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Case Report

Three Pediatric Patients with Congenital Nephrogenic Diabetes Insipidus due to *AVPR2* Nonsense Mutations and Different Clinical Manifestations: A Case Report

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Keywords
Congenital nephrogenic diabetes insipidus · AVPR2 nonsense mutations · Children · Case report

Abstract
Congenital nephrogenic diabetes insipidus (CNDI), a rare hereditary disorder, is characterized by the inability of the kidneys to concentrate urine in response to the antidiuretic hormone arginine vasopressin (AVP); as a result, large volumes of unconcentrated urine are excreted. In addition to the clinical manifestations of CNDI, such as dehydration and electrolyte disturbances (hypernatremia and hyperchloremia), developmental delay can result without prompt treatment. In approximately 90% of cases, CNDI is an X-linked disease caused by mutations in the arginine vasopressin receptor 2 (*AVPR2*) gene. In approximately 9% of cases, CNDI is an autosomal recessive disease caused by mutations in the water channel protein aquaporin 2 (*AQP2*), and 1% of cases are autosomal dominant. We report a case of CNDI caused by a novel *AVPR2* nonsense mutation, c.520C>T (p.Q174X), and cases of siblings in another family who had a different *AVPR2* nonsense mutation, c.852G>A (p.W284X). Both cases responded well to treatment with hydrochlorothiazide and spironolactone. If CNDI is suspected, especially in carriers and neonates, aggressive genetic testing and early treatment may alleviate growth disorders and prevent irreversible central nervous system disorders and developmental delay.

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Introduction

Congenital nephrogenic diabetes insipidus (CNDI), a rare hereditary, mainly X-linked renal disorder [1, 2], is characterized by the inability of the kidneys to concentrate urine in response to the antidiuretic hormone arginine vasopressin (AVP); as a result, large volumes of unconcentrated urine are excreted. Clinical manifestations of CNDI include polyuria, compensatory polydipsia, dehydration, electrolyte disturbances (hypernatremia and hyperchloremia), and, without prompt treatment, developmental delay [2, 3]. The majority of CNDI cases (approximately 90%) are caused by mutations in the arginine vasopressin receptor 2 (*AVPR2*) gene. In approximately 9% of cases, CNDI is an autosomal recessive disease caused by mutations in the water channel protein aquaporin 2 (*AQP2*), and 1% of cases are autosomal dominant [2, 4].

The incidence of X-linked CNDI is 4–8 per million males [5]. So far, more than 200 types of mutations in the *AVPR2* gene have been reported; the mutations are present throughout the gene, but most are in the transmembrane region [6]. Missense mutations are common, and they often exhibit abnormal folding within the endoplasmic reticulum. In such two cases, transport of water from the inside to the outside of the endoplasmic reticulum is impaired, and *AQP2* cannot function as a membrane receptor [7]. We report a case of CNDI caused by a novel *AVPR2* nonsense mutation and cases of siblings in another family who had another *AVPR2* nonsense mutation, of whom responded well to treatment.

Case Presentation

Case 1

A 6-month-old Japanese boy was admitted because of poor body weight gain, vomiting, and fever that had persisted for 1 week. He was born at a gestational age of 38 weeks 1 day, 49 cm tall, weighing 2,980 g by elective cesarean section (because the mother had delivered previously by cesarean section). Although he was mixed-fed, poor feeding was noted immediately after birth. He weighed 3,128 g at the 1-month checkup; after that, only formula was given. At 6 months of age, he was again noted to have poor weight gain and was brought to our hospital for further evaluation.

His father did not have polydipsia and polyuria, but he experienced frequent daytime urination; he did not urinate at night. The patient's mother was in good health and did not drink or urinate excessively. No history of diabetes insipidus was known within three generations of the family. The family tree is shown in Figure 1a.

At the time of admission, the patient had polyuria, with a urine output of 900–1,100 mL/day (2,893–3,536 mL/m^2/day). Results of laboratory examinations are listed in Tables 1 and 2. Brain magnetic resonance imaging yielded normal findings. Because of the presence of polyuria and the high serum level of antidiuretic hormone (Tables 1, 2), CNDI was diagnosed; low-sodium milk, hydrochlorothiazide, and spironolactone were administered orally, and the infant's urine output did not change (Fig. 2). Figure 3 shows the clinical course. Analysis of the *AVPR2* gene revealed a nonsense mutation, c.520C>T (p.Q174X). At the time of writing, the patient was 6 years old, 108.6 cm tall (2.00 standard deviations [SDs] below average), and weighed 17.6 kg (1.35 SD below average). He exhibited mild developmental delay (DQ of 68). His urine output was approximately 3 L/day, and he had mild bilateral hydronephrosis.

Case 2

A 7-month-old Japanese boy was admitted because of poor body weight gain and vomiting. He was born at a gestational age of 40 weeks 4 days, 51 cm tall, weighing 2,912 g. No abnormalities were noted during his gestation. Results of tandem mass screening was normal. He was exclusively breastfed and suckled well, but he vomited frequently. At the 1-month

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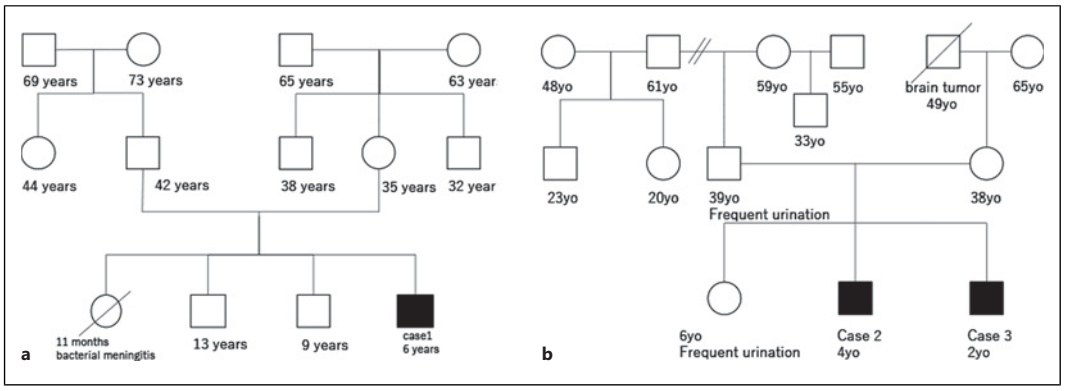

Fig. 1. a A family tree of case 1 is shown. There is no family history of polydipsia and polyuria. **b** The family tree of cases 2 and 3 is shown. His father and sister admit to frequent urination during the day. No one else has frequent urination.

Table 1. Clinical characteristics of 3 patients with CNDI and AVPR2 mutations

	Case 1	Case 2	Case 3
Sex	Male	Male	Male
Age	6 months	7 months	1 month
Height (SD)	61 cm (−2.83SD)	63.1 cm (−2.54S)	55.0 cm (+0.68SD)
AVPR2 mutation	c.520C>T (p.Q174*)	c.852G>A (p.W284*)	c.852G>A (p.W284*)
Symptoms	Poor body weight gain, vomiting, fever	Poor body weight gain, vomiting	Viral infection
Serum NA, mEq/L	157	153	148
ADH, pmol/L	22.0	34.3	22.7
Plasma osmolality, mOsm/L	351	305	304
Urine osmolality, mOsm/L	183	123	187
Urologic complications	Bilateral hydronephrosis grade 1	Left-sided hydronephrosis grade 2	Bilateral hydronephrosis grade 1
Current treatment	Hydrochlorothiazide, spironolactone	Hydrochlorothiazide, spironolactone	Hydrochlorothiazide, spironolactone
Current height (SD)	108.6 cm (−2.00 SD)	102.2 cm (−0.69 SD)	88.1 cm (−1.35 SD)
Current age	6 years old	4 years old	2 years old

checkup, he weighed 4,180 g (weight gain of 34.4 g/day), and his height was 56.8 cm (1.5 SD above average), indicative of good growth. At 2 months of age, however, his weight gain was poor, and a health checkup at 4 months revealed that he weighed 5,105 g (2.3 SD below average). During the same period, fevers (temperature, ~38°C) began to occur frequently. Although he began receiving solid food when he was 7 months of age, anorexia, and growth failure persisted, and so he was hospitalized for detailed examination and treatment.

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Table 2. AVP load test of case 1 (0.1U/kg subcutaneous injection)

	Before load	2 h after load
Urine osmolarity, mOSM/Kg	183	151
Na, mEq/L	156	156
Serum osmolarity, mOSM/Kg	351	314

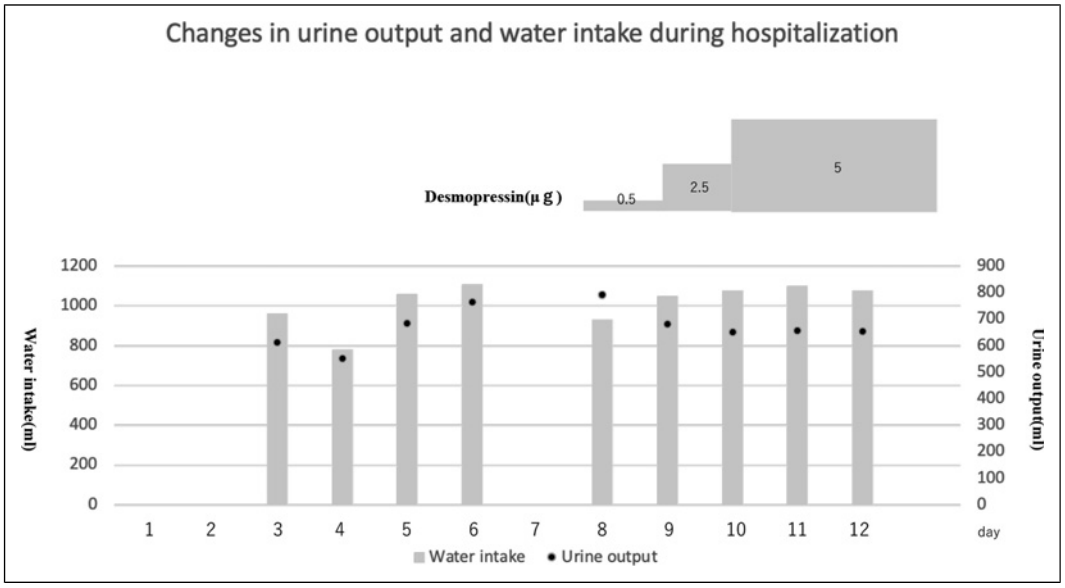

Fig. 2. Water intake and urine volume at the first hospitalization of case 1 are shown. Water intake ranged from 930 mL to 1,110 mL, and urine output ranged from 553 mL to 792 mL. There was no significant change in water intake and urine volume after administration of desmopressin.

His father and sister reported frequent urination during the day. His mother and other relatives had no symptoms of CNDI. The family tree is shown in Figure 1b.

At the time of admission, he had polyuria with a urine output of 850–950 mL/day (2,700–3,017 mL/m^2/day). Results of laboratory examinations are listed in Tables 1 and 2. Because of the presence of polyuria and a high serum level of antidiuretic hormone (Tables 1, 3), CNDI was diagnosed. Treatment consisted exclusively of breast milk in combination with low-sodium milk. After AVP loading, siblings of the patients did not show an increase in urine osmolality. Hydrochlorothiazide and spironolactone were administered orally, and his urine output decreased to 650–700 mL/day (Fig. 4). The patient's daily urine output decreased by approximately 30%. Thus, treatment with hydrochlorothiazide and spironolactone acetate may be effective. Figure 5 shows the clinical course. Genetic analysis revealed a W284X (c.852G > A) mutation of *AVPR2*.

At the time of writing, the patient was 4 years old, was 102.2 cm tall (0.69 SD below average), and weighed 14.6 kg (1.01 SD below average). He exhibited normal cognitive development. He had mild left-sided hydronephrosis.

Case 3

A 1-month-old Japanese boy was admitted because of poor feeding during a bout of hand-foot-and-mouth disease. He was the younger brother of the patient described in "Case 2." Figure 1b shows the family tree.

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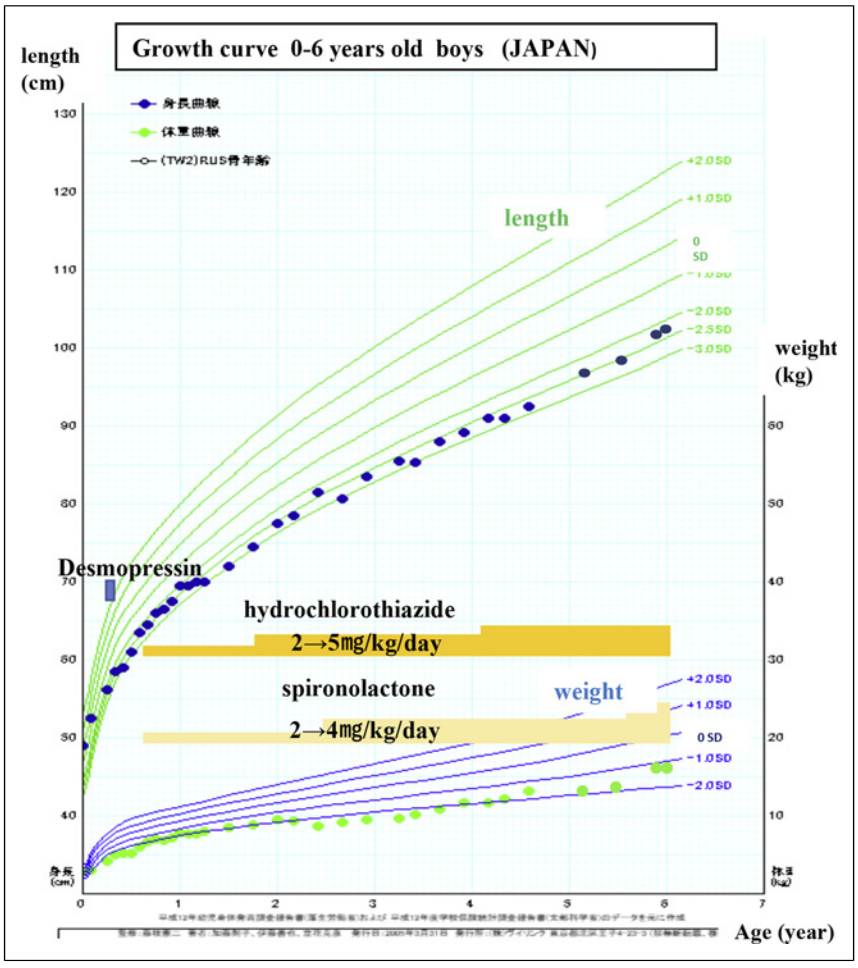

Fig. 3. The progress of height and weight and the course of treatment of case 1 are shown. He admits that he has a growth disorder. He was tube-fed until age 3 years and was on low-sodium milk until age 3 years due to poor oral intake. He is on hydrochlorothiazide and spironolactone. Both started at 2 mg/kg and are currently taking hydrochlorothiazide 5 mg/kg and spironolactone 4 mg/kg.

The symptoms of hand-foot-and-mouth disease improved after symptomatic treatment such as fluid transfusion. At the time of admission, he had polyuria with a urine output of 1,100–1,200 mL/day (4,126–4,501 mL/m^2/day). Results of laboratory examinations are listed in Tables 1 and 2. After blood and urine tests (Tables 1, 3), CNDI was diagnosed, as in his brother's case.

He was fed breast milk and low-sodium milk, and hydrochlorothiazide and spironolactone were administered orally. His urine output decreased to 650–750 mL/day (Fig. 6). The patient's daily urine output decreased by approximately 30%. Thus, treatment with hydrochlorothiazide and spironolactone may be effective. Figure 7 shows the clinical course. Genetic analysis revealed a W284X (c.852G>A) mutation of *AVPR2*.

At the time of writing, the patient was 2 years old, was 88.1 cm tall (1.35 SD below average), and weighed 12.6 kg (0.07 SD above average). He exhibited normal cognitive development. He had mild left-sided hydronephrosis.

Table 3. Urinalysis before and after DDAVP (240 μg) administration test of cases 2 and 3

	DDAVP before administration	DDAVP 1 h after administration
Case 2		
Urine osmolarity, mOSM/L	95	109
Urine specific gravity	1.002	1.003
Case 3		
Urine osmolarity, mOSM/L	96	Unable to collect urine
Urine-specific gravity	1.005	Unable to collect urine

Table 3 shows the urine osmolality and urine-specific gravity before and after DDAVP loading in cases 2 and 3.

In case 2, there was little change in urine osmolality and urine specific gravity 1 h after administration. In case 2, urine osmotic pressure increased slightly 1 h after administration, but urine specific gravity did not show any change.

In case 3, urine could not be collected and examination could not be performed.

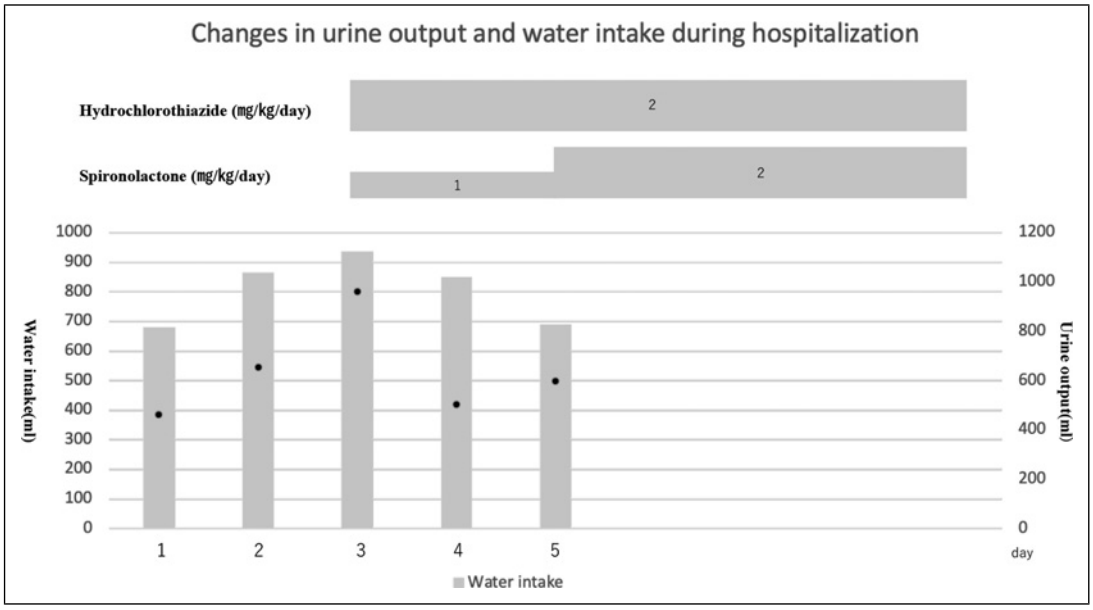

Fig. 4. Water intake and urine volume at first hospitalization for case 2 are shown. Water intake ranged from 680 mL to 9,350 mL, and urine output ranged from 461 mL to 960 mL. Hydrochlorothiazide and spironolactone were administered from day 3 of hospitalization. Both water intake and urine volume tended to decrease.

Discussion

More than 250 mutations in the *AVPR2* gene have been reported to cause CNDI [8]. In all three cases diagnosed at our hospital, abnormalities in the *AVPR2* gene were present. Genetic analysis in case 1 revealed a nonsense mutation, c.520C>T (p.Q174X) (Fig. 8a), that had not been previously reported. Although at the same site no other nonsense mutations have been reported, three missense mutations have been reported. The first patient reported to have a Q174R (g.882A>G) mutation was of German descent, and CNDI was diagnosed at 1 month of

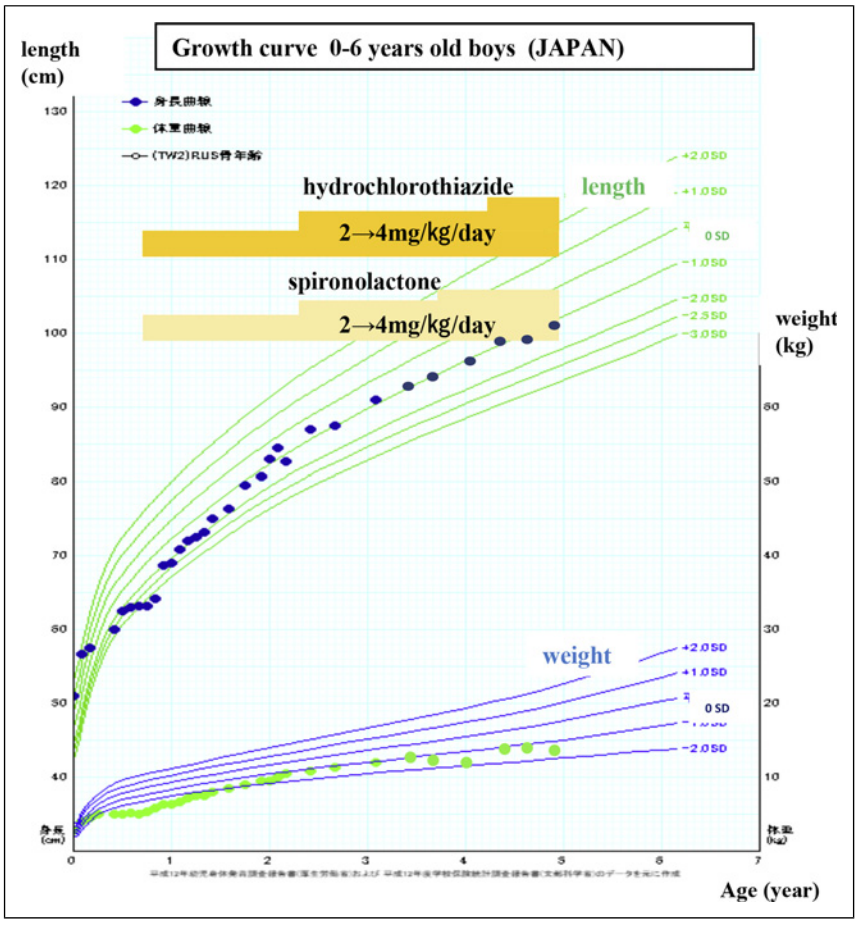

Fig. 5. The progress of height and weight and the course of treatment for case 2 are shown. He had growth retardation until age 1, but improved after age 2, and is now within normal limits for height and weight. He is on hydrochlorothiazide and spironolactone. Both started at 2 mg/kg and are currently taking 4 mg/kg. He used low-sodium milk during his infancy. Salt restriction was 1 mEq/kg/day before starting baby food and 3 g/day after starting baby food.

age [9]. In comparison with the wild type, AVP stimulation in this mutation revealed complete absence of receptor function, no cyclic adenosine monophosphate production, and no receptor expression on the cell surface. The laboratory values were also lower than those for A89P, G107R, and ΔR247-G250 mutations, which were examined at the same time. The second patient was a 5-month-old boy with a Q174H (g.883G>C) mutation and concomitant Wilms tumor [10]. He exhibited growth failure, fever, vomiting, polydipsia and polyuria, hypernatremia, and decreased urine osmolarity. The same gene mutation could not be confirmed in the boy's mother, and the relationship between Wilms tumor and CNDI was not clear. The third patient was Latino and had a Q174L (g.882A>T) mutation; other details were unknown [11]. These cases indicate that the Q174X mutation may be responsible for CNDI, although its expression has not been studied extensively.

In contrast to our case 1, clinical symptoms were relatively mild in cases 2 and 3, and the patients had a W284X (c.852G>A) mutation (Fig. 8b). This mutation at the same site was previously reported in an African American patient, but that patient's clinical manifestations are unknown [12, 13]. Since the nonsense gene mutation is located closer to the N-terminal side in case 1 than in cases 2 and 3, the structure of vasopressin V2 receptor may change

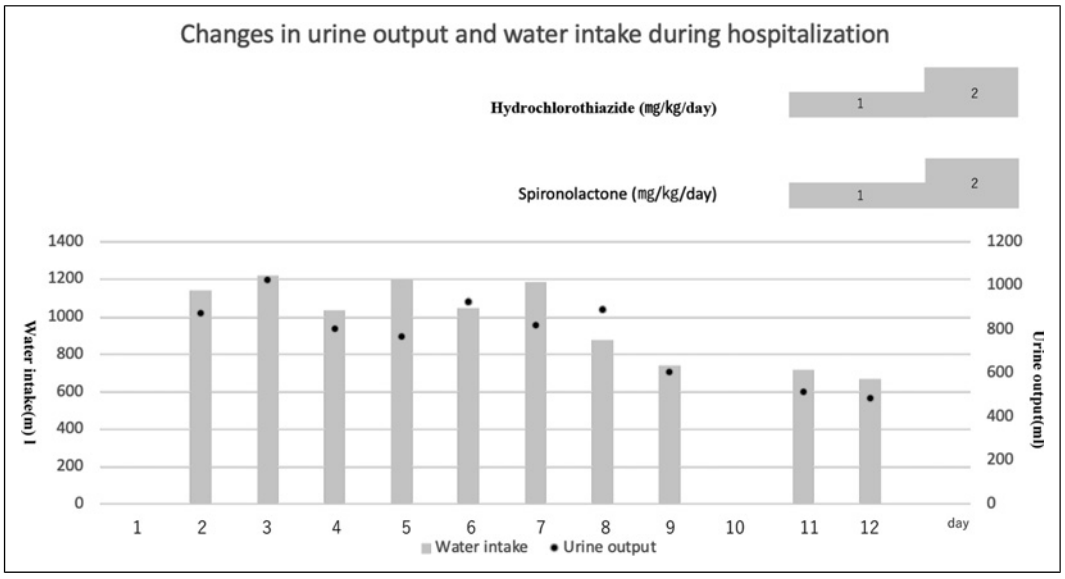

Fig. 6. Water intake and urine volume at initial hospitalization for case 3 are shown. Water intake ranged from 669 mL to 1,198 mL, and urine output ranged from 485 mL to 1,025 mL. From day 11 of hospitalization, hydrochlorothiazide, and spironolactone were administered. Both water intake and urine volume tended to decrease.

substantially. However, the relationship between genetic abnormalities (genotype) and clinical symptoms (phenotype) in CDNI is unclear. In addition, the sites of nonsense mutations reported so far in patients with CNDI and relatively mild clinical symptoms have varied [14]. In investigations of mutant receptor expression, the vasopressin V2 receptor protein has exhibited altered properties, such as impaired activation of the G protein and decreased ability to bind to ligands [15]. In such cases, clinical symptoms might be expressed at the site of a nonsense mutation of the *AVPR2* gene. In the future, CNDI may be subclassified on the basis of genetic abnormalities, and genetic testing should be considered when CNDI is suspected.

In addition, because CNDI had been diagnosed in case 2, it was diagnosed early in case 3 and so treatment was started earlier. These cases show that genetic analysis that reveals mutations is important. If the carrier status of the X-linked mutation is known, neonates at risk for developing CNDI can be identified easily and can start treatment to prevent severe dehydration and hypernatremia. Early intervention may prevent long-term physical and intellectual disability, which has occurred in some patients with CNDI. Genetic testing for CNDI can also prevent misdiagnosis.

The diagnosis of nephrogenic diabetes insipidus is generally based on symptoms, findings in a 24-h urine collection, and results of a fluid deficit test. Such tests can be difficult to perform, especially in infants, and can lead to severe dehydration. In addition, clinical characterization of forms of partial diabetes insipidus and other conditions involving polyuria can be difficult. Genetic testing not only confirms the diagnosis but also enables a better understanding of the genotype-phenotype relationship and of the causes of CNDI.

The mainstay of treatment for CNDI is prevention and correction of dehydration and improvement of polyuria through free intake of water. Depending on the degree of thirst, the patient is instructed to drink water freely if he or she is old enough to drink. Neonates and infants, however, cannot complain of dry mouth; therefore, they may need to drink regularly every 2–3 h. In addition, if dehydration is severe, or if oral intake is difficult as a result of

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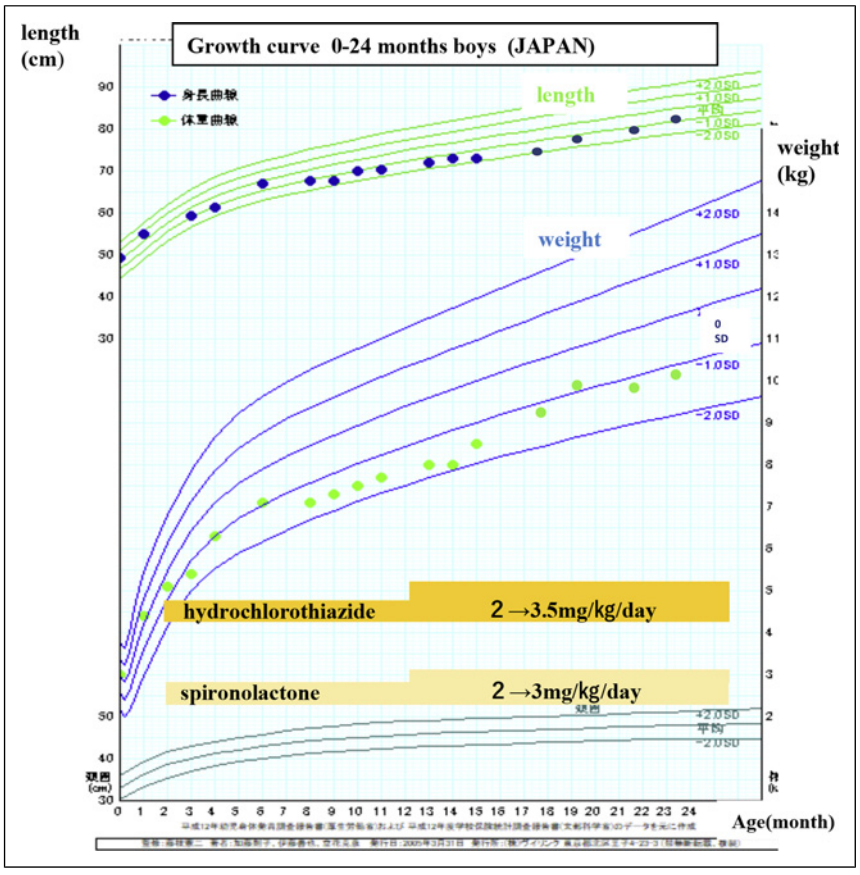

Fig. 7. The height and weight of case 3 and the course of treatment are shown. His height and weight are passing within normal limits. He is on hydrochlorothiazide and spironolactone. Both were started at 2 mg/kg, and he is currently taking hydrochlorothiazide 3.5 mg/kg and spironolactone 3 mg/kg. He also used low-sodium milk during his infancy. Salt restriction was 1 mEq/kg/day before starting baby food and 3 g/day after starting baby food.

surgery or infection, an appropriate amount of fluid should be given intravenously to replace progressive loss. In such cases, fluids with high sugar concentrations should be avoided because they may cause osmotic diuresis.

Pharmacotherapy commonly involves thiazide diuretics; urine output can be reduced 20–50% when the diuretics are used in conjunction with salt restriction [16]. Spironolactone, a potassium-sparing diuretic, and sustained-release preparations of potassium may also be used concomitantly to prevent hypokalemia, which is an adverse effect of thiazide diuretics. Also, non-steroidal anti-inflammatory drugs such as indomethacin have been used in combination, but sufficient effects have not been obtained. In partial CNDI, antidiuretic hormone is thought to reduce urine output to some extent. Of our patients, the third had received the diagnosis at 1 month of age, but the other two had shown no progress with solid food. Because the third patient had been drinking breast milk, adding low-sodium milk resulted in correction of dehydration and sodium levels. For all 3 patients, pharmacotherapy consisted of hydrochlorothiazide and spironolactone.

Delay in starting treatment may result in growth failure, central nervous system disorders, and developmental delay. In our 3 patients, diagnosis, and treatment began at the ages of 6 months, 7 months, and 1 month, respectively. With regard to height and development, the first patient was shorter than average and had mild developmental delay. The second and third patients had normal

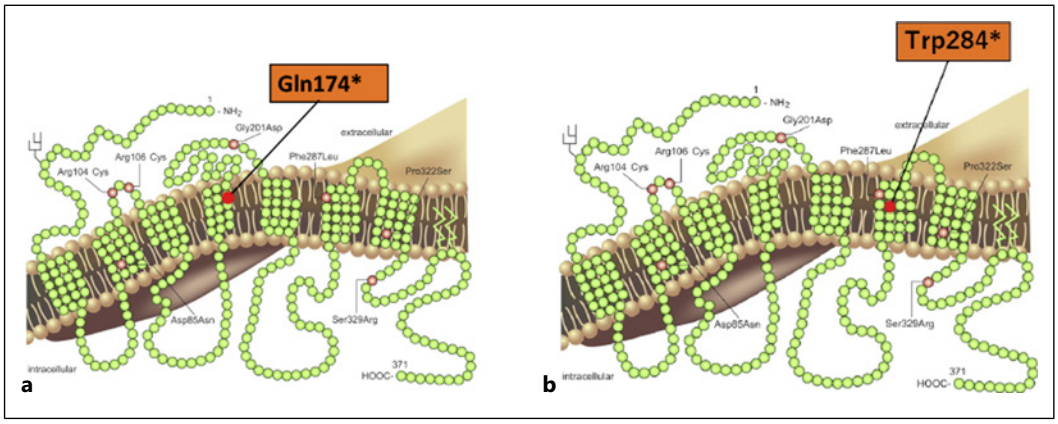

Fig. 8. **a** c.520C>T (p.Q174*): There was a C to T nucleotide change at position 520, resulting in a nonsense substitution. **b** c.852G>A (p.W284*): there was a G to A nucleotide change at position 852, resulting in a nonsense substitution.

cognitive development, and their heights were within the normal range. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533895).

Conclusion

No definitive treatment of CNDI has been established. Fever of unknown origin should be investigated. If CNDI is suspected especially in carriers and neonates, genetic testing and early treatment may alleviate growth disorders and prevent irreversible central nervous system disorders and developmental delay.

Acknowledgments

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Statement of Ethics

All the procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Committee and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards (64th WMA General Assembly, Fortaleza, Brazil, October 2013). Written informed consent was obtained from the parents of the patients for publication of the details of their medical case and any accompanying images. Ethical approval is not required for this study in accordance with local guidelines.

Conflict of Interest Statement

All authors declare that this manuscript has no conflict of interest.

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Author Contributions

H.W. reviewed the patient's clinical data. H.W. and H.T. wrote the initial draft of the manuscript. H.W., H.T., K.F., S.K., and H.N. treated the patient, contributed to writing the manuscript, and revised the final version of the manuscript. The authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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