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Case Report

A *de novo* novel missense mutation in *AVPR2* with severe nephrogenic diabetes insipidus

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Abstract

We describe a paediatric case of nephrogenic diabetes insipidus (NDI) with a novel mutation in the arginine vasopressin receptor 2 gene (*AVPR2*) in the absence of a family history of congenital polyuria. The patient, a 5-month-old Caucasian boy, had failure to thrive and hypernatraemia. On admission to hospital, he had a plasma sodium of 171 mEq/L with a concomittant urine osmolality of 131 mOsm/kg. Molecular genetic analysis demonstrated that the patient had an *AVPR2* mutation (c.861C>G) resulting in a substitution of tryptophan for serine at amino acid position 167 (p.Ser167Trp). His mother was heterozygous for the same Ser167Trp mutation which was found to be *de novo* from the DNA analysis of the maternal grandparents.

Keywords: arginine vasopressin receptor 2; nephrogenic diabetes insipidus; S167W; X-linked recessive disease

Introduction

Nephrogenic diabetes insipidus (NDI) is a disorder characterized by renal insensitivity to arginine vasopressin (AVP). It is defined as the excretion of increased (typically >30 mL/kg/day) volumes of diluted urine (<250 mOsm/kg) [1]. About 90% of patients with congenital NDI are males with an X-linked recessive inheritance (OMIM 304800) of mutations in the arginine vasopressin receptor 2 gene (*AVPR2*) [1]. The gene is located in chromosomal region Xq28. The incidence of X-linked NDI was estimated to be ~8.8 per million of male live births in the Quebec region [2]. Spanakis *et al.* reported 211 *AVPR2* gene mutations among symptomatic NDI in 326 families and 21 variants among asymptomatic NDI in 71 families [3]. Bichet *et al.* suggested that family members of the index cases with NDI should have their molecular defect identified since early diagnosis and treatment of affected infants can avert the physical and mental retardation which occurs as a result of repeated dehydration episodes [4].

Case report

A 5-month-old Caucasian boy was admitted to a community hospital for failure to thrive and hypernatraemia. His weight had decreased from the 10th percentile to below the 3rd percentile over a 1-month time period. His serum sodium was 170 mEq/L. He took 120–145 mL/kg/day of formula with 6–10 wet diapers daily. He was born at 36 weeks of gestation via induction delivery due to oligohydramnios. There was no perinatal stress. After birth, he was prescribed lamsoprazole for gastroesophageal reflux. His mother was diagnosed with type 1 diabetes at 16 years of age.

His weight and height were 4.68 kg (below 3rd percentile) and 59.0 cm (below 3rd percentile), respectively. Serum sodium was 171 mEq/L, potassium 4.4 mEq/L, blood urea nitrogen 16 mg/dL, creatinine 0.3 mg/dL, albumin 4 g/dL and osmolality 348 mOsm/kg. Urine-specific gravity was 1.003 with an osmolality of 136 mOsm/kg. Urine sodium was <20 mEq/L. Daily urinary output was 1488 mL/day (5131 mL/m^2/day). Renal ultrasound showed mild bilateral hydronephrosis.

His sodium increased to 180 mEq/L after fluid resuscitation with normal saline (NS), which subsequently failed to respond to three consecutive doses of desamino-arginine vasopressin (dDAVP) at 0.21 mcg/kg/dose or intravenous infusion of vasopressin at 111 milliunits/kg/h.

On admission, his blood pressure was 96/49 mm Hg with a heart rate of 188 beats/min. Serum sodium had decreased to 164 mEq/L. Intravenous administration of dDAVP at 0.21 mcg/kg during a water deprivation test (see Discussion) increased serum sodium from 167 to 173 mEq/L with signs of dehydration in one and half hours. Serum and urine osmolalities 1 h after the initiation of

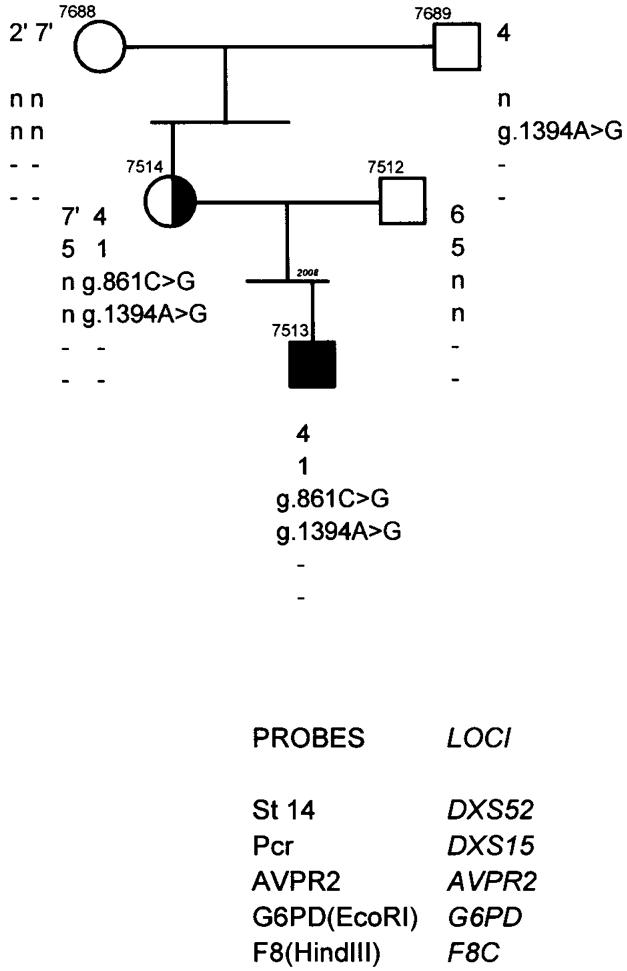

Fig. 1. Pedigree of X-linked nephrogenic diabetes insipidus in the patient's family, due to a *de novo* mutation which occurred on the grandpaternal allele, demonstrated by Xq28 haplotype and *AVPR2* sequencing analysis. n, normal *AVPR2* gene sequence. To follow the segregation of the *AVPR2* allele, haplotype analysis was done by genotyping of four loci (DXS52, DXS15, G6PD and F8) flanking the *AVPR2* gene in chromosome region Xq28, as described previously [2].

water deprivation were 368 and 98 mOsm/kg, respectively. A diagnosis of NDI was made. During the rest of the hospitalization, serum sodium was gradually corrected with careful free water provision. Oral hydrochlorothiazide and amiloride were initiated.

Mutation analysis of the *AVPR2* gene was performed after informed consent was obtained. Genomic DNA was prepared from peripheral leukocytes by standard methods, and DNA sequencing was performed as described previously [2]. The analysis identified a C to G nucleotide transition (c.861C>G) in exon 2 of the *AVPR2* gene (GenBank: L22206.1), which resulted in substitution of tryptophan for serine at amino acid residue 167. Further testing of family members revealed that his mother was heterozygous for the same mutation. Xq28 haplotype and *AVPR2* sequencing analysis of the DNA obtained from the maternal grandparents revealed that this was a *de novo* mutation which occurred on the grandpaternal allele (Figure 1).

Discussion

We describe a 5-month-old Caucasian boy with NDI due to a novel *AVPR2* missense mutation with his mother being an asymptomatic heterozygous carrier. We determined that this novel *AVPR2* mutation was a *de novo* mutation which occurred on the mother's grandpaternal allele. In a previous study, 17 *de novo AVPR2* mutations were identified in the mothers of affected boys and 16 mutations were inferred to occur during spermatogenesis [2]. The lack of family history of male family members affected with polyuria and polydipsia may delay the recognition of polyuric and dehydration signs and symptoms by the mother and may explain the delay in diagnosis seen with similar cases.

The phenotype due to this Ser167Trp mutation is severe because urine osmolality after water deprivation followed by DDAVP administration remained below 100 mOsm/kg with concomitant plasma sodium higher than 150 mEq/L. The water deprivation test with a baseline plasma sodium of 167 mEq/L was inappropriate and potentially dangerous since a strong indication for the diagnosis of NDI was already given by a plasma sodium of 171 mEq/L with a concomittant urine osmolality of 131 mOsm/kg. Also, the increase in plasma sodium observed after NS administration should be expected since a net gain of 100 mEq of Na^+ will result from the infusion of 1 L of NS (150 mEq of Na^+) and excretion of 1 L of dilute urine with a Na^+ = 50 mEq. We do not have any specific explanation for the oligohydramnios observed here; pregnancies leading to the birth of infants subsequently found to have congenital sodium-losing nephropathies are often complicated by large polyhydramnios leading to repeated taps and prematurity but we know of no pregnancy leading to the birth of X-linked NDI children and complicated with a polydramnios. There is, however, one report of a patient with untreated central diabetes insipidus and oligohydramnios at 33 weeks gestation with resolution of the oligohydramnios after desmopressin [5], indicating that amniotic fluid volume may be affected by hydration. The mother was not polyuric at the time of the oligohydramnios but she did not have a 24-h urine volume evaluation. Some *AVPR2* mutations (p.Asp85Asn, p.Val88Met, p.Gly201Asp and p.Pro322Ser) may be associated with a milder or partial phenotype and clinically important response to dDAVP and these 'milder' mutations are associated with urine osmolalities >250 mOsm/kg [6,7].

The mutant protein Ser167Trp is likely misfolded since a full polyuric phenotype without a response of urine osmolality to dehydration or dDAVP is observed. Most of the *AVPR2* mutations lead to mutant receptors that cannot reach the cell surface due to defective intracellular transport [1]. These misfolded vasopressin 2 receptor mutants could be rescued *in vitro* and *in vivo* by nonpeptide antagonists that function as pharmacologic chaperones [8].

The p.Ser167Trp is a novel mutation. In contrast, the p.Ser167Leu *AVPR2* mutation reported in 14 apparently independent families was the largest case series among all the published mutations [3,9]. The p.Ser167Leu and p.Ser167Thr mutations have been expressed in COS.M6

cells as misfolded and non-functional [10]. Other missense mutations affecting the same amino acid have been reported: p.Ser167Ala, p.Ser167Thr and p.Ser167Leu [3,9] as well as p.Ser167X [2]. The *AVPR2* mutation at Ser167-Leu is considered a recurrent one since it occurs on different haplotypes [2].

The clinical differential diagnosis of this case was rather straightforward: this is a male with NDI with free-water loss from a non-inbred family, it was therefore indicated to sequence the *AVPR2* gene. If an *AVPR2* mutation was not identified, we would have sequenced the *AQP2* gene searching for homozygous or compound heterozygous mutations [11]. Polyuric patients with prematurity, hypokalaemia and a pregnancy history of polydramnios would suggest Bartter syndrome, but polyhydramnios during pregnancy has not been described in infants bearing *AVPR2* or *AQP2* mutations [12]. Familial hypomagnesemia with hypercalciuria (FHHNC) and nephronophthisis (NPHP) are also characterized by polydipsia and polyuria in early childhood. However, their polyuric phenotypes are less severe, as compared to that with *AVPR2* or *AQP2* mutations, and appear progressively after a few months of life with associated features such as hypomagnesemia, bilateral nephrocalcinosis, urinary tract infections and progressive renal failure in FHHNC and anaemia and renal failure in NPHP [13,14]. Patients with cystinosis are also polyuric although other phenotypic features of cystinosis are present. However, in infants, corneal opacity may be absent causing a delay in the diagnosis of cystinosis [15].

In conclusion, we encourage early clinical identification and molecular confirmation of all congenital polyuric and polydipsic cases.

Conflict of interest statement. None declared.

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