutation of Neurophysin II Gene

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Abstract. We present a 10-year old boy with central diabetes insipidus (CDI) showing hyperintensity in a normal-sized posterior pituitary on magnetic resonance (MR) T1-weighted image (T1WI). He complained of nocturnal enuresis and polyuria. Daily urine volume increased to 4 to 5 L, and AVP plasma level was very low. Polymerase chain reaction (PCR)-amplified exons of the arginine vasopressin (AVP)-neurophysin (NP) II gene were sequenced. Nucleotide-1884 guanine in Exon 2 was substituted with thymine, which induced a substitution of glycine for valine at amino acid position 65 in the NP II moiety. However, MR imaging showed hyperintensity in the posterior pituitary on T1WI. These results suggest that the MR findings of the posterior pituitary in CDI may vary.

Key words: Central diabetes insipidus, Single base substitution, Arginine vasopressin-neurophysin II gene, Magnetic resonance imaging, Posterior pituitary

CENTRAL diabetes insipidus (CDI) is a disease characterized by polyuria and polydipsia, which typically begins between 1 and 6 years of age. These signs and symptoms are caused by progressive deficiency of arginine vasopressin (AVP). It may be primary (idiopathic, sporadic, familial) or secondary to tumor, infection, inflammatory disease or trauma. Familial CDI is a rare hereditary disease and is generally transmitted in an autosomal-dominant fashion. The vasopressin prohormone consists of four main segments: vasopressin, neurophysin II (NP II), a signal peptide and a glycoprotein. In familial CDI, about 30 mutations have been found in vasopressin, NP II and a signal peptide [1, 2]. Magnetic resonance (MR) findings in CDI usually reveal the loss of normal high intensity in the posterior pituitary on T1WI. For example, Gudinchet et al. [3] and Sato et al. [4] reported that the high intensity signal of the posterior pituitary was absent in patients with CDI. However, Miyamoto et al. [5] reported an interesting pedigree of familial CDI with a high intensity signal detected in the posterior pituitary in 2 patients, but not in 3 other patients, of the same family. Maghnie et al. [6, 7] also reported that the posterior bright signal was recognizable in 2 cases with a familial autosomal-dominant form and one with an idiopathic form. They also reported an idiopathic CDI boy who had a persistent high intensity signal in the posterior pituitary after a ten year follow-up.

We present a CDI patient with a single base substitution in the arginine vasopressin (AVP)-neurophysin (NP)-II gene, who showed a high intensity signal in the posterior pituitary on MR T1WI.
Case report

A 10-year old boy visited our hospital, complaining of polyuria and nocturnal enuresis every night. He had a history of polyuria and polydipsia. However, his mother did not pay attention to these symptoms. A laboratory test in an outpatient clinic revealed that AVP was under 0.2 pg/ml, and he was admitted for further examination. Family history revealed that his father appeared to have polyuria and polydipsia, while his mother had no polyuria and polydipsia.

On admission, he weighed 30 kg and was 133 cm tall. His blood pressure was 100/52 mmHg, his pulse was regular at 80 bpm and his body temperature was 37.0°C. Eye ocular movement was normal, there were no heart murmurs and normal vesicular sounds were audible. The abdomen was soft and flat. He had no edema. There were no abnormal signs on neurological examinations.

Laboratory data on admission showed the following: WBC 4400/μl, RBC 518 x 10^4/μl, hemoglobin 15.2 g/dl, hematocrit 43.6%, platelet 26.7 x 10^4/μl, sodium 139 mEq/l, potassium 4.2 mEq/l, chloride 101 mEq/l, AST 20 U/l, ALT 14 U/l, urea nitrogen 11 mg/dl, creatinine 0.4 mg/ml, total protein 7.1 g/dl, glucose 96 mg/dl. Venous blood gas analysis showed a pH of 7.35, P1 CO2 54.2 torr, P1 O2 22.1 torr, base excess 3.2 mEq/l, and HCO3- 29.4 mEq/l. Endocrine data on ACTH, GH, PRL, LH, FSH, TSH and cortisol were all normal. AVP plasma level was under 0.2 pg/ml. Urinary and plasma osmolality were 68 and 285 mOsm/kgH2O, respectively. Urinalysis was normal. MR imaging of the posterior pituitary gland revealed hyperintensity on T1WI (Fig. 1). Its size was normal and no mass was found. Echosonography and X-ray examination after enhanced computed tomography revealed hydronephrosis and a dilated urinary bladder. Voiding cystourethrogram showed no vesicoureteral reflux. AVP secretion in response to a water deprivation test was low (<0.2 and 0.6 pg/ml). Loading test of 5% sodium chloride (0.05 ml/kg/min for 2 hours) showed no increase in AVP levels in response to high plasma osmolalities (Fig. 2). Intranasal administration of 20 μg 1-desamino-8-arginine vasopressin (DDAVP) effectively reduced urine volume and increased hourly urine osmolality (Fig. 3).

Sequence analysis of the AVP-NP II gene was performed following extraction of genomic DNA from peripheral mononuclear cells from the patient and his mother. Unfortunately, sequence analysis of the AVP-NP II gene of his father was not available because of the parents’ divorce. The primers described in a previous report [8] were used for the polymerase chain reaction (PCR). PCR was performed using recombinant Taq DNA polymerase (Takara Shuzo, Kyoto, Japan) to amplify Exons 1 and 3, and LA Taq DNA polymerase with a GC buffer (Takara Shuzo) was used for Exon 2. DNA fragments amplified by PCR were sequenced directly via fluorescence-based dideoxy sequencing using a Model 377 sequencer (Perkin-Elmer, Norwalk, CT). In the patient, there were no mutations in Exons 1 and 3, while nucleotide 1884 guanine (G) in Exon 2 was substituted with thymine (T), inducing a glycine (Gly) substitution for valine (Val) at amino acid position 65 in the NP II moiety. The patient was considered to be heterozygous for the mutation because he had normal and mutant alleles. In his mother, there were no mutations in Exons 1, 2 and 3. Informed consent for genetic studies was obtained from the patient and his mother.

Discussion

Our case is compatible with CDI because of the data on water deprivation test data and loading tests of 5% sodium chloride and DDAVP. Ueta et al. [8]
reported a point mutation of Gly65 to Val (Gly65 → Val) in the AVP-NP II gene in CDI patients. They showed that the familial pedigree displayed an autosomal-dominant form of inheritance, and that affected members of the family were heterozygous for the mutation because they had both normal and mutant alleles. However, they did not report MR findings on the patients. Our case had the same mutation as that of Ueta et al., and is considered to be heterozygous for the mutation. Thus, our case of CDI is thought to represent a dominant form of inheritance, although sequence analysis of the AVP-NP II gene of his father was not performed. Thus, sequence analysis of the AVP-NP II gene is extremely important for the diagnosis of CDI, as well as genetic counseling, in the future.

MR findings in CDI usually reveal the loss of normal high intensity of the posterior pituitary on T1WI. However, Miyamoto et al. [5] and Maghnine et al. [6, 7] reported cases of CDI that showed high intensity signals in the posterior pituitary. Few cases of CDI are reported with a high intensity signal in the
posterior pituitary who were shown to have a mutation in the NP II gene. Gagliardi et al. [9] reported an attenuated bright spot in the posterior pituitary gland on MR T1WI in an adult with familial CDI. Analysis of the AVP-NP II gene revealed a single transversion of a T for a G at nucleotide 1758 in Exon 2. This mutation encoded a Val substitution for Gly at amino acid 23 of NP II. In the present study, the posterior pituitary gland demonstrated an apparent bright spot. However, CDI is a slowly progressive disease [10], and thus the high intensity signal in the posterior pituitary in our case may be less intense in the future as reported by Fujii et al. [1] and Gagliardi et al. [9]. Thus, long-term observations are necessary to clarify the MR findings of our patient.

In our case, Gly$^{65}$ was replaced with Val. Nijenhuis et al. [11] demonstrated in cell lines that the mutant prohormone (Gly$^{65}$ → Val) could not exit the endoplasmic reticulum to the Golgi apparatus, and that it was largely retained in the endoplasmic reticulum. Thus, the prohormone is not transported to the posterior pituitary, leading to high intensity signal loss in the posterior pituitary gland. However, a high intensity signal was detected in the posterior pituitary in our case, who had the same mutation reported by Nijenhuis et al. [11]. This contradiction could be explained by the incomplete effect of mutations in the storage of prohormone in the endoplasmic reticulum, or because we only observed the early stage of the posterior pituitary where a high intensity signal would be less intense in the future in our CDI patient.

In conclusion, we reported a case of CDI with a high intensity signal in the posterior pituitary on MR T1WI, who was proven to have a mutation (Gly$^{65}$ → Val) in the AVP-NP II gene.

Acknowledgement

We thank Dr. Takashi Kageyama (Department of Environmental Medicine, Osaka Medical Center and Research Institute for Maternal and Child Health, Izumi, Japan) for technical assistance.

References


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