A NOVEL INTRAGENIC DELETION RELATED TO THE ARGININE VASOPRESSIN V2 RECEPTOR CAUSES NEPHROGENIC DIABETES INSIPIDUS

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Abstract

Background. Nephrogenic diabetes insipidus (NDI) is a disease characterized by a defective response to the antidiuretic hormone (ADH) of the renal collecting duct leading to a decline in the ability of the pro-urine concentration.

Case presentation. A 23-year-old man presented with an over 20-year history of polyuria concomitant with hydronephrosis. The diagnosis of NDI was established by gene analysis as well as a water-deprivation and vasopressin test. All exons of arginine vasopressin V2 receptor (AVPR2) gene were amplified and sequenced. A novel hemizygous intragenic inframe deletion, cDNA 255th bp to 263th bp in exon 2 of AVPR2, was identified. These relevant translations from the 85th amino acid Asp to 88th amino acid Val were missed and replaced by amino acid Glu. After treating the patient with hydrochlorothiazide, his symptoms improved significantly.

Conclusion. The genetic analysis revealed a novel X-linked intragenic inframe deletion, AVPR2 gene cDNA 255th bp to 263th bp, causing NDI.

Keywords: Nephrogenic diabetes insipidus, polyuria, arginine vasopressin V2 receptor, intragenic inframe deletion.

INTRODUCTION

Nephrogenic diabetes insipidus is a rare disorder with polyuria resulting from renal defects of antidiuretic hormone response (nephrogenic diabetes insipidus, NDI) (1). Congenital NDI is caused by pathogenic variants of the arginine vasopressin V2 receptor (AVPR2) gene located in X-chromosome at Xq28, or by mutation of the vasopressin-sensitive water channel aquaporin 2 (AQP2) gene located in chromosome at 12q13(2, 3). We report a patient with NDI caused by a new intragenic inframe deletion.

CASE PRESENTATION

A 23-year-old man had presented with

polyuria and polydipsia for more than 20 years, but with no history of dysplasia, craniocerebral trauma and hyperglycemia. He was utterly unconcerned with polyuria and polydipsia, and did not receive further treatment. In June 2017, bilateral hydronephrosis was found in a health examination. For relieving it, a bladder catheter was inserted (Fig. 1A). Upon hospital admission, his daily urine and drinking volumes were approximately 10-14L and 10-15L respectively. A routine urine test showed that the urine specific gravity was 1.005. Urodynamics indicated that the maximum urine flow rate was 43 mL/s. Bladder residual urine volume was 100 mL. CT scans indicated hydronephrosis with ureteral dilatation (Fig. 1B). Radioisotope renogram showed the glomerular filtration rate was 82.45 mL/min. The following laboratory blood tests were normal: electrolyte, liver and renal functions, erythrocyte and leukocyte counts, prolactin, follicle-stimulating hormone, luteinizing hormone, thyroid-stimulating hormone, triiodothyronine, thyroxine, free triiodothyronine, free thyroxine, adrenocorticotrophic hormones and cortisol. On the 5th day of admission, he underwent a water deprivation-vasopressin test. During 5 hours of water-deprivation, urine specific gravity had no significant change. The urine osmolality fluctuated between 64 mOsm/kg H₂O and 87 mOsm/kg H₂O. After subcutaneous injection of pituitrin (5 units), urine volume, specific gravity and osmolality did not change significantly (Table 1). After the test, the patient received oral desmopressin 0.1 mg twice daily, but his urine volume did not decrease (Table 2). On the 6th day of admission, he underwent hypothalamic-pituitary MRI scans, which showed that the feature of pituitary was hyperintensity (Fig. 1C). On the eighth day of admission, desmopressin was replaced by hydrochlorothiazide 25 mg twice daily, and then his polyuria (Table 2), polydipsia, and urine osmolality significantly improved, favoring the diagnosis of

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NDI. The DNA analysis of the AQP2 and AVPR2 genes was performed. All exons of both genes were amplified and sequenced. A novel intragenic inframe deletion, cDNA 255th bp to 263th bp in exon 2 of

AVPR2, was identified. And 85th amino acid Asp to 88th amino acid Val of the relevant translated protein were absent, and were replaced by Glu (Fig. 1D).

Figure 1. The images of the patient with NDI and the comparison of the base sequences between the normal AVPR2 gene and the AVPR2 gene with the intragenic inframe deletion. Notes: A) To reduce the impact of the large output of nocturnal urine interfering the patient's rest, a bladder fistula was placed in his lower abdomen; B) CT scan indicated hydronephrosis; C) A sagittal MRI image showed that the feature of pituitary was hyperintensity in this patient with NDI, which was totally different from hypointensity of pituitary in CDI; D a) Normal base sequences for AVPR2 gene ranging from 253th to 264th are -GACCTGGCCGTG-; D b) The intragenic inframe deletion of AVPR2 with half-zygote was detected: c.255_263del9. The relevant translated protein from the 85th amino acid Asp to 88th amino acid Val was lost, and it is replaced by the amino acid Glu, d. (Asp85_Val88 delinsGlu).

Table 1. Water deprivation-vasopressin test

Time of water deprivation (hours)	Urine volume (mL)	Urine specific gravity	Urine pH	Urine osmolality (mosm/kgH ₂ O)	Blood osmolality (mosm/kgH ₂ O)
0	10	1.005	7.0	64	288
1	700	1.005	7.0	67	293
2	500	1.005	7.5	64	295
3	300	1.005	7.5	71	288
4	200	1.005	7.5	87	300
5*	300	1.005	8.0	98	286
6	300	1.005	7.5	82	291
7	300	1.005	7.5	75	298

Note: * Subcutaneous injection of pituitrin (5 units).

Table 2. The trend of the patient's urine volume in relationship to hydrochlorothiazide therapy

Date (Day, D)	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16
Urine volume (L)	9	7	9.3	7.8	4.9	6	4	3.1	3.6	3.6	3	2.6

Note: On the first day after admission (D1); On the fifth day of admission (D5), the patient underwent a water deprivation-vasopressin test; On the sixth day of admission (D6), he started taking minirin 0.1mg twice daily; On the eighth day (D8), minirin was replaced by hydrochlorothiazide 25mg twice daily; On the eleventh day (D11), hydrochlorothiazide was taken 25mg three times daily.

DISCUSSION

The AVPR2 is abundant in the kidneys (4) regulating the action of vasopressin on the principal cells of collecting ducts. It is encoded by AVPR2 gene located in the chromosome Xq28. Vasopressin binding to AVPR2 leads to the increase of cAMP, which initiates a signalling cascade and phosphorylates the target proteins including AQP2 (2, 5). Hence, AVPR2 pathogenic variants cause NDI. AVPR2 mutations are divided into five different types. Type I: missense, aberrant splicing, frame-shift or nonsense; Type II: missense or insertion/deletion, or last exon nonsense; Type IIIa: missense results in losing the Gs protein binding site; Type IIIb: missense results in losing the AVP binding site; Type IV: missense causes the defects in intracellular trafficking (6). We report this case with polyuria, polydipsia, uretero-hydronephrosis. The water-deprivation and vasopressin test confirmed the diagnosis of NDI. Moreover, the genetic analysis also revealed a novel X-linked intragenic inframe deletion causing the loss of four amino acids, which may lead to unstable and easily degradable protein, suggesting a decrease of AVPR2 function. This kind of intragenic inframe deletion has not been reported in the HGMD, ESP6500, 1000 genomes and dbSNP databases. After treating with hydrochlorothiazide at a dose of 25 mg q8h and a low-salt diet (Na≤2g/ day), his daily urine volume decreased by up to 70-80 percent before discharge. Unfortunately, his parents and other relatives refused to take the relevant genetic tests.

A limitation of this report is that we did not request a biopsy for renal tissue to further test if this

intragenic deletion can reduce the reaction of AVPR2 to AVP *in vitro*. Once the biopsy for this patient is approved by the Ethics Committee, we may measure the related indexes.

In conclusion, NDI is a disease characterized by polyuria and polydipsia. Here, we report an intragenic inframe deletion in AVPR2 gene causing NDI, which was confirmed by gene, water-deprivation and vasopressin tests. The genetic analysis found a novel X-linked intragenic inframe deletion, AVPR2 gene cDNA 255th bp to 263th bp.

Conflict of interest

The authors declare that they have no conflict of interest.

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