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Case Report

# Nephrogenic Diabetes Insipidus in a Neonate

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**Abstract**

Nephrogenic diabetes insipidus (NDI) is a rare disorder that develops as a result of resistance to antidiuretic hormone and is characterized by polyuria and polydipsia, high serum osmolality, and low urine osmolality. Eight-day-old male patient applied with the complaints of excessive sucking and drowsiness. In physical examination, collapse of anterior fontanel, decreased mucosal wetness, and impaired turgor tonus were observed. Polyuria, hypernatremia, high blood osmolality, and low urine osmolality were detected. After initiation hydrochlorothiazide treatment, the clinical and laboratory findings improved. In genetic analysis, hemizygous mutation was detected in the AVPR2 gene c.299_319del21bp (p.100_107delRPTASV) which was previously described in the literature. Early diagnosis and treatment of NDI has vital importance and can prevent mental retardation and growth retardation due to possibility of recurrent dehydration and hypernatremia. This case is presented to keep the diagnosis of NDI in mind in patients with severe hypernatremic dehydration in the neonatal period and to emphasize the prevention of comorbid conditions with early diagnosis and prompt treatment.

**Keywords:** Hypernatremic dehydration, Neonatal, Nephrogenic diabetes insipidus

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Diabetes insipidus (DI) is a rare disease that results in polyuria and polydipsia due to impaired urinary concentration function. The disease has different symptoms and findings in neonatal period and childhood.[1,2] In case of antidiuretic hormone (ADH) vasopressin deficiency, central DI develops and nephrogenic DI (NDI) develops due to inadequate response to ADH.[1] ADH plays role in maintaining the body's fluid balance in healthy individuals. It is secreted from hypothalamus and stored in the pituitary gland and its release is regulated by the stimulation of the baroreceptors and osmoreceptors. Congenital NDI is a 90–95% X-linked disease and inadequate response to normal ADH levels occurs as a result of V2 receptor gene mutation. About 5–10% of congenital NDI cases have aquaporin 2 gene mutations with autosomal dominant/recessive inheritance.[2,3] The incidence of X-linked NDI in men is estimated to be 4–8/million.[2] Apart from congenital causes, it may occur due to drugs and metabolic problems such as hypercalcemia, hypocalcemia, and medullary damage.[4]

Polyuria, polydipsia, and weight loss occur as a result of impaired urine concentration ability, increased plasma osmolality, and decreased urine osmolality.[2] In the neonatal period, symptoms begin to occur in the 1st week of life. However, in some cases, polyuria and polydipsia may not be obvious. Patients with vomiting, poor nutrition, constipation/diarrhea, developmental retardation, unexplained fever, lethargy, or irritability should be considered.[3,4] Seizures can develop in case of rapid rise and fall of blood osmolality, as well as can give symptoms such as hydronephrosis, hydroureter, or megacystis.[3] Early diagnosis and treatment is important because mental and developmental retardation can occur as a result of recurrent dehydration and hypernatremia attacks which can be prevented.[3] While 24 h urine volume, kidney function tests, urine and

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serum osmolality, urine density, desmopressin test, plasma ADH level, genetic tests, and water restriction test can be performed for diagnosis, water restriction test in neonates cannot be performed.[3] The aim of the treatment is to ameliorate the underlying cause and to prevent severe dehydration attacks, mental, and growth retardation.

This case is presented to keep the diagnosis of NDI in mind in patients with severe hypernatremic dehydration in the neonatal period and to emphasize the prevention of comorbid conditions with early diagnosis and prompt treatment.

## Case Report

Eight-day-old male neonate was applied to our hospital with the complaints of requirement of excessive breastfeeding and tendency to fall asleep. It was learned that mother was followed up because of polyhydramnios and the patient was born with a birth weight of 3300 g after 40 weeks of gestation. The APGAR score was found to be 8 and 10 in 1–5 min, respectively. There was a cousin marriage between the parents. Physical examination revealed hypoactive – decreased neonatal reflexes, decreased turgor tonus, and dry mucous membranes. Body temperature was 36.5°C, weight was 2800 g, heart rate was 150/min, and blood pressure was 55/32 mmHg. Laboratory results are presented in Table 1. Complete blood count, infection markers, and arterial blood gases were normal. As treatment for hypernatremia, 0.9% sodium chloride with 10 ml/kg load and daily maintenance + deficits (150 ml/kg/day + 50 ml/kg/day) was ordered. While it was planned to decrease the blood sodium level by 8–10 mEq/L/day, 0.2% sodium chloride-5% dextrose mixture was adjusted. The amount of urine was recorded per hour using a urinary catheter to monitor diuresis. Despite appropriate hydration therapy, laboratory parameters did not improve. Blood osmolality (*Na x 2+Glucose/18+Urea/28*) and urine amount were calculated. The patient had high blood osmolality, high amount of urine output, and low urine density. The patient was accepted as DI and desmopressin treatment with 5% dextrose intravenous fluid was started. Cranial MRI was performed for intracranial pathology to rule out for the acute causes. No pathological finding was obtained. Blood thyroid hormone levels (TSH: 4.21 mIU/mL – normal range 0.98–5.63 and free T4: 1.28 ng/dL – normal range 0.88–1.51) were normal. Although the desmopressin dose was gradually increased and the maximum dose (4 mcg) was reached, excessive feeding request, high blood sodium levels, increased blood osmolality, low urine density, and polyuria did not improve. The diagnosis of central DI diagnosis was ruled out due to the lack of clinical and laboratory response to desmopressin. Medical history of the parents was questioned again, and it was learned that patient's uncle had polyuria and polydipsia complaints and he was treated with hydrochlorothiazide. After starting hydrochlorothiazide treatment, the patient's clinical and laboratory findings began to improve (Table 1). On the 6$^{th}$ day of the treatment, the enteral status was sufficient, clinical and laboratory findings improved, and the patient was completely discharged with hydrochlorothiazide. The patient was genetically tested by next generation sequence (Miseq Illumina) method and a hemizygous mutation was detected c.299_319del21bp (p.100_107delRPPTASV) in the AVPR2 gene. Genetic counseling was given to the family. The patient is currently being followed in the pediatric nephrology outpatient clinic and growth/development and renal functions are also monitored. The written consent was obtained from parents for this study.

## Discussion

NDI is a rare disease seen in the neonatal period.[1] Despite intensive liquid infusion; resistant hypernatremia, high blood osmolality, low urinary osmolality, polyuria, and weight loss are important findings in diagnosis. The main control mechanism of the urinary output is the arginine vasopressin (AVP)

**Table 1.** Laboratory values according to treatment

| | Sodium (mEq/L) | Potassium (mEq/L) | Urea (mg/dL) | Creatinine (mg/dL) | Urine output ml/kg/hour | Blood osmolality | Urine density |
|---|---|---|---|---|---|---|---|
| 1$^{st}$ day | 163 | 4.5 | 9 | 0.4 | 7.2 | | |
| 2$^{nd}$ day | 160 | 5.4 | 9 | 0.4 | 5.8 | 314.5 | 1000 |
| 3$^{rd}$ day | 164 | 5.4 | 12 | 0.48 | 6.7 | 335.4 | 1000 |
| Desmopressin 1$^{st}$ day | 166.6 | 4.67 | 8 | 0.5 | 7.2 | 328.97 | 1002 |
| Desmopressin 2$^{nd}$ day | 165 | 4.12 | 10 | 0.51 | 8 | 339.3 | 1002 |
| Desmopressin 3$^{rd}$ day | 170 | 4.08 | 9 | 0.6 | 5 | 348.6 | 1004 |
| Hydrochlorothiazide 1$^{st}$ day | 165 | 4.32 | 7 | 0.5 | 3.4 | 337 | 1004 |
| Hydrochlorothiazide 2$^{nd}$ day | 155 | 5.2 | 5 | 0.44 | 3.4 | 336.4 | 1008 |
| Hydrochlorothiazide 3$^{rd}$ day | 149 | 4.5 | 10 | 0.5 | 2.8 | 308 | 1007 |
| Hydrochlorothiazide 6$^{th}$ day | 137 | 4.99 | 28 | 0.4 | 1.5 | 280 | 1014 |

hormone, which is produced in the hypothalamus and released from posterior area of pituitary gland, which increases reabsorption of water in collecting system of the kidneys. Vasopressin with a peptide structure of nine amino acids is a hormone secreted from magnocellular neurons in paraventricular and supraoptic regions of the hypothalamus.[1,4] In general, polyuria occurs due to excessive fluid replacement, decreasing of the production of AVP hormone (central DI), or decreased response to the kidney's AVP hormone (NDI).

In our case, dehydration associated with polyuria, hypotonic urine, hypernatremia, and high plasma osmolality made us to suspect of DI. In addition, the presence of family medical history, normal central imaging, and lack of response to desmopressin support the diagnosis of NDI. The previously reported AVP receptor mutation was obtained in the genetic analysis. Although diagnosis and treatment of DI has been defined previously, NDI is a very rare disease in newborn infants.[3]

Although intravenous 0.9% sodium chloride is the first choice in the treatment of childhood dehydration, this crystalloid infusion can be exacerbated hypernatremia in NDI patients. After intravenous of 0.9% sodium chloride infusion, because of reduced absorption in kidneys plasma, water decreases rapidly and sodium content increases even more due to reduced absorption of sodium-free water in renal plasma. The general statement is worsening of hypernatremia when using high osmolality of replacement fluids compared to urine osmolality (usually 100–150 mos/kg in NDI patients). In addition, if intravenous hypotonic fluids are administered more than urine losses or increased sodium loss (due to diarrhea), hyponatremia may develop. Therefore, the first approach to be preferred should be water or breast milk enteral but if necessary, intravenous dextrose will be preferred.[2] Our case presented with weight loss and hypernatremia in the neonatal period. Although fluid support is recommended for infants with hypernatremia, sodium, and weight loss, the treatment fluid was revised due to lack of improvement in the sodium amount.

In the treatment of NDI, first, appropriate fluid support followed by thiazide diuretics, amiloride, or nonsteroidal anti-inflammatory drugs should be provided.[1,4] In addition, AVPR2 chaperones which are still under investigation are being tested with AVP2 bypass treatments (statins, phosphodiesterase inhibitors, and calcitonin).[4-7] It was found that all clinical and laboratory findings were improved after diuretic use of thiazide group, as in our patient.

Today, more than 250 mutations in AVPR2 are defined as the cause of NDI.[8] Although most of the NDI cases are diagnosed in the 1st year of life, some are diagnosed lately due to mild symptoms. In particular, it is related to some of the light phenotypes of the missense NDI.[8]

In our case, hemizygous mutation was detected in the AVPR2 gene c.299_319del21bp (p.100_107delRPPTASV) that has been defined before. We believe that clinically, it is important to detect the case in the early stages of the neonatal period.

## Conclusion

Although NDI is a rare disease in children, all clinicians should be aware of NDI in cases of severe hypernatremia and dehydration in neonatal period. Early diagnosis and prompt management could preserve patients from dehydration attacks and mental and growth retardation.

### Disclosures

**Informed consent:** Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

**Authorship Contributions:** Concept – M.C.; Design – M.C.; Supervision – M.A.K.; Materials – M.C.; Data collection &/or processing – M.A.K., M.C.; Analysis and/or interpretation – M.A. K.; Literature search – M.C.; Writing – M.C.; Critical review – M.A.K.

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