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Case Report

Oral disintegrating desmopressin tablet is effective for partial congenital nephrogenic diabetes insipidus with *AVPR2* mutation: a case report

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Highlights

- Oral disintegrating DDAVP can be effective and safe in patients with partial congenital NDI due to *AVPR2* gene mutations.
- Treatment with 720 μg of DDAVP per day reduced our patient's urine output by approximately 30%.

Abstract. Congenital nephrogenic diabetes insipidus (NDI) is a rare disease that causes polydipsia and polyuria, and there are currently no effective treatments for most cases, particularly severe ones. The present report describes the case of a 1-yr-5-mo-old male patient with partial congenital NDI who was successfully treated with oral disintegrating 1-deamino-8-D-arginine vasopressin (DDAVP). The patient presented with poor weight gain and polydipsia (fluid, 1.5 L/d) and received a diagnosis of NDI after genetic analysis revealed an *AVPR2* mutation (c.383A>C, p.Y128S). His water-restricted urine osmolality increased from 360 mOsm/kg/H_2O to 667 mOsm/kg/H_2O after subcutaneous AVP injection, indicating that he had some urine concentrating ability. Oral disintegrating DDAVP therapy was started at 360 μg/d with hydrochlorothiazide and increased to 720 μg/d without any adverse effects. A 30% decrease in urine output and water intake was followed by an increase in body weight. The present study is the first to report the effectiveness and safety of oral disintegrating DDAVP in a patient with partial congenital NDI due to an *AVPR2* gene mutation. The severity of NDI at which DDAVP therapy is the most effective remains to be determined.

Key words: oral disintegrating 1-deamino-8-D-arginine vasopressin (DDAVP), congenital nephrogenic diabetes insipidus, AVPR2, partial nephrogenic diabetes insipidus (NDI)

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Introduction

Congenital nephrogenic diabetes insipidus (NDI) is a rare inherited disorder characterized by insensitivity of the distal nephron and collecting duct to the antidiuretic action of AVP and a consequent reduction in the ability of the kidneys to concentrate the urine, possibly leading to severe dehydration and electrolyte imbalance (1). In about 90% of cases, X-linked mutations in the vasopressin type 2 receptor (*AVPR2*) gene are responsible for the disease (2, 3). Current approaches to the treatment of congenital NDI consist of reducing urine output. However, standard therapy using thiazide diuretics can only partially decrease urine output (1).

Although partial congenital NDI is difficult to define, most researchers agree that it is characterized by residual urine concentrating ability (4). According to one definition, the partial type presents with further increases in urine osmolality after vasopressin injection at the plateau phase of water restriction (5).

Nasal or oral high-dose 1-deamino-8-D-arginine vasopressin (DDAVP), a V2-receptor-selective agonist, is reportedly effective in patients with partial congenital NDI (6–9). A nationwide Japanese survey revealed that DDAVP was used to treat approximately 20% of patients with congenital NDI and was effective in approximately 25% of these patients (10). However, given the small number of previous reports and the limited clinical information available from each case, further accumulation of data is necessary.

There are two forms of DDAVP approved for central diabetes insipidus treatment in Japan: nasal spray and oral disintegrating tablets. The latter formulation is more readily absorbed, has a lower peak concentration, and is therefore considered safer (11). To the best of our knowledge, no previous studies have examined the use of oral disintegrating DDAVP for NDI.

Herein, we report the case of a 1-yr-5-mo-old male patient with a diagnosis of partial congenital NDI with partially preserved AVPR2 function who was successfully treated with oral disintegrating DDAVP.

Case Presentation

A 1-yr-5-mo-old male infant was referred to us to evaluate weight gain failure and polydipsia. He was born as the second child to Japanese parents at 36 wk gestation with a birth weight of 2202 g and a height of 46.0 cm. He habitually consumed approximately 1.5 L of fluids per day (4.1 L per body surface area) from around seven months. He had no history of recurrent fever or dehydration. He had poor weight gain since the age of eight months (**Fig. 1**). His parents had no symptoms of polydipsia or a past medical history.

On his first visit, his body weight was 7.1 kg (–3.0 standard deviation [SD]), and his height was 71.6 cm (–2.9 SD). Laboratory examinations revealed no abnormalities, and his serum sodium (Na) level was 144 mEq/L. Because the patient had not gained weight

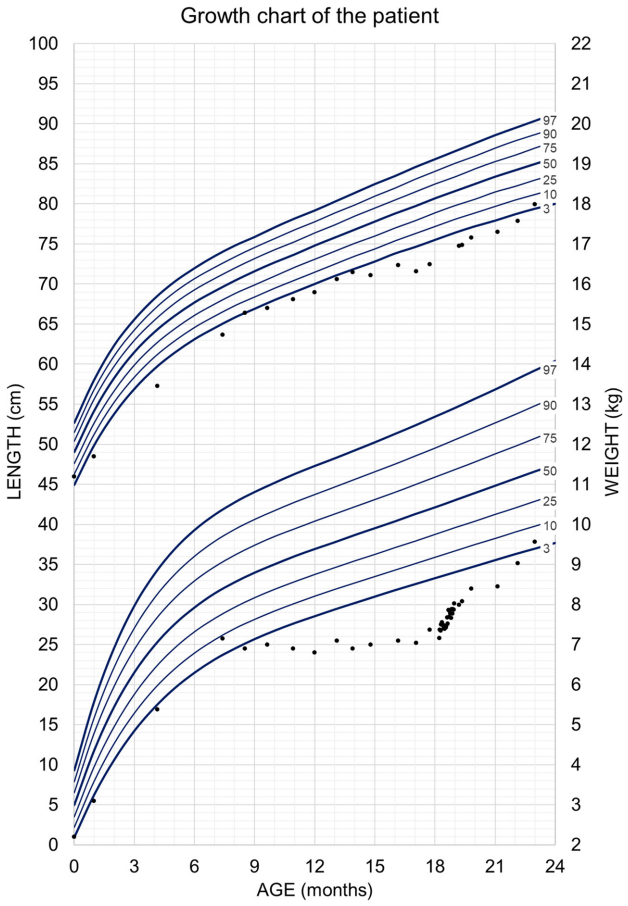

Fig. 1. Growth chart of the patient (22). The upper and lower charts show height and weight, respectively. The patient was referred to our hospital at the age of 1 yr and 5 mo, with a weight of 7.1 kg (–3.0 SD) and a height of 71.6 cm (–2.9 SD). After treatment, the patient's weight and height increased.

for nine months, the diagnosis was thought to be more likely to be diabetes insipidus than primary polydipsia.

On his second visit, the patient's fluid intake was restricted after 8 am. His urine output from 8 am to 11 am (three hours) was 230 mL (5.0 L/m^2/d). He weighed 7485 g at 10 am, and 7230 g at 12 am. Laboratory examination at 11 am revealed a high serum AVP level and low urine osmolality (**Table 1**). NDI was suspected based on the high urine volume with high AVP and the absence of increased urine osmolality during the water deprivation test described above.

On admission, a stricter water deprivation test was performed to confirm the diagnosis (**Table 2**). Water intake was stopped after 6 am. Urine and blood samples were collected every 15 min for 1 h, and their weight was measured every 30 min for 1 h. After water deprivation, his weight decreased (4.29% weight loss after 6.5 h of water deprivation). The serum Na level and plasma osmolality increased to 147 mEq/L and 300 mOsm/kg/H_2O, while his urine osmolality plateaued at 360 mOsm/kg/H_2O, suggesting diabetes insipidus. His urine osmolality increased to 667 mOsm/kg/H_2O

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after a subcutaneous injection of 1.5 U (5 U/ m^2) AVP injection (12), indicating that his renal tubules were responsive to AVP.

Mutation screening for two major causative genes for congenital NDI (*AVPR2* and *AQP2*) was performed. Consequently, we identified a previously reported mutation in *AVPR2* (c.383A>C, p.Y128S), based on which the NDI was diagnosed. No further, rare variants were detected in these genes. His mother also harbored the same hemizygous mutation.

Figure 2 shows the clinical course of the patient. Hydrochlorothiazide was started at the age of 1 yr and 5 mo during hospitalization at an initial dosage of 1.0 mg/kg/d administered in two equal portions twice a day and was subsequently increased to 2.0 mg/kg/d five days later, then to 3.0 mg/kg/d after five more days. After his urine output stabilized with 3 mg/kg/d hydrochlorothiazide, a high-dose oral disintegrating DDAVP treatment consisting of 360 μg/d (three times per day) was administered, followed by an increase to 720 μg/d four days later. The treatment finally lowered his urine output by about 30% (approximately 1.3 L/d vs. 1.9 L/d) and decreased water intake (approximately 1.2 L/d vs. 1.8 L/d). Because the water intake decreased, strict water restriction was not performed. Since his serum potassium (K) had decreased (3.5 mEq/L) at the time of hospital discharge, the hydrochlorothiazide dosage was lowered to 2.0 mg/kg/d.

After discharge, the patient was followed up at the outpatient clinic. The mean (SD) water intake from age of 1 yr 6 mo to 2 yr 0 mo was 1321.5 (282.0) mL/d (N = 164), which did not differ greatly from the levels during hospitalization. Serum Na and K levels remained stable during this period. His weight and height increased to 9.7 kg (–1.7 SD) and 79.5 cm (–2.1 SD) at 2 yr (**Fig. 1**).

At two years of age, the oral disintegrating DDAVP dosage was changed weekly at the outpatient clinic to determine the optimal dosage for the patient (**Fig. 3**). During week one, the mean (SD) water intake was 1831.4 (204.2) mL/d when the DDAVP dosage was 360 μg/d. During week two, the mean (SD) intake was 1427.1 (234.3) mL/d at 720 μg/d. During week three, the mean (SD) intake showed no further change (1454.2 [368.5] mL per day) at 1080 μg/d. The optimal dosage for the patient was determined to be 720 μg/d, and his treatment continued to be effective during the subsequent nine months. Ethics approval was obtained from the ethics committee at Tokyo Metropolitan Children's Medical Center (2021a-19, 2021b-76), and written informed consent was obtained from the patient's parents

Table 1. Laboratory findings at the second visit

Laboratory test	
Blood	
Na (sodium, mEq/L)	143
K (potassium, mEq/L)	4.9
Cl (chloride, mEq/L)	107
Plasma osmolality (mOsm/kg/H_2O)	291
Plasma AVP (pg/mL)	46.9
Urine	
Urine specific gravity	1.005
Urine osmolality (mOsm/kg/H_20)	206

Table 2. Water deprivation test findings

Time	Weight (g)	Weight loss rate (%)	Urine output (mL)	Total urine output (mL)	Urine Osm (mOsm/kg/H_2O)	Serum Osm (mOsm/kg/H_2O)	Serum Na (mEq/L)	AVP (pg/mL)
6:00	7230		0	0	222			
7:00	7220	0.14	14	14	237		143	
7:30			8	22	464			
8:00	7150	1.11	13	35	386	292	143	18.8
8:30			18	53	255			
9:00	7060	2.35	24	77	285	293	145	
9:30			26	103	202			
10:00	7030	2.77	28	131	183	295	147	
10:30			26	157	237			
11:00	6930	4.15	18	175	291	298	148	
11:15			8	183	310			
11:30			10	193	346			
11:45			5	198	360			
12:00	6930	4.15	5	203	351	296	148	
12:15			7	210	330			
12:30	6920	4.29	10	220	353	300	147	42
12:40	Vasopressin 1.5 unit sc							
13:00			5	225	394			
13:30			7	232	667			
14:00	6880	4.84	3	235	489	299	148	
14:30			10	245	451			
15:00	6880	4.84	2	247	602	303	149	90.9

sc, subcutaneous injection; osm, osmolality.

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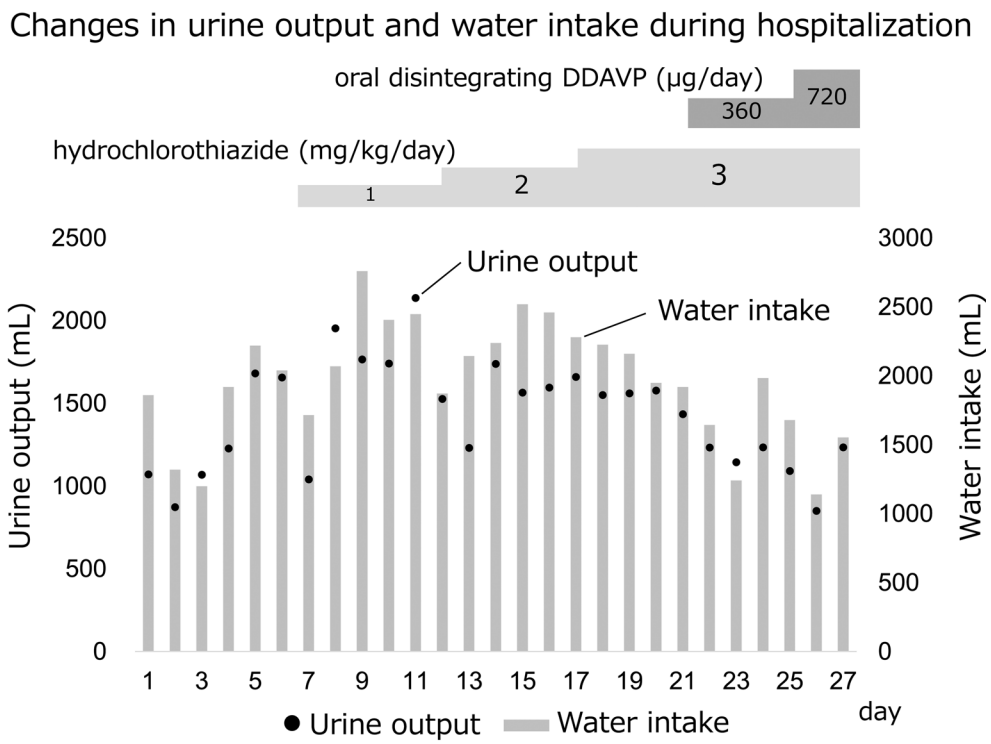

Fig. 2. Changes in urine output and water intake during hospitalization. The horizontal and vertical axes show the number of days after clinical diagnosis and the trends in water intake and urine output, respectively. Treatment was initiated with hydrochlorothiazide 1 mg/kg/d on day seven. The dosage was increased, and oral disintegrating DDAVP was added. Finally, the patient received hydrochlorothiazide 3 mg/kg/d and oral disintegrating DDAVP (720 μg/d). Thereafter, his urine output and water intake decreased by approximately 30%.

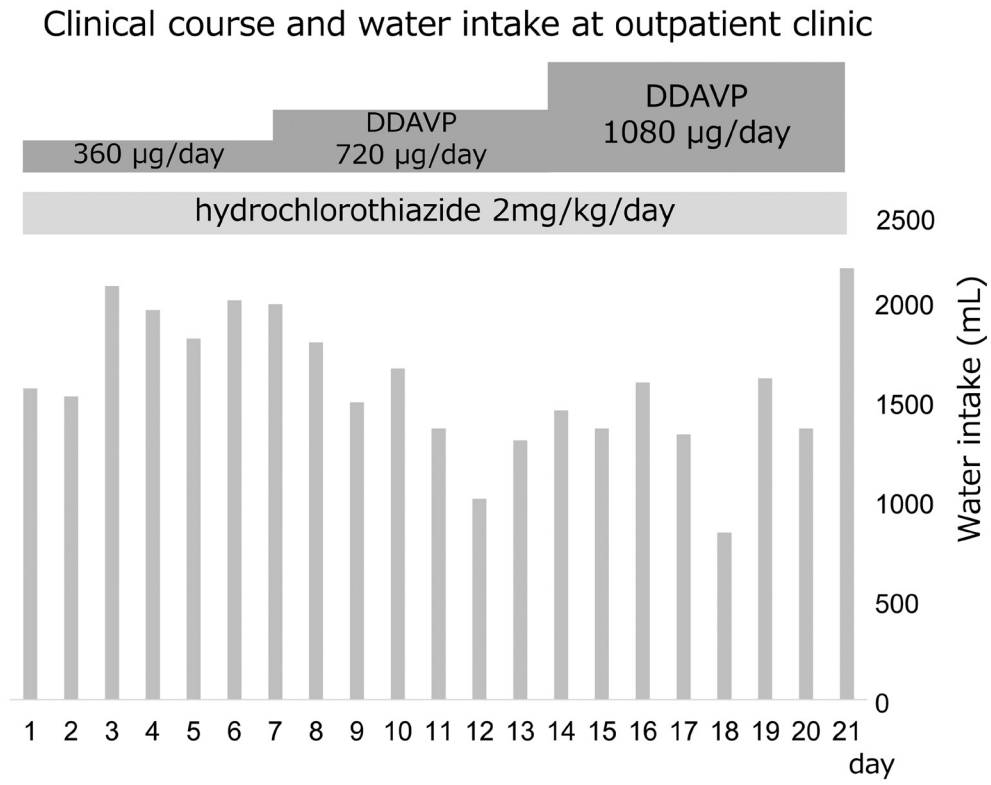

Fig. 3. Clinical course and water intake at outpatient clinic. Day 1 indicates the start of the dose-adjustment trial. The oral disintegrating DDAVP dosage was increased weekly at the outpatient clinic. After the dosage was increased from 360 μg/d to 720 μg/d, the water intake decreased. However, water intake did not differ significantly between 1080 and 720 μg/d.

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for treatment with oral disintegrating DDAVP and publication of this case report.

Discussion

The present study demonstrated that treatment with oral disintegrating DDAVP tablets has the potential to reduce urine output in patients with partial NDI with *AVPR2* mutation. However, the function of AVPR2 and the clinical symptoms of NDI vary; thus, responses to DDAVP treatment can vary widely (4).

The present patient was thought to have partial congenital NDI prior to DDAVP treatment based on observations of his clinical response to AVP and genotype analysis. First, vasopressin administration in the water restriction test demonstrated an increase in urine osmolality from 360 to 667 mOsm/kg/H_2O. The results satisfied one of the definitions of partial congenital NDI (5). Second, p.Y128S is known to cause "partial loss of function" (13). Previous studies have described 274 and 17 known mutations in the *AVPR2* gene as "complete loss of function" and "partial loss of function" mutations, respectively (1).

Oral disintegrating DDAVP was effective in the present case of partial congenital NDI, which was due to an *AVPR2* gene mutation, and reduced urine output and water intake by approximately 30%. Previous studies reported a similar efficacy for nasal and oral DDAVP, which decreased urine output by 30–50% (4, 6, 8). Six *AVPR2* mutations, p.A37P, pD85N, p.V88N, p.R104C, p.Y128S, and p.T164C, are associated with the response to high-dose DDAVP (4, 7, 8, 10). High-dose DDAVP was also reportedly effective in patients with partial congenital NDI with AQP2 gene mutations (10, 14).

The appropriate dosage of oral disintegrating DDAVP for the present patient was approximately 720 μg/day based on the results of the trial at the outpatient clinic. In a previous study, the dosage of intranasal DDAVP for partial NDI was 10–40 μg/d (7, 8). In another study, an adult patient with NDI received 1800 μg oral DDAVP/d, which reduced his urine output by 50% (6). Previous reports demonstrated that a dosage ratio of 1:24 and 1:0.6 for nasal or oral disintegrating DDAVP and oral or oral disintegrating DDAVP, respectively, were comparable (15, 16). The optimal dosage for the present patient was 720 μg/d of oral disintegrating DDAVP, corresponding to 30 μg/d of intranasal DDAVP and 1200 μg/d of oral DDAVP. Therefore, the dosage for this patient was close to that previously reported for the other two types of formulations. A previous study demonstrated a dose-dependent increase in urine osmolality with up to 120 μg of oral disintegrating DDAVP in a pediatric patient with nocturnal enuresis (17). With respect to the molecular mechanism involved, cells with an *AVPR2* mutation exhibited concentration-dependent activation of the second messenger system, cAMP (cyclic adenosine monophosphate), after stimulation with DDAVP (18). In patients with partial congenital NDI, AVPR function is partially preserved; therefore, the DDAVP dosage required to achieve maximal urine osmolality may be higher than in other, severer patients.

Treatment with high-dose oral disintegrating DDAVP for partial congenital NDI was safe in the present patient. Theoretically, the adverse effects of high-dose therapy with this analog can be divided into those related to vasopressin receptor 2 (the receptors in the renal tubules) and vasopressin receptor 1. Among the former, the most serious potential adverse effect is water intoxication, which was not observed in the present case. In type 1-related adverse effects, DDAVP, a highly specific V2 receptor agonist, binds only to 1/2000 V1 receptors (19, 20). Indeed, no V1 receptor-related adverse effects, including hypertension and diarrhea, were observed in our patient, nor has any been reported for other DDAVP formulas used to treat congenital NDI (6–9, 21).

In conclusion, oral disintegrating DDAVP can be effective and safe in patients with partial congenital NDI due to *AVPR2* gene mutations. Since the severity of this disease varies, further research is warranted to investigate the severity at which this treatment is most effective.

Conflict of interests: The authors have nothing to declare.

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