

# Nephrogenic Syndrome of Inappropriate Antidiuresis Mimicking Hyporeninemic Hypoaldosteronism: Case Report of Two Infants

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## What is already known on this topic?

Nephrogenic syndrome of inappropriate antidiuresis (NSIAD) is a very rare disorder caused by activating mutations in the arginine vasopressin (AVP) receptor-2 gene (*AVPR2*). Patients with NSIAD can manifest at any age from birth with euvolemic hyponatremia and concentrated urine excretion. Undetectable AVP levels distinguish this syndrome from inappropriate antidiuretic hormone secretion.

## What this study adds?

In NSIAD, plasma renin activity is suppressed and aldosterone level is relatively low. This profile can be confused with hyporeninemic hypoaldosteronism, especially in infants with no apparent gross cranial, pulmonary and renal pathology. Diagnosing NSIAD correctly may prevent complications, such as hyponatremia, and unnecessary treatment with fludrocortisone, which would most likely result in hypertension.

## Abstract

Nephrogenic syndrome of inappropriate antidiuresis (NSIAD) is an X-linked disease caused by activating mutations in the arginine vasopressin (AVP) receptor-2 (*AVPR2*) gene. Affected patients excrete concentrated urine despite very low levels of AVP, and consequently develop euvolemic hyponatremia. Due to its low frequency, patients may be misdiagnosed and treated incorrectly. We report two related male infants with NSIAD that was initially confused with hyporeninemic hypoaldosteronism (HH). First, a 2-month-old male presented with hyponatremia, low plasma osmolality, relatively high urine osmolality, and low plasma renin-aldosterone levels. These clinical and laboratory findings were compatible with syndrome of inappropriate antidiuretic hormone (ADH) secretion without apparent cause. Consequently, fludrocortisone was initiated with a presumptive diagnosis of HH. While correcting hyponatremia, fludrocortisone treatment led to hypertension and was discontinued promptly. The second patient, aged one year, was admitted with a history of oligohydramnios, had been hospitalized four times due to hyponatremia since birth, and had a diagnosis of epilepsy. Similarly, the second infant had clinical and laboratory findings compatible with syndrome of inappropriate ADH secretion with no apparent cause. Fluid restriction normalized his serum sodium despite the plasma AVP level being undetectable. In both infants, *AVPR2* gene analysis revealed a known mutation (c.409C > T; p.R137C) and confirmed the diagnosis of NSIAD. In conclusion, NSIAD should be considered in all patients with unexplained euvolemic hyponatremia despite high urine osmolality. If NSIAD is not considered, the plasma renin-aldosterone profile can be confused with HH, especially in infants.

**Keywords:** *AVPR2* gene, hyponatremia, inappropriate antidiuretic hormone secretion



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## Introduction

The vasopressin type 2 receptor (V2R) plays a central role in the control of water homeostasis by the kidney (1). While inactivating mutations in the V2R gene (AVPR2) causes X-linked nephrogenic diabetes insipidus (1,2), activating mutations result in nephrogenic syndrome of inappropriate antidiuresis (NSIAD) (3). NSIAD, first described in 2005, is a rare disorder with about 30 cases reported so far. It shares the same clinical features with syndrome of inappropriate antidiuretic hormone secretion (SIADH). Both syndromes are associated with euvolemic hyponatremia, decreased serum osmolality, and inappropriate increases in urine osmolality, but differ in arginine-vasopressin (AVP) levels, which are high in SIADH and not detectable in NSIAD (3,4). Increased extracellular volume due to the excessive effect of AVP induces atrial natriuretic peptide (ANP) secretion. ANP directly reduces plasma renin activity (PRA), and thereby decreased aldosterone production which leads to increased output of urinary sodium and water (5,6). This compensatory event, which occurs due to inappropriate antidiuresis, can give a false impression that the primary pathological process underlying hyponatremia is hyporeninemic hypoaldosteronism (HH). Therefore, if NSIAD is not considered in the differential diagnosis of hyponatremia, this rare disorder can be mistaken for HH. Presence of chronic hyperkalemia distinguishes HH from NSIAD (7,8), thus hyponatremic but normokalemic infants have been reported with a diagnosis of HH (9,10). Here, we present two related male infants with NSIAD that was initially confused with HH. The aim of this report is to raise awareness of NSIAD, which is very rare cause of chronic or recurrent hyponatremia.

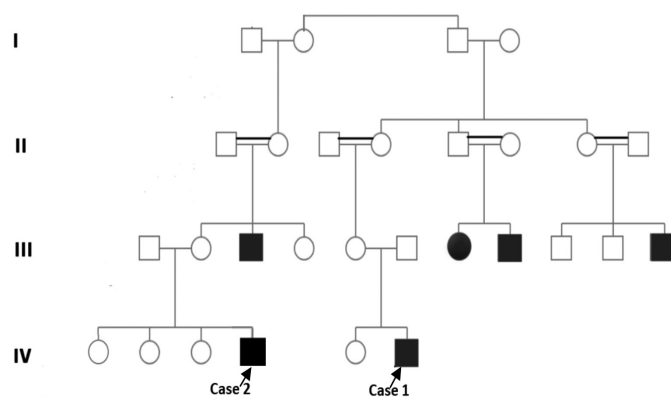
## Case Reports

### Case 1

A 2-month-old male who was scheduled for inguinal hernia surgery was seen because of hyponatremia. He was the second child of non-consanguineous parents. His parents and older sister were healthy, but his cousins suffered from hyponatremia (Figure 1). His mother was not taking any medications. Personal medical history was unremarkable with a normal pregnancy, birth by cesarean section at 39 weeks of gestation, and a birth weight of 3290 g. He was exclusively breastfed. On admission, the infant was an apparently healthy male with normal physical exam findings. On examination, his weight was 5.83 kg [-0.27 standard deviation score (SDS)], length 59 cm (-0.37 SDS), temperature 36.5 °C, blood pressure 80/40 mm Hg (49<sup>th</sup> percentile/77<sup>th</sup> percentile). Initial laboratory testing was as

follows: serum sodium 126 mEq/L [reference range (RR): 135-145], potassium 5.7 mEq/L (RR: 3.5-5.5), serum osmolality 257 mOsm/kg (RR: 275-295), uric acid 1.5 mg/dL (RR: 1.8-5.0), PRA 0.02 ng/mL/h (RR: 0.4-15), aldosterone 26 ng/dL (RR: 5-90), urine osmolality 132 mOsm/kg (RR: 50-1400) and urine sodium 24 mEq/L (RR: 54-190). Other laboratory values of the patient are given in Table 1. When serum sodium was normalized subsequently by treatment, urinary sodium concentration increased to 87 mEq/L.

The findings of an inappropriately concentrated urine (>100 mOsm/kg), low serum osmolality (<280 mOsm/kg) and serum sodium (<135 mEq/L) were compatible with SIADH, but there was no apparent cause to explain it, including cranial or pulmonary pathologies and drugs. Kidney ultrasound was also normal. Other hyponatremic states were also ruled out on the basis of his history, physical examination and laboratory studies (Table 1). Due to suppressed PRA and relatively low levels of aldosterone despite hyponatremia and mild hyperkalemia, a presumptive diagnosis of HH was made. To correct hyponatremia, fludrocortisone treatment (0.1 mg/day) was started together with oral sodium chloride supplement (6 mEq/kg/day). He did not have marked variations in weight. Subsequently serum sodium increased to 140 mEq/L within two weeks, sodium chloride was discontinued and the dose of fludrocortisone was reduced to 0.05 mg/day. At the end of two-month follow-up, blood pressure was found to be elevated [100/60 mmHg (96<sup>th</sup> percentile/99<sup>th</sup> percentile)], and therefore fludrocortisone was discontinued. During the subsequent observation period of four months, serum



**Figure 1.** Patients pedigree

Black squares with arrows indicate genetically confirmed NSIAD. Black squares and circles indicate the cases that are followed up with hyponatremia

NSIAD: *nephrogenic syndrome of inappropriate antidiuresis*

sodium level remained in the range of 130-136 mEq/L, and blood pressure was normalized without intervention.

## Case 2

Six months after the first patient's admission, the second boy, at the age of one year, was referred to our clinic for recurrent hyponatremia. He was born weighing 3000 g at 37 weeks of gestation by emergency C-section due to oligohydramnios, which developed within the last trimester. He was treated for diagnoses of hyponatremia and sepsis for ten days after birth. Subsequently, he was hospitalized for hyponatremia three more times up to the age of six months. At the age of 10 months, he had a seizure and oxcarbazepine treatment was started. When inquiring about the family history, his non-consanguineous parents and three sisters were healthy but his maternal uncle had a history of hyponatremia and epilepsy (Figure 1). On physical examination, his temperature was 36.8 °C, blood pressure 85/45 mmHg (60<sup>th</sup> percentile/85<sup>th</sup> percentile), pulse of 75 beats per minute, weight was 9.2 kg (-0.7 SDS)

and length was 72.8 cm (-1.27 SDS). He appeared well and euvolemic. Initial serum sodium level was 120 mEq/L, PRA was 0.02 ng/mL/h and all laboratory findings were compatible with SIADH, as shown in Table 1. After fluid restriction to 1000 mL/m<sup>2</sup>/day, serum sodium concentration increased up to 141 mEq/L and PRA 19.2 ng/mL/h. Since oxcarbazepine was known to cause SIADH and the patient's electroencephalography was normal, this treatment was discontinued. Further studies were conducted to determine the cause of SIADH. Chest X-ray and magnetic resonance imaging of the brain were normal. When daily fluid intake became unrestricted, hyponatremia recurred. After exclusion of usual causes of SIADH, a nephrogenic origin of inappropriate antidiuresis was considered and the AVP level was checked. Plasma AVP level, measured by double-antibody radioimmunoassay, was undetectable (<0.5 pg/mL) in the presence of euvolemic hyponatremia (128 mEq/L). Therefore, we switched our clinical diagnosis of SIADH to NSIAD. The diagnosis of NSIAD was confirmed by genetic testing, which showed a known mutation in *AVPR2* c.409C>T, corresponding to arginine to cysteine mutation at amino acid 137 (p.R137C). Detailed pedigree analysis showed that the second case was a relative of the first case (Figure 1). Plasma AVP level was also measured in the first case and was also undetectable (<0.5 pg/mL) in the presence of euvolemic hyponatremia (126 mEq/L). Clinical and laboratory data of both cases were also similar (Table 1). Therefore, genetic analysis was also performed in the first case, and confirmed the diagnosis of NSIAD by detecting the same mutation in the *AVPR2* gene. Both patients are continuing to be followed up with normal serum sodium levels on limited fluid intake for three years. Their motor and mental development is normal.

**Table 1. Laboratory values of cases**

Laboratory studies	Case 1	Case 2	Reference ranges
<b>Serum/plasma</b>			
Sodium (mEq/L)	126	120	135-145
Potassium (mEq/L)	5.7	4.9	3.5-5.5
Chloride (mEq/L)	95.1	93.2	98-106
Glucose (mg/dL)	77	79	70-111
Bicarbonate (mmol/L)	22	21	22-29
Creatinine (mg/dL)	0.22	0.21	0.2-0.4
Urea (mg/dL)	2	2.8	5-18
Uric acid (mg/dL)	1.5	2.1	1.8-5.0
Albumin (g/dL)	3.72	3.6	3.5-5.0
Osmolality (mOsm/kg H <sub>2</sub> O)	254	236	275-295
Renin activity (ng/mL/h)	0.02	0.02	0.4-15
Aldosterone (ng/dL)	26	84	5-90
Arginine vasopressin (pg/mL)	< 0.05	<0.05	1.5-12 <sup>a</sup>
fT4 (ng/dL)	1.69	1.2	0.96-1.77
TSH (μIU/mL)	1.97	2.55	0.7-5.97
ACTH (pg/mL)	22.9	24	25-100
Cortisol (μg/dL)	16.4	22.4	8.5-23
<b>Urine</b>			
Osmolality (mOsm/kg H <sub>2</sub> O)	132	571	50-1400 <sup>b</sup>
Sodium (mEq/L)	24	58	54-190 <sup>c</sup>
Potassium (mEq/L)	13	14	20-80
Sweat chloride (mEq/L)	19	ND	< 60

<sup>a</sup>Serum osmolality dependent.

<sup>b</sup>Fluid intake dependent.

<sup>c</sup>Diet dependent.

ACTH: adrenocorticotrophic hormone, TSH: thyroid stimulating hormone

## Discussion

We report two consanguineous male infants with a diagnosis of NSIAD, which was confirmed by genetic analysis which revealed a known mutation in *AVPR2*. NSIAD is a very rare disorder reported in about 30 cases since 2005 when it was first described (3,11-21). The prevalence of activating mutation of *AVPR2* is unknown. Due to as many as 10% of patients with SIADH having undetectable levels of AVP, activating mutations of *AVPR2* are likely to account at least for some of these cases (11). Due to its low frequency, it is not usually considered in the differential diagnosis of euvolemic hyponatremia. Therefore, lack of awareness of this rare disease may cause delay in determining the etiology of hyponatremia and even misdiagnosis. Indeed, in our first case with hyponatremia, the laboratory data (low

renin-aldosterone and borderline-high potassium levels) were erroneously interpreted as HH. This confusion led to fludrocortisone treatment. A therapeutic approach to correct the serum sodium level by increasing renal sodium and water reabsorption in a patient with elevated plasma volume naturally resulted in hypertension. This erroneous management was immediately corrected, but the patient remained undiagnosed for a while. Luckily, the second case presented with similar clinical and laboratory findings in a short time. Even though unable to identify an etiology, we established a clinical diagnosis of SIADH by observing that the hyponatremia improved with fluid restriction. Then, it was shown that the syndrome was of renal origin by way of undetectable AVP levels. Thus, molecular analysis of the renal AVP receptor gene confirmed the diagnosis of NSIAD.

HH, the initial diagnosis of our first case, in fact pointed to the renal origin of underlying defect. Hyporeninemia occurs in many kidney diseases, including diabetic nephropathy, lupus nephritis, sickle cell anemia, amyloidosis, urinary tract obstructions, and due to abuse of drugs impairing renin production. The typical patient with HH usually presents at elderly ages with mild renal insufficiency and metabolic acidosis, and asymptomatic chronic hyperkalemia, without hyponatremia (7,8). Therefore, a diagnosis of HH does not seem to be appropriate for a hyponatremic infant without any apparent renal pathology. On the other hand, HH has been rarely described in infants who have hyponatremia, but no hyperkalemia and hyperchloremic acidosis (9,10). Unlike the clinical picture in adults, this electrolyte profile in the infants has been related to renal characteristics of the age period, and the absence of gross renal pathology (10) but the etiology of HH in these infants has remained undetermined. Interestingly, as seen in our first case, fludrocortisone treatment led to hypertension in one of male siblings described by Landier et al. (10). HH has been occasionally defined in children with acquired, chronic or acute kidney diseases (22,23), whereas its congenital form has been reported only in a few infants (9), and an underlying genetic defect has not been identified to date. However, in a retrospective analysis by Storey et al. (24), the prevalence of genetic defects of the mineralocorticoid pathway including hypoaldosteronism and pseudohypoaldosteronism was considerably higher than expected in the hyponatremic neonates and infants. However, no infant in this large patient group had HH. As a result, in our infant cases, after initial confusion with HH, we correctly described NSIAD as a genetic cause of hyponatremia originating from the kidney. We also consider that the unusual hyponatremic infant cases of HH reported before recognition of NSIAD might be the earliest examples of undiagnosed NSIAD.

NSIAD is a disorder characterized by hyponatremia, normal or slightly elevated plasma volume, an inappropriately concentrated urine and normal-to-high urine sodium (3). SIADH and NSIAD have the same clinical features of impaired free water excretion (4). In affected patients, plasma volume increases due to reduced free water excretion. The volume increment results in high secretion of natriuretic peptides, leading to suppression of renin-aldosterone levels. Secondary mineralocorticoid deficiency causes renal salt wasting and hyponatremia (5,6). When SIADH or NSIAD are not correctly identified as a main source, the patients can be mistakenly diagnosed as HH. Thus, in a patient with suspected SIADH, if its classical causes of cranial and pulmonary origin or the use of drugs inducing AVP secretion are not found, NSIAD should be considered first in the differential diagnosis. Despite the findings compatible with SIADH, the demonstration of undetectable plasma AVP levels makes a clinical diagnosis of NSIAD (3,13,14).

Feldman et al. (3) first reported hemizygous gain of function point mutations (p.Arg137Cys and p.Arg137Leu) in *AVPR2* in two male infants with NSIAD. Almost all the patients with NSIAD presented in the literature have had one of these two *AVPR2* mutations (3,11,12,13,14,20,21). Our NSIAD patients also had p.Arg137Cys mutation. Functional analysis reported by previous studies have already shown that this variant is responsible for a constitutive activation of the AVP type 2 receptor, leading to inadequate water reabsorption in spite of low AVP levels.

In our case study, detailed family inquiry revealed that these two infants who independently presented were related and also had the five adult relatives with history of hyponatremia and/or epilepsy. We learned that these adults were not diagnosed with NSIAD, but consumed limited fluid of their own free will. Since the cousins of the first infant's mother and the second infant's uncle lived abroad, we could not perform genetic testing for these family members. While symptoms in our infant cases began in the neonatal and even antenatal period, manifested by oligohydramnios due to low urination, the other family members' complaints, including tiredness, headache and seizures, had started at different ages ranging from childhood to later life. So, the age range in the seven patients (one female) in our large family varied from infancy to adulthood. Decaux et al. (11) demonstrated that NSIAD shows a wide variation of expressivity. It is not limited to infants, and the diagnosis should also be considered in adults. Albeit NSIAD is an X-linked genetic disease, it has been reported in heterozygous females, and this is explained as random X-inactivation (25).

Early detection and treatment of NSIAD are essential to prevent severe hyponatremia, which can have dangerous effects on neonates and infants, and can potentially lead to death or, if survived, neurological sequelae. The goal of therapy is to limit free-water intake (3,11-21). Since AVP stimulates thirst, low to undetectable levels of AVP encountered in NSIAD could induce a diminished thirst sensation and thus explain the good compliance to water restriction (26). Fludrocortisone treatment rescues otherwise potentially life-threatening hyponatremia due to renal salt wasting and the secondary mineralocorticoid deficiency driven by elevated ANP and/or brain natriuretic peptide (27). However, long-term use of mineralocorticoids can lead to hypertension, as seen in our first case. The vaptans, AVP antagonists that interfere with the hormone's antidiuretic effect by competitively binding to AVPR2, are effective in SIADH but ineffective in NSIAD due to the receptor's constitutive activation (11,17). Therefore, fluid restriction remains the mainstay of therapy, as applied in the two cases presented herein.

## Conclusion

In conclusion, NSIAD should be considered as a diagnosis in patients presenting at any ages with unexplained hyponatremia and low plasma osmolality, despite relatively high urine osmolality. As a first step in the investigation, plasma AVP levels should be measured. In patients with undetectable AVP levels, genetic testing of AVPR2 can simply confirm diagnosis. It should be noted that if NSIAD is not considered, the plasma renin-aldosterone profile can be confused with HH, especially in infants.

## Ethics

**Informed Consent:** Consent form was filled out by all participants.

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

## Authorship Contributions

Surgical and Medical Practices: Jamala Mammadova, Cengiz Kara, Eda Çelebi Bitkin, Elif İzci Güllü, Murat Aydın, Concept: Jamala Mammadova, Cengiz Kara, Murat Aydın, Design: Jamala Mammadova, Cengiz Kara, Murat Aydın, Data Collection or Processing: Jamala Mammadova, Cengiz Kara, Analysis or Interpretation: Jamala Mammadova, Cengiz Kara, Literature Search: Jamala Mammadova, Cengiz Kara, Writing: Jamala Mammadova, Cengiz Kara.

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