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Case Report

Partial nephrogenic diabetes insipidus with a novel arginine vasopressin receptor 2 gene variant

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Highlights

- We report a partial NDI with a novel *AVPR2* variant (NM_000054:c.371A>G,p.(Tyr124Cys)).
- The patient could concentrate urine up to 500 mOsm/kg after water deprivation.
- Markedly elevated plasma AVP with intermediate urine osmolality may suggest partial NDI.

Abstract. X-linked nephrogenic diabetes insipidus (NDI) is caused by variations in arginine vasopressin receptor 2 (*AVPR2*). Some patients show partial resistance to arginine vasopressin (AVP). A 19-month-old Japanese boy presented with polydipsia since infancy. His mother had a history of polydipsia during pregnancy, and his maternal granduncle also had polydipsia. Intermediate urine osmolality and markedly high plasma AVP levels were observed in the water deprivation test. Subsequent pitressin administration caused no further elevation in urine osmolality. We diagnosed the patient with partial NDI, initiated therapy with hydrochlorothiazide, and placed him on a low-sodium diet. Although his urine volume decreased by 20–30% after the initiation of therapy, progressive hydronephrosis and growth retardation developed 2 years later. We investigated his genetic background by multiplex targeted sequencing of genes associated with inherited renal diseases, including *AVPR2* and aquaporin-2 (*AQP2*). We identified a hemizygous missense variant in *AVPR2* NM_000054:c.371A>G,p.(Tyr124Cys) in the boy and a heterozygous variant in the mother at the same locus. Distinguishing partial NDI from primary polydipsia is difficult because of its mild symptoms. Markedly elevated plasma AVP levels with intermediate urine osmolality may suggest partial NDI, and genetic analysis can be useful for such patients.

Key words: polyuria, polydipsia, nephrogenic diabetes insipidus (NDI), arginine vasopressin receptor 2 (AVPR2) gene, novel variant

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Introduction

Nephrogenic diabetes insipidus (NDI) is a rare inherited disease characterized by the inability to concentrate urine due to renal resistance to the antidiuretic hormone, arginine vasopressin (AVP). There are two forms of inherited NDI: a common (approximately 90%) X-linked recessive form caused by a variant of the vasopressin type 2 receptor (V2R)-encoding gene, arginine vasopressin receptor 2 (*AVPR2)*, and a less common (approximately 10%) autosomal recessive or dominant form caused by a variant of aquaporin-2 (*AQP2)* (1). Most patients with inherited NDI appear to have complete or nearly complete resistance to the antidiuretic effect of AVP, with a urine osmolality of less than 300 mOsm/kg (2). However, some patients with NDI have mild phenotypes that present with intermediate urine osmolality. These mild forms, called partial NDI, are difficult to distinguish from primary polydipsia. To date, more than 200 variants of *AVPR2* have been identified in cases with X-linked NDI (3), and several *AVPR2* variants have been associated with a mild phenotype (4). Here, we report a case of partial NDI with a novel *AVPR2* variant. The patient was able to concentrate urine up to 500 mOsm/kg and had markedly elevated plasma AVP levels after water deprivation.

Patient and Methods

A 19-month-old boy presenting with polydipsia was referred to our hospital. The mother became aware of his polydipsic tendency from six months of age. He got up several times during the night to drink water, and drank more than 2 liters of water recently. He was born at the 40th gestational week as the second of two children of non-consanguineous parents. His birth weight was 3,282 g (+ 0.2 SD) and birth height was 51.0 cm (+ 0.9 SD). He did not have a history of dehydration or recurrent fever. The mother had an episode of polydipsia during pregnancy, and the maternal granduncle also had polydipsia; however, they had not been diagnosed. The sister, father, and other relatives did not have polydipsia. His neurodevelopment was appropriate for his age. His height was 80.2 cm (−0.4 SD) and weight was 9.9 kg (−0.7 SD). No growth retardation was observed prior to admission (**Fig. 1**). The initial investigation revealed that the plasma AVP, urine, and plasma osmolality were 15.7 pg/mL, 86 mOsm/kg, and 279 mOsm/kg, respectively. His serum electrolytes, creatinine, glucose, and HbA1C levels were normal (**Table 1**). Brain magnetic resonance imaging showed a normal pituitary gland and posterior lobe with high intensity on a T1-weighted image. Ultrasound revealed no hydronephrosis or dilation of the lower urinary tract. The volumes of 24-h drinking water and urine volume during hospitalization were 2,880 mL and 3,300 mL (7,221 mL/m^2/d), respectively. After 7 h of water deprivation, urine osmolality reached 506 mOsm/kg, and his weight had decreased by 6.6%. The concurrent plasma osmolality and AVP were 294 mOsm/kg and 65.1 pg/mL, respectively. Subsequent exogenous vasopressin (Pitressin) loading showed no further increase in urine osmolality (**Table 2**).

On the basis of these findings, the patient was diagnosed with NDI. Therapy was initiated with hydrochlorothiazide (2 mg/kg/d) and a low sodium diet (< 3 g/d), but his sodium intake remained higher than desired. The urine volume decreased by 20–30% with a gradual increase in hydrochlorothiazide up to 6 mg/kg/d. Spironolactone (1 mg/kg/d) was added when mild hypokalemia became evident at 2 yr and 11 mo of age (**Table 1**). Ultrasound showed bilateral hydronephrosis (Society for Fetal Urology grade: right 2, left 1) after 2 yr of therapy. His height growth velocity slightly decreased as his recent height was 94.2 cm (−1.3 SD), while his weight was 13.8 kg (−0.8 SD) (**Fig. 1**).

DNA analysis

After obtaining informed consent from the parents and approval from the institutional ethical committee, multiplex targeted sequencing of 95 genes associated with renal inherited disease, including *AVPR2* and *AQP2*, was performed on peripheral blood-derived DNA from the patient and his mother, as described in a previous publication (5).

All procedures were performed in accordance with the 1964 Helsinki Declaration and the 2003 Japanese Ethical Guidelines for Clinical Research, as well as their later amendments.

Ethical Consideration

The parents provided informed consent for genetic testing and approved the clinical and genetic data of the boy and his mother for publication. This study was approved by the institutional ethical committee.

Results

The analysis revealed a hemizygous missense variant in *AVPR2* (NM_000054:c.371A>G,p.(Tyr124Cys)) in the boy and a heterozygous variant in the mother at the same locus. Variants were confirmed using Sanger sequencing of all exons and exon-intron boundaries (**Fig. 2**). This variant has not been registered in either ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) or the Human Genome Mutation Database (www.hgmd.org) and is very rare as it is absent in the public databases of minor allele frequencies, such as gnomAD (v2.1.1, https://gnomad.broadinstitute.org/) and 8.3KJPN, which include 8,300 Japanese reference genomes (https://jmorp.megabank.tohoku.ac.jp/202102/). *In silico* prediction scores for the variants also supported the interpretation of pathogenicity (SIFT 0: deleterious, Polyphen2 1: damaging, CADD_phred 24, MCAP 0.386, and REVEL 0.743). Clinical interpretation of the variant by the American College of Medical Genetics and Genomics guidelines (6) is “Uncertain Significance” (PM1, PM2,

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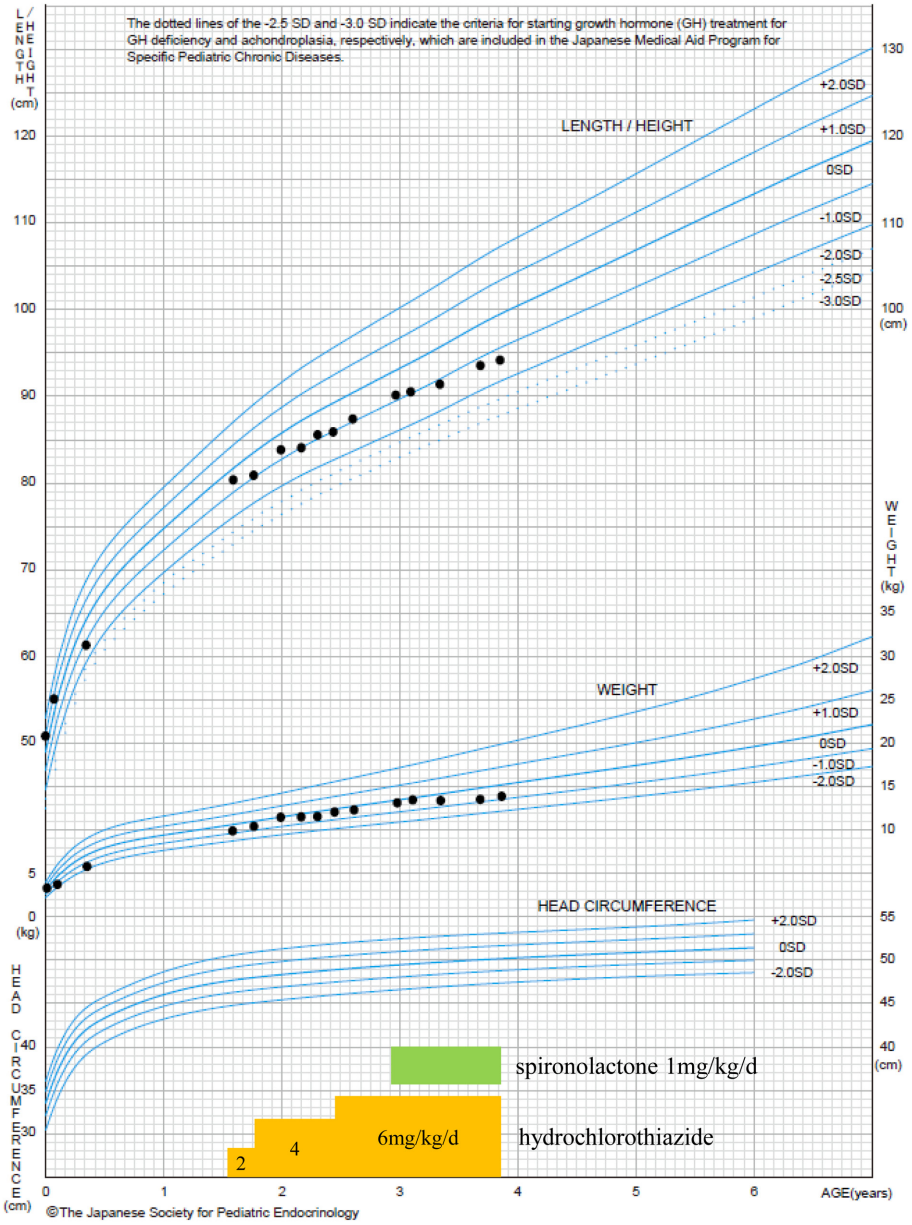

Fig. 1. Growth chart and therapeutic dosages of drugs.

PP3), which supports the possibility of pathological significance (7). Considering all our observations, we considered this variant to be pathogenic. No variants in *AQP2* or other genes associated with renal-inherited diseases were detected.

Discussion

We report a case of partial NDI with a novel *AVPR2* variant, Tyr124Cys (Y124C). The amino acid, Y124, is highly conserved among mammals, according to the UCSC Genome Browser (https://genome.ucsc.edu/). We hypothesized the following mechanism in which the Y124C V2R molecule decreases water reabsorption. The majority of missense variants in the *AVPR2* gene have been reported to generate misfolded V2R proteins located in the endoplasmic reticulum (ER), leading to the abnormal expression of V2R on the cell surface (8). The Y124C variant produces an additional cysteine residue, indicating that it may generate an additional inter- or intra-disulfide bond that disrupts proper folding in the ER and translocation to the membrane. Furthermore, Y124 has been shown to be a binding site for AVP by computerized 3D analysis of molecular docking (9). Therefore, we speculate that the binding efficiency of AVP would be reduced, and the urine concentration would be attenuated even if AVPR2 was properly expressed on the membrane to some extent in this case.

Most patients reported to have inherited NDI have a phenotype characterized by early dehydration episodes, such as fever or hypernatremia, observed as early as the first week of life (1); however, a few NDI patients with mild symptoms and intermediate urine osmolality have been reported (4, 10–14). Our patient

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Table 1. Laboratory data

Age	1 yr 7 mo admission	2 yr 7 mo	2 yr 11mo	3 yr 4 mo	4 yr 2 mo
Blood					
Na (mEq/L)	139	140	138	141	139
K (mEq/L)	4.6	3.9	3.3	3.5	3.8
Cl (mEq/L)	107	104	102	105	104
Ca (mg/dL)	10.7	11	10.2	10.5	10.2
P (mg/dL)	5.5	4.1	4.2	3.4	3.2
UN (mg/dL)	10.8	9.7	8.3	9.5	10.8
Creatinine (mg/dL)	0.31	0.33	0.32	0.35	0.33
HbA1C (NGSP) (%)	5.1				
Osmolality (mOsm/kg)	279	281	276	281	280
AVP (pg/mL)	15.7	42.8	41.1	22.8	13.7
Urine					
Protein	(–)	(–)		(–)	(–)
Sugar	(–)	(–)		(–)	(–)
RBC (/HPF)	0–1	0–1		0–1	0–1
WBC (/HPF)	0–1	0–1		0–1	0–1
Specific gravity	1.003	1.002		1.003	1.002
Osmolality (mOsm/kg)	86	94		106	125

NGSP, National Glycohemoglobin Standardization Program.

Table 2. Water deprivation and arginine vasopressin (AVP) loading test

Time (h)	1	2	3	4	5	6	7	7.5	8	8.5	9
Urine Osmolality (mOsm/kg)	77	105	193	267	371	399	506	531	481	494	537
Plasma Osmolality (mOsm/kg)	285	287	290	293	292	293	294				294
Plasma Na (mEq/L)	142	142	143	146	145	144	144				146
Plasma AVP (pg/mL)							65.1				

After 7 h, exogenous vasopressin (Pitressin 5 U/m^2) was subcutaneously administered.

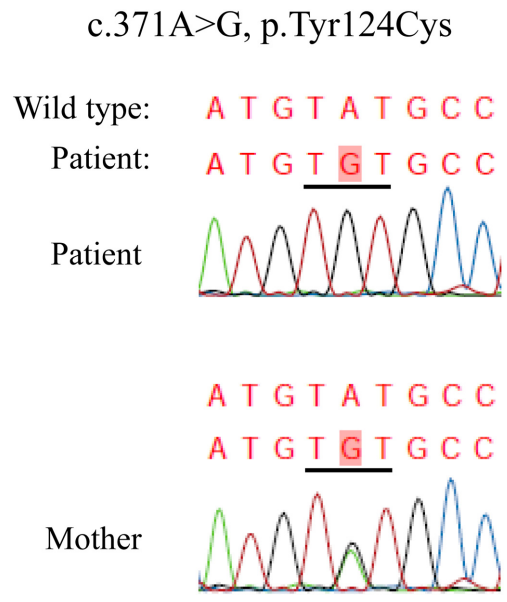

Fig. 2. Result of arginine vasopressin receptor 2 (*AVPR2*) sequencing. The sequence chromatogram of *AVPR2* in the patient and mother.

had a mild phenotype with a missense variant (Y124C), whereas Bichet *et al.* had reported a patient with a nonsense variant at the same locus (Y124*) who showed a lifelong history of polydipsia and unconcentrated urine despite the administration of desmopressin (DDAVP), suggesting a complete form (15). Based on a MEDLINE search, 19 *AVPR2* variants (A37P, D85N, V88M, R104C, R106C, Y128S, L161P, W200R, G201D, T273M, F287L M311V, N317K, N317S, N321Y, P322S, S329R, S333del, and the splice variant c.276A>G) were associated with a mild phenotype (3, 4, 10–14). Bockenhauer *et al.* reported the phenotypic diversity in six patients with V88M variants. Four of these six patients demonstrated a substantial increase in the urine concentration after the administration of DDAVP, while two did not show any response. The *in vitro* analysis suggested that this diversity may be attributed to both the cell surface expression of V88M-V2R and the AVP-binding affinity, which is affected by the variant (16). Partial NDI has been rarely reported as mild symptoms may be misdiagnosed as primary polydipsia or nocturnal enuresis. The variants associated with partial NDI may become more evident if genetic analyses of milder cases are performed more frequently.

Interestingly, the mother had a history of polydipsia

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during pregnancy. A few symptomatic females with heterozygous *AVPR2* variants have been described. A Japanese nationwide survey on NDI identified 10 symptomatic females among 65 patients with *AVPR2* variants (10). Furthermore, 16 of 64 Japanese female heterozygotes exhibited some degree of polydipsia or polyuria (17). Phenotypic expression in females has been attributed to skewed X chromosome inactivation, which has been demonstrated in some cases (18). This variant may be associated with polydipsia in the mother during pregnancy.

Partial NDI may often be missed or misdiagnosed as primary polydipsia or nocturnal enuresis due to the mild symptoms. In our case, the water deprivation test showed that urine osmolality was > 500 mOsm/kg, whereas the plasma AVP levels were disproportionally high when compared with the plasma osmolality (**Fig. 3**) (2, 19). We suspected NDI and identified a novel *AVPR2* missense variant. Various complications occur in NDI, such as mental retardation, failure to thrive, and urinary tract disorders. Early diagnosis is of great importance in preventing these complications. In NDI, plasma AVP level tends to be elevated due to the insensitivity of the collecting tubule. Careful attention to not only the urine osmolality, but also the plasma AVP levels is warranted when diagnosing NDI.

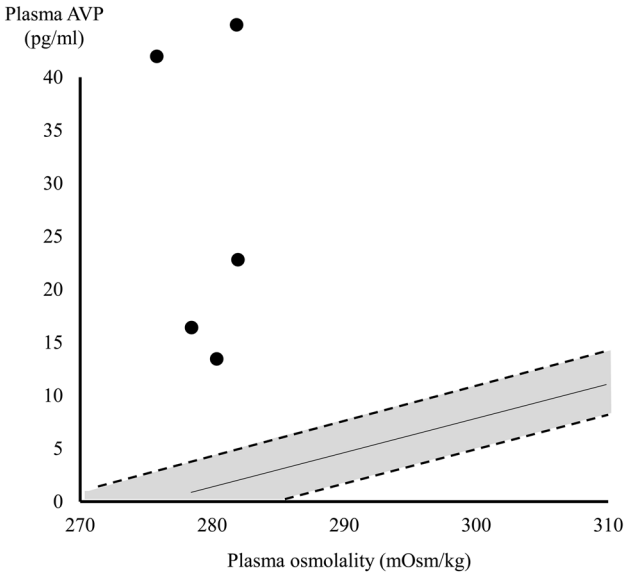

Fig. 3. The plasma AVP levels and osmolality of this case. The plasma AVP levels are shown as black dots. The reference range of AVP levels is shown in the gray area (19).

Conflict of Interests: The authors declare no conflict of interest.

Conclusions

We identified a novel *AVPR2* missense variation that caused partial NDI. We found that in addition to urine osmolality, plasma AVP levels are important for the diagnosis of partial NDI. Moreover, genetic analysis of *AVPR2* or *AQP2* can be useful for evaluating patients with intermediate urine osmolality and elevated plasma AVP levels.

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References

1. Bockenhauer D, Bichet DG. Pathophysiology, diagnosis and management of nephrogenic diabetes insipidus. Nat Rev Nephrol 2015;11: 576–88. [Medline] [CrossRef]
2. Babey M, Kopp P, Robertson GL. Familial forms of diabetes insipidus: clinical and molecular characteristics. Nat Rev Endocrinol 2011;7: 701–14. [Medline] [CrossRef]
3. Bichet DG. GENETICS IN ENDOCRINOLOGY Pathophysiology, diagnosis and treatment of familial nephrogenic diabetes insipidus. Eur J Endocrinol 2020;183: R29–40. [Medline] [CrossRef]
4. Neocleous V, Skordis N, Shammas C, Efstathiou E, Mastroyiannopoulos NP, Phylactou LA. Identification and characterization of a novel X-linked *AVPR2* mutation causing partial nephrogenic diabetes insipidus: a case report and review of the literature. Metabolism 2012;61: 922–30. [Medline] [CrossRef]
5. Mori T, Hosomichi K, Chiga M, Mandai S, Nakaoka H, Sohara E, *et al*. Comprehensive genetic testing approach for major inherited kidney diseases, using next-generation sequencing with a custom panel. Clin Exp Nephrol 2017;21: 63–75. [Medline] [CrossRef]
6. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, *et al*. ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17: 405–24. [Medline] [CrossRef]
7. Morales A, Hershberger RE. Variants of uncertain significance: Should we revisit how they are evaluated and disclosed? Circ Genom Precis Med 2018;11: e002169. [Medline] [CrossRef]
8. Robben JH, Knoers NVAM, Deen PMT. Characterization of vasopressin V2 receptor mutants in nephrogenic diabetes insipidus in a polarized cell model. Am J Physiol Renal Physiol 2005;289: F265–72. [Medline] [CrossRef]

9. Jankowski M, Danalache BA, Plante E, Menaouar A, Florian M, Tan JJ, *et al*. Dissociation of natriuresis and diuresis by oxytocin molecular forms in rats. PLoS One 2019;14: e0219205. [Medline] [CrossRef]
10. Fujimoto M, Okada S, Kawashima Y, Nishimura R, Miyahara N, Kawaba Y, *et al*. Clinical overview of nephrogenic diabetes insipidus based on a nationwide survey in Japan. Yonago Acta Med 2014;57: 85–91. [Medline]
11. Yamashita S, Hata A, Usui T, Oda H, Hijikata A, Shirai T, *et al*. Novel *AVPR2* mutation causing partial nephrogenic diabetes insipidus in a Japanese family. J Pediatr Endocrinol Metab 2016;29: 591–6. [Medline] [CrossRef]
12. Schernthaner-Reiter MH, Adams D, Trivellin G, Ramnitz MS, Raygada M, Golas G, *et al*. A novel *AVPR2* splice site mutation leads to partial X-linked nephrogenic diabetes insipidus in two brothers. Eur J Pediatr 2016;175: 727–33. [Medline] [CrossRef]
13. Makita N, Sato T, Yajima-Shoji Y, Sato J, Manaka K, Eda-Hashimoto M, *et al*. Analysis of the V2 vasopressin receptor (V2R) mutations causing partial nephrogenic diabetes insipidus highlights a sustainable signaling by a non-peptide V2R agonist. J Biol Chem 2016;291: 22460–71. [Medline] [CrossRef]
14. Joshi S, Kvistgaard H, Kamperis K, Færch M, Hagstrøm S, Gregersen N, *et al*. Novel and recurrent variants in AVPR2 in 19 families with X-linked congenital nephrogenic diabetes insipidus. Eur J Pediatr 2018;177: 1399–405. [Medline] [CrossRef]
15. Bichet DG, Birnbaumer M, Lonergan M, Arthus MF, Rosenthal W, Goodyer P, *et al*. Nature and recurrence of AVPR2 mutations in X-linked nephrogenic diabetes insipidus. Am J Hum Genet 1994;55: 278–86. [Medline]
16. Bockenhauer D, Carpentier E, Rochdi D, van't Hoff W, Breton B, Bernier V, *et al*. Vasopressin type 2 receptor V88M mutation: molecular basis of partial and complete nephrogenic diabetes insipidus. Nephron, Physiol 2010;114: 1–10. [Medline] [CrossRef]
17. Sasaki S, Chiga M, Kikuchi E, Rai T, Uchida S. Hereditary nephrogenic diabetes insipidus in Japanese patients: analysis of 78 families and report of 22 new mutations in *AVPR2* and *AQP2*. Clin Exp Nephrol 2013;17: 338–44. [Medline] [CrossRef]
18. Ding C, Beetz R, Rittner G, Bartsch O. A female with X-linked Nephrogenic diabetes insipidus in a family with inherited central diabetes Insipidus: Case report and review of the literature. Am J Med Genet A 2020;182: 1032–40. [Medline] [CrossRef]
19. Hasegawa Y. The relationship between antidiuretic hormone and plasma or urine osmolalities during water restriction test and hypertonic saline loading test in normal children--a change in the apparent tubular response to AVP during these two tests. Endocrinol Jpn 1991;38: 451–6. [Medline] [CrossRef]

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