Arch Argent Pediatr. 2026;e202511001

Malnutrition and hypernatremic dehydration as the initial presentation of nephrogenic diabetes insipidus in an infant

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ABSTRACT

Congenital nephrogenic diabetes insipidus (CNDI), also known as arginine vasopressin resistance, is a rare inherited disorder of water homeostasis in which the kidneys lose their ability to concentrate urine, leading to polyuria, polydipsia, and a risk of hypertonic dehydration.

We report the case of a 3-month-old infant with symptoms present for approximately 2 months, characterized by episodes of fever, irritability, and poor growth. Upon admission, severe malnutrition and dehydration were noted. A diagnosis of CNDI was made based on vasopressin levels, plasma and urine osmolarity values, hypernatremia, and family history. The patient's treatment was challenging; he responded favorably and remains under outpatient follow-up.

The presentation, results of additional tests, and short-term course are described.

Keywords: *nephrogenic diabetes insipidus; arginine vasopressin; polyuria; osmolar concentration; antidiuretic hormone.*

doi: http://dx.doi.org/10.5546/aap.2025-11001.eng

To cite: Valdez M, Quiroga Viola MA, Flores R, De La Rosa S, Voigt J, Gómez Lund O. Malnutrition and hypernatremic dehydration as the initial presentation of nephrogenic diabetes insipidus in an infant. *Arch Argent Pediatr.* 2026;e202511001. Online ahead of print 2-JUL-2026.

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***Funding**: None.*

***Conflict of interest**: None.*

***Received**: 12-22-2025*
***Accepted**: 4-27-2026*

INTRODUCTION

Congenital nephrogenic diabetes insipidus (CNDI), also known as arginine vasopressin (antidiuretic hormone) resistance, is a rare inherited disorder of water homeostasis caused by the distal nephron's insensitivity to arginine vasopressin. Consequently, the kidney loses its ability to concentrate urine, leading to polyuria, polydipsia, and a risk of hypertonic dehydration.[1] In 2022, the working group for the renaming of diabetes insipidus proposed replacing CNDI with arginine vasopressin resistance, distinguishing it from central arginine vasopressin deficiency.[2] However, this new terminology has not been officially adopted.[3] Therefore, we will use the term CNDI to describe the disease caused by renal insensitivity to arginine vasopressin. CNDI can result from genetic abnormalities, such as mutations in the arginine vasopressin receptor 2 gene (*AVPR2*) or in the aquaporin-2 gene (*AQP2*), or from acquired causes such as chronic lithium therapy. Mutations in *AVPR2* account for approximately 90% of patients with congenital CNDI and follow an X-linked inheritance pattern. In approximately 10% of cases, congenital CNDI follows an autosomal recessive or dominant inheritance pattern, with mutations in the *AQP2* gene. In 2% of cases, the genetic cause is unknown.[4]

CLINICAL CASE

A 3-month-old infant, born at the early term with a weight appropriate for gestational age (37 weeks/2560 g). The metabolic screening and auditory brainstem response tests were normal. The infant was discharged. Immunizations were incomplete for the age (3 months).

He had been experiencing intermittent fever and irritability for two months and had made multiple visits to the hospital. During the last visit, he was diagnosed as a febrile infant with no identifiable source of fever and was therefore referred to the regional referral hospital. Upon admission, the patient was dehydrated and malnourished, with a Z-score for height-for-age of -2.55, weight-for-age of -2.43, and head circumference-for-age of -2.30, all below the 0.1 percentile (weight: 3.91 kg, height: 54 cm, head circumference: 37 cm), with no other relevant findings on physical examination.

Blood cultures, urine cultures, serology tests (cytomegalovirus, human immunodeficiency virus, Epstein-Barr virus, and parvovirus B-19), stool cultures, and testing for rotavirus and adenovirus in stool samples were performed; all results were negative. Laboratory tests were requested, which reported severe hypernatremia (166 mmol/L) and hypermagnesemia (3.2 mg/dL), with the rest of the tests within normal ranges. Polyuria of up to 7 ml/kg/hour was observed, along with negative fluid balances of -14 ml/kg, elevated plasma osmolarity (338 mOsm/kg), and decreased urinary osmolarity (175 mOsm/kg).

Given suspicion of central diabetes insipidus, a consultation was obtained from the Endocrinology Department, and a desmopressin test was initiated, which showed no response. Concurrently, free water levels were corrected, and hypernatremia was managed according to recommendations.

During the targeted medical history, a relevant finding emerged: a diagnosis of nephrogenic diabetes insipidus in a paternal first cousin. In collaboration with the Nephrology Department, treatment was initiated with ibuprofen (6 mg/kg per dose) and hydrochlorothiazide (1 mg/kg per day) in two divided doses. During hospitalization, vasopressin levels were within normal limits (*Table 1*).

The patient showed a favorable clinical course. After a 20-day hospital stay in the intermediate care unit, he was discharged and placed under multidisciplinary outpatient follow-up. The family was educated, and genetic counseling was provided due to the possibility of disease recurrence in future pregnancies.

DISCUSSION

CNDI is difficult to diagnose, as the median age at diagnosis is 4 months;[5] polyuria, growth retardation, and signs of dehydration are the typical presenting features, as seen in our patient.

During the first two years of life, increased urine output can be difficult to detect; therefore, a diagnostic algorithm is proposed (*Figure 1*). The pediatrician needs to ask about diaper changes throughout the day and night and, if possible, to weigh the infant. Other findings suggestive of diabetes insipidus in the medical history of young infants include recurrent febrile episodes, hypernatremic dehydration, irritability due to intense thirst, difficulty falling asleep, and postural stagnation.[6]

The diagnostic laboratory findings for diabetes insipidus include a urine osmolarity <300 mOsm/kg, a blood osmolarity ≥295 mOsm/kg, and a serum sodium ≥145 mEq/L. To determine the etiology of diabetes insipidus—central (CDI) vs.

Table 1. Selected laboratory tests for the patient at admission, at 72 hours, and at discharge

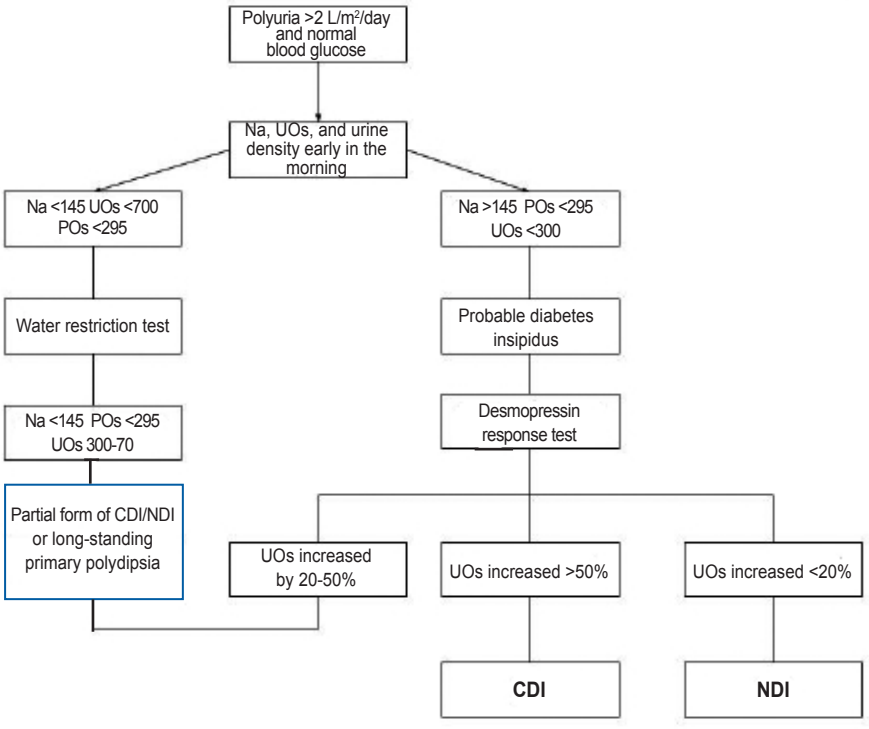
Laboratory	Admission	72-hours follow-up	Discharge
Hb/Hct	7.5 g/dL/24.4%	-	9 g/dL/29.7%
White blood cells	4200/mm^3	-	12 300/mm^3
Platelets	198 000/mm^3	-	479 000/mm^3
Sodium/potassium	166/39	162/3.6	145/4.2
pH	7.37	7.43	7.47
pCO_2/pO_2	46/50.3	43.9/48.4	38.5/52.2
HCO_3/BE	24.9/0.8	28.5/4.9	27.6/3.9
Urea/creatinine (mg/dL)	15/0.52	21/0.3	15/0.25
Complete urinalysis	Appearance: slightly cloudy Density: 1010 pH: 6		Appearance: clear Density: 1005 pH: 6
Urinary ionogram (mmol/L)	Na 80/ K 7.4		14/30.6
ADH (pmol/L)		0.8	
Urinary osmolarity (mOsm/kg)	182.4		330.6
Plasma osmolality (mOsm/kg)	339.61		297.78

Hb: hemoglobin; Hct: hematocrit; pCO_2: partial pressure of carbon dioxide; pO_2: partial pressure of oxygen; HCO_2: bicarbonate; BE: base excess; ADH: antidiuretic hormone.

nephrogenic (NDI)—it is necessary to evaluate the response to administration of 1-deamino-8-D-arginine vasopressin (DDAVP), whether intranasally, orally, or intravenously. A consistent response characterized by a decrease in polyuria and an increase in urinary osmolarity will confirm the diagnosis of CDI.[6]

However, urinary osmolarity may exceed 200

Figura 1. Algoritmo diagnóstico para diabetes insípida



UOs: urinary osmolarity, POs: plasma osmolarity, CDI: central diabetes insipidus, NDI: nephrogenic diabetes insipidus, Na: sodium. Adapted from: Molano F, Soriano Guillén L. Diabetes insipidus. Diagnostic and therapeutic approach. Rev Esp Endocrinol Pediatr. 2021;12(Suppl 2):56-66. doi: 10.3266/RevEspEndocrinolPediatr.pre2021.Apr.644.

mOsm/kg in milder cases.[7,8] For intermediate cases without a definitive diagnosis (urinary osmolarity between 300 and 700 mOsm/kg), a water restriction test is recommended. It is important to note that, in the pediatric population, NDI is more common than CDI.[9] Infants are at particular risk of dehydration, as they do not have free access to fluids. In addition, the intake of large amounts may cause diarrhea.

Secondary forms of NDI are more common and can be caused by inherited kidney diseases (mutations in the vasopressin V2 receptor gene and the aquaporin 2 gene) that affect the ability to concentrate urine, by medications (amphotericin B, aminoglycosides, cisplatin, etc.), by systemic diseases (cystic kidney disease, systemic lupus erythematosus, etc.), by vascular causes (sickle cell disease and acute tubular necrosis), and by metabolic causes (severe hypokalemia, malnutrition with low protein intake).[10]

According to a multicenter study, urological findings were observed in 37% of the children. Abnormal findings on renal ultrasound included unilateral/bilateral hydronephrosis (18%, 10/12 *AVPR2*), renal dysplasia (14%, 3/5 *AVPR2*), bladder distension and/or trabeculation (8%, 4/9 *AVPR2*), and enuresis in 44% of the children.[5]

A preliminary study in patients with NDI showed that hydrochlorothiazide, combined with a standard diet containing 9 mEq of sodium per day, reduced urine output to approximately 50% of baseline after 3 days.[11] Hydrochlorothiazide can be initiated at a dose of 1-4 mg/kg/day, divided into 1 or 2 daily doses. In our patient, an adequate response was observed, similar to that reported in the literature.

Thiazide diuretics work by causing a slight reduction in fluid volume and can reduce urine output by up to 50% in the short term when combined with a low-salt diet. They may be used in combination with inhibitors of prostaglandins (cyclooxygenase, COX).[12] This combination requires careful clinical and laboratory monitoring.[11]

This effect is presumably mediated by increased proximal sodium and water reabsorption induced by hypovolemia, thereby decreasing the water supply to antidiuretic hormone-sensitive sites in the collecting ducts and reducing diuresis.[13] It is often used in combination with amiloride. This potassium-sparing diuretic has an additive effect with hydrochlorothiazide on the proximal reabsorption of sodium and water, without causing potassium loss.

Ideally, protein intake should be limited to no more than 1 g/kg, and sodium intake to no more than 2-3 g/day (less than 100 mEq/day). This restriction in pediatric patients can compromise normal growth and development, making dietary management challenging.[13]

Numerous novel therapies are currently being investigated to improve the treatment of NDI. In approximately 90% of patients with congenital NDI, mutations in the *AVPR2* gene cause AVPR2 to fold incorrectly and become trapped in the endoplasmic reticulum.[6] One of the most extensively studied therapeutic strategies involves rescuing these receptors using molecular chaperones.

A significant proportion of children have persistent short stature (38%) and low weight (29%) at follow-up, which may be associated with long-term psychosocial functioning issues. Adverse events are common: hospitalizations (61%), urological complications (37%), and stage 2 or higher chronic kidney disease (27%), which underscores the need for clinical trials to improve outcomes and reduce the burden of disease.[5]

Given the above, pediatricians need to remain highly vigilant regarding this condition and its clinical presentation, given its low prevalence and the complexity of its treatment. Recognizing it is essential because it is important to provide the family with genetic counseling regarding the possibility of recurrence. ■

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