A Novel X-linked Variant in Congenital Nephrogenic Diabetes Insipidus. Case Report

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Abstract

Congenital nephrogenic diabetes insipidus (NDI) is a rare hereditary renal disorder caused by variants in the arginine vasopressin receptor 2 (*AVPR2*) or aquaporin 2 (*AQP2*) genes, resulting in the kidney's inability to concentrate urine.
We report the case of a 52-day-old boy presenting with feeding difficulties and poor weight gain. Laboratory findings revealed hypernatremia and hyperchloremia, associated with a marked disparity between high serum osmolality and low urine osmolality. Genetic analysis identified a novel missense variant in the *AVPR2* gene. The therapeutic approach consisted of nasogastric free water supplementation and oral hydrochlorothiazide therapy, with good clinical response.
This case highlights the importance of early recognition and genetic testing in infants with suspected diabetes insipidus and expands the phenotypic spectrum of *AVPR2*-related NDI.

Introduction

In recent years, there has been a growing initiative—supported by both the scientific community and patient advocacy groups—to adopt the term "arginine vasopressin resistance (AVP-R)" instead of nephrogenic diabetes insipidus (NDI). This nomenclature better reflects the underlying pathophysiology and aims to reduce confusion with diabetes mellitus or central (pituitary) diabetes insipidus, now often referred to as "arginine vasopressin deficiency". While this terminology has not yet been formally incorporated into international classifications such as ICD-11, we have chosen to acknowledge it here in response to recent consensus efforts. For clarity and continuity, however, we will continue to use the term NDI throughout this report to describe the condition of renal unresponsiveness to vasopressin.

In this case report, we use the term variant instead of mutation in accordance with current genetic nomenclature guidelines. The term mutation has historically been used in clinical contexts to imply pathogenicity; however, it scientifically encompasses all types of genetic variation, regardless of clinical consequence. To avoid ambiguity and to align with the recommendations of the American College of Medical Genetics and Genomics (ACMG), we therefore adopt the term variant, which can be further specified by adjectives such as benign, likely pathogenic, or pathogenic.

Congenital nephrogenic diabetes insipidus (NDI) is a rare hereditary tubular dysfunction characterized by the kidney's inability to concentrate urine in response to vasopressin (antidiuretic hormone, ADH). This results in the excretion of large volumes of diluted urine (1,2).

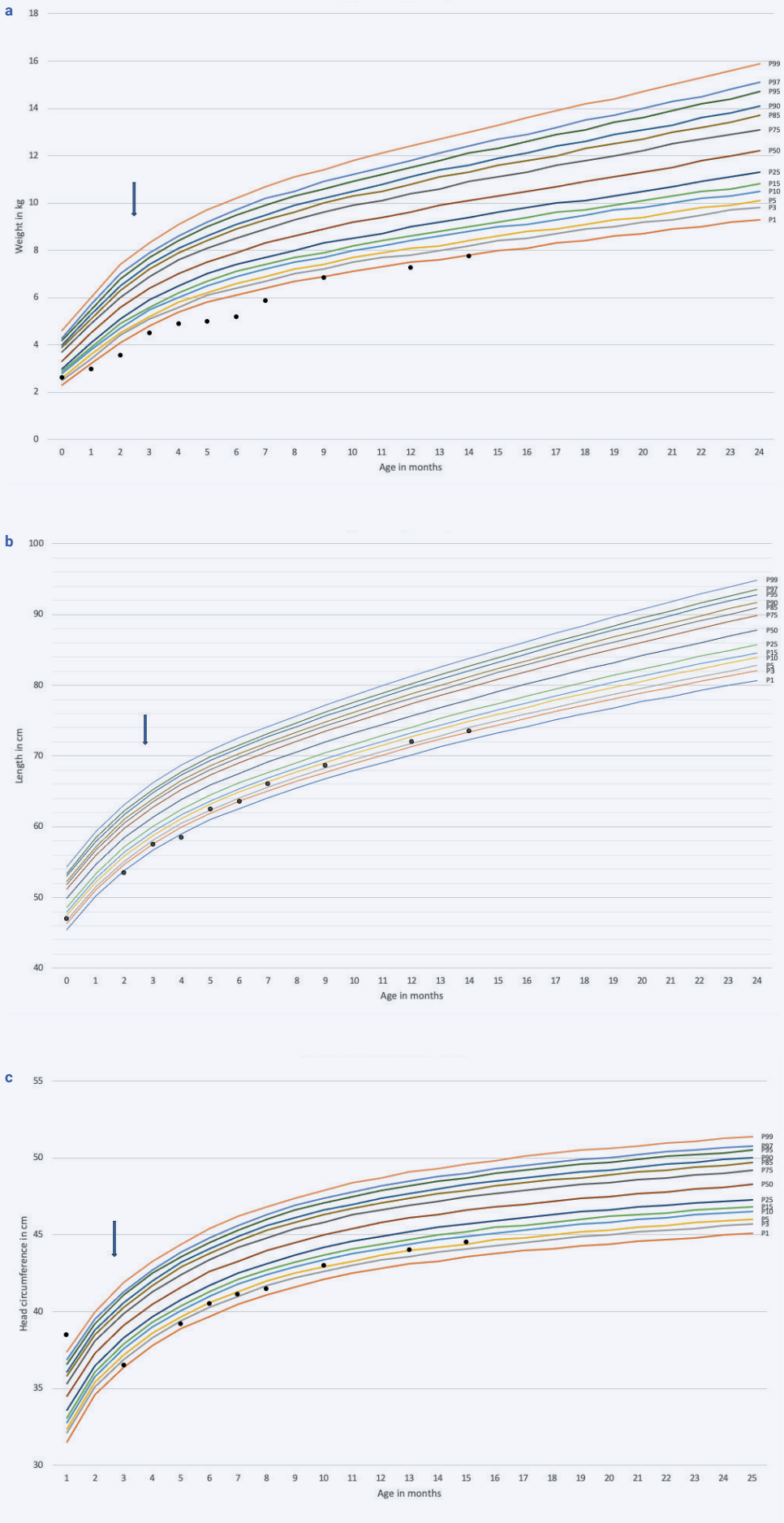
Clinical signs may include polyuria, polydipsia, electrolyte disorders (hypernatremia, hyperchloremia), dehydration, constipation, irritability, and developmental delay (2,4).

Approximately 90% of NDI cases are caused by variants in the *AVPR2* gene, transmitted in an X-linked pattern of inheritance. The remaining 10% are due to variants in the *AQP2* gene (9% autosomal recessive and 1% autosomal dominant) (2,3).

The incidence of NDI due to *AVPR2* variants is 4 to 8 boys per million with over 250 types of mutations reported (5).

Here, we would like to report a case of NDI in a male infant caused by a novel *AVPR2* gene variant. We will discuss the diagnostic and management challenges associated with this condition,

FIGURE 1 a, b, c: Auxological parameters of the patient. Weight (a), height (b), and head circumference (c) are plotted on WHO growth charts. The arrow indicates the time at which treatment was initiated (oral hydrochlorothiazide and free water supplementation).



highlighting the importance of early recognition and treatment to prevent severe dehydration episodes. Such episodes can lead to neurological complications, acute kidney injury, or growth impairment if not promptly managed.

Case Report

A 52-day-old European boy was admitted to the pediatric ward for feeding difficulties and failure to thrive.

He was the first child of the family, born with a history of intrauterine growth retardation of undetermined origin (weight: 2.63 kg, height: 47 cm, head circumference: 38 cm at 39 4/7 weeks of gestation). There was no polyhydramnios and the parents were non-consanguineous. Family history was unremarkable. At the one-month checkup, the pediatrician noted a lack of weight gain (below the 3rd percentile). At 5 weeks of age, due to persistent poor weight gain, several formula changes were attempted—including those aimed at increasing caloric density and managing potential gastroesophageal reflux. Despite these adjustments, the parents reported ongoing feeding difficulties, and the child was referred to our clinic for further evaluation.

Upon admission, the child had normal hemodynamic and respiratory parameters. His body weight was 3.58 kg (<P3), height was 53.5 cm (<P3), and head circumference was 36.5 cm (<P3) (Figure 1). Clinical examination was unremarkable except for plagiocephaly. Notably, there were no signs of dehydration, irritability, lethargy, or other neurological abnormalities.

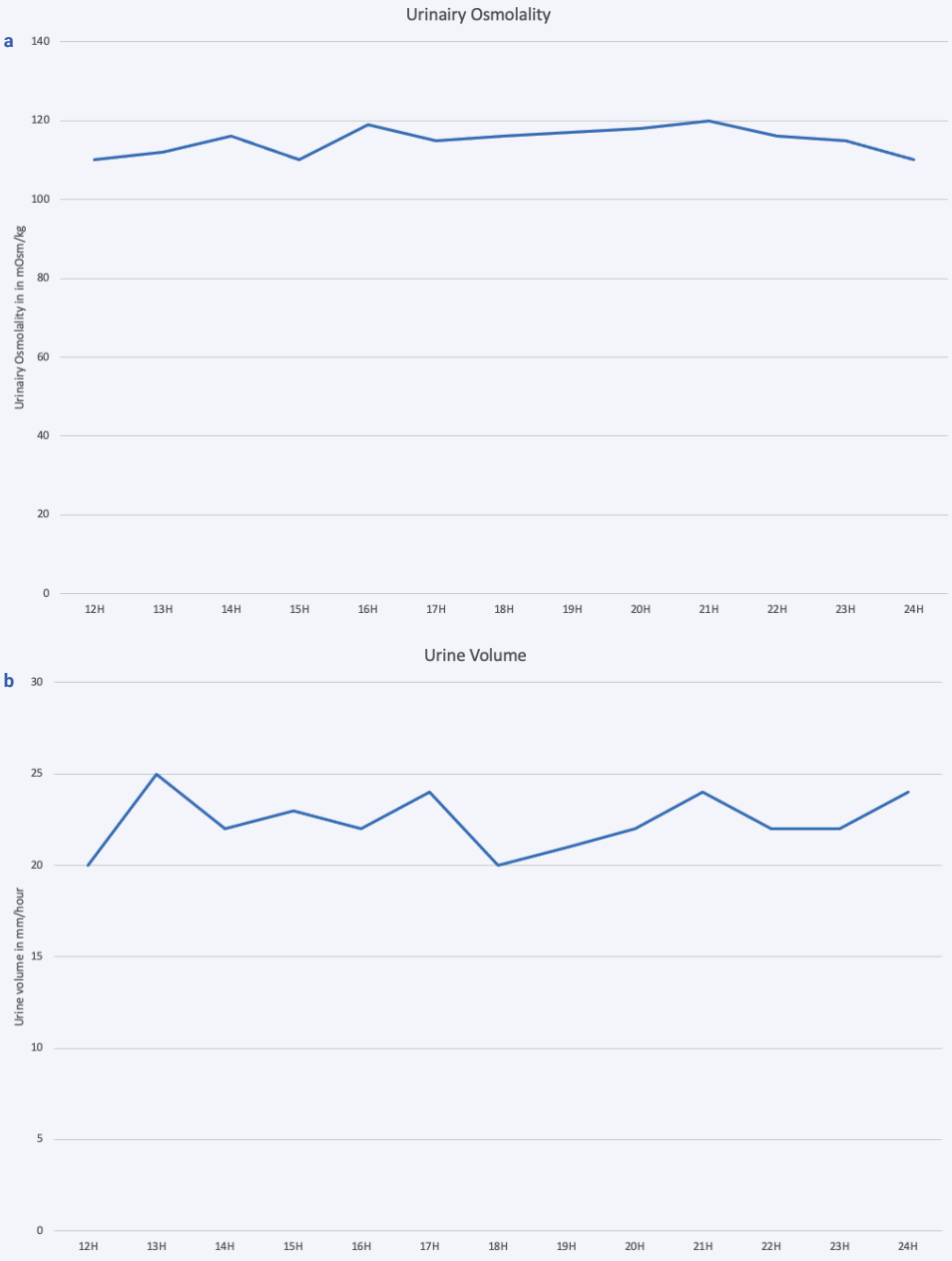
A series of investigations was performed because of persistent poor weight gain and reduced appetite.

Laboratory findings revealed severe hypernatremia (162 mmol/L [N 130-145]) and hyperchloremia (126 mmol/L [N 97-108]), with a corresponding elevated serum osmolality (317 mOsm/kg [N 275-295]). Urine osmolality was markedly decreased (115 mOsm/kg), demonstrating a clear dissociation between concentrated plasma and diluted urine. The association of polyuria (>8 mL/

kg/h), significant hypernatremia, and inappropriately low urine osmolality raised the suspicion of diabetes insipidus. Abdominal ultrasound showed normal-sized kidneys with preserved corticomedullary differentiation and no pelvic dilatation. Heart and brain ultrasounds were normal. The metabolic assessment—including serum creatinine, bicarbonate, and glucose—was unremarkable, confirming preserved renal function and excluding other common metabolic disorders.

A DDAVP (desmopressin) trial (administered as an intranasal spray at a dose of 10 µg) was conducted to differentiate between central and nephrogenic diabetes insipidus (12). DDAVP is a synthetic analogue of arginine vasopressin (AVP) that selectively stimulates type 2 receptors in the kidney, without activating type 1 receptors involved in vascular vasoconstriction. As shown in Figure 2, the child's weight, blood pressure, urine output, serum osmolality, urine osmolality, and serum sodium levels remained unchanged during the 8 hours following administration.

FIGURE 2 a, b: Results of laboratory examinations before and after administration of desmopressin (administered as an intranasal spray; the time of administration is indicated by the arrow). We show via these figures that urinary osmolality (a) and urinary volume (b) remain unchanged after the administration of desmopressin. Plasma osmolality remained stable throughout the test (data not shown).



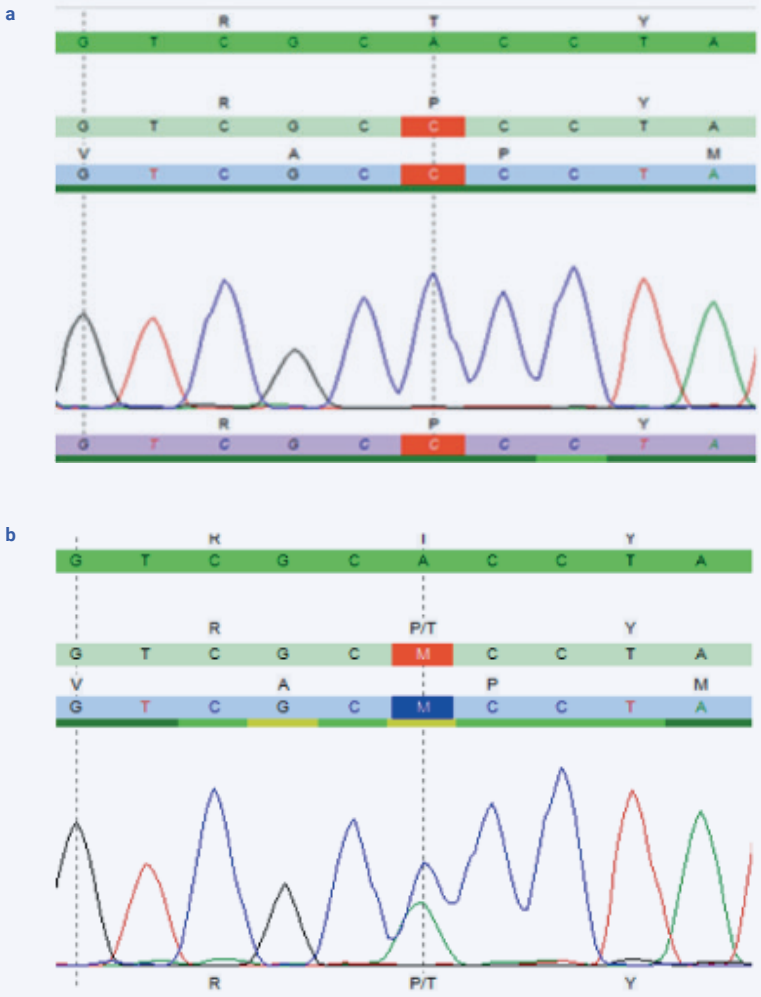
Exome sequencing identified a hemizygous A>C substitution at nucleotide 610 in the *AVPR2* gene (Figure 3), resulting in a missense variant : threonine was substituted by proline at amino acid position 204 (Thr204Pro). This variant was initially classified as a variant of uncertain significance (class 3), but given the strong clinical phenotype and elevated copeptin levels, it can be considered likely pathogenic. This interpretation aligns with ACMG criterion PP4 applied at a moderate level. Given the phenotype and the very high serum copeptin level (294 pmol/L, which—although not pathognomonic—supports the diagnosis in the context of hyperosmolality and hypotonic urine, reference range: 1–28.2 pmol/L), the variant is considered likely pathogenic in this context. Although copeptin thresholds >21.4 pmol/L are validated in adults for diagnosing nephrogenic diabetes insipidus, pediatric reference data are limited (12). Further studies are needed to assess the reliability of copeptin in infants. The authors encourage further research into the utility of plasma copeptin in pediatric diagnostic workups.

In silico analysis using polymorphism prediction tools such as PolyPhen was not conducted but could further support pathogenicity evaluation. Early genetic testing is essential not only to confirm the diagnosis and guide management, but also to enable genetic counseling and family planning. Maternal analysis demonstrated a healthy heterozygous carrier status.

The therapeutic approach consisted of gradually correcting hypernatremia using free water administered via a nasogastric tube. Gradual correction is important to avoid rapid shifts in serum sodium that may lead to cerebral edema. Enteral administration is preferred over intravenous hydration when possible. After confirming the diagnosis through lack of response to DDAVP, oral hydrochlorothiazide (1 mg/kg/day) was started. At discharge, the patient was prescribed 60 mL of oral water three times daily and continued hydrochlorothiazide therapy. Prior to treatment, the patient had a urine output estimated at approximately 10–12 mL/kg/h, based on diaper weight and fluid balance records. Following the initiation of hydrochlorothiazide and fluid management, urine output progressively decreased to 4–5 mL/kg/h, remaining within a physiologically acceptable range for age (generally considered <4–6 mL/kg/h in infants). Although urine osmolality was not re-measured during follow-up, the progressive weight gain, normalization of serum sodium (from 162 to 141 mmol/L), and reduction in fluid intake requirements (from 300 to approximately 140 mL/kg/day) support the effectiveness of the therapeutic strategy. These objective markers were used to define clinical improvement and therapeutic response in this case.

FIGURE 3 a, b: Sequencing analysis for AVPR2.

3a: Sequencing analysis shows hemizygous mutation in children (reference = A (green line), child = C). 3b: Sequencing analysis of the mother shows a heterozygous mutation (reference = A (green line), mother = M, i.e. mixture of C and A).



The patient's clinical course was marked by slow but steady improvement. He did not show dramatic catch-up growth, but progressively—though with difficulty—reached the 1st percentile for weight. Head circumference and length also increased gradually over time, following a consistent upward trend on the growth chart.

The clinical course was marked by gradual weight gain, eventually reaching the third percentile. At 7 months of age, he required hospitalization for a COVID-19 infection, which was managed without major complications. Due to persistent feeding refusal and inadequate oral intake, a nasogastric tube was placed at 16 months of age to ensure sufficient caloric and fluid intake. Hydrochlorothiazide therapy was continued and progressively adjusted according to the patient's weight gain and indomethacine was added.

Literature Review and Discussion

Pathophysiology

The kidneys play a crucial role in regulating urine concentration in response to vasopressin (antidiuretic hormone, ADH), which is produced by the hypothalamus and released by the posterior pituitary gland. Vasopressin release is primarily triggered by increased plasma osmolality or decreased blood volume. It acts by binding to V2 receptors on the basolateral membrane of cells in the distal tubules and collecting ducts. Vasopressin binding activates G-protein–coupled receptors, stimulating adenylate cyclase to convert ATP into cyclic adenosine monophosphate (cAMP). This increase in cAMP activates protein kinase A (PKA), which phosphorylates aquaporin-2 (AQP2) water channels.

Phosphorylated AQP2 is then translocated to the apical membrane of the principal cells in the collecting duct, allowing water reabsorption from the tubular lumen. This mechanism concentrates the urine and conserves body water (1,3,4,5,12).

Variants in *AVPR2* or *AQP2* impair this vasopressin-mediated signaling cascade, resulting in reduced water reabsorption and the characteristic polyuria and polydipsia observed in congenital nephrogenic diabetes insipidus (NDI) (3,12).

Clinical Manifestations

The hallmark features of congenital NDI include polyuria, polydipsia, dehydration, and electrolyte imbalances. Infants typically present with failure to thrive, irritability, and recurrent dehydration episodes. Excessive urination can lead to electrolyte disturbances such as hypernatremia, hyperchloremia, metabolic acidosis and urinary tract dilation. The correlation between genotype and phenotype is crucial to understand ow genetic variations can influence the severity of conditions related to water reabsorption and vasopressin responsiveness. In cases where there is a genetic variant affecting the aquaporin channels or vasopressin receptors, the degree of impairment in water reabsorption can lead to varying phenotypic expressions, such as different levels of polyuria or dehydration (2,3,12).

Diagnostic Challenges

Diagnosing congenital NDI is challenging due to its rarity and clinical overlap with other causes of polyuria and polydipsia. Key diagnostic tests include measurements of serum and urine electrolytes, serum and urine osmolality, and responsiveness to desmopressin or AVP, which can also be used in infants. If needed, a water deprivation test may be performed, although it carries risks and requires strict monitoring. Copeptin measurement is highly specific and can aid in the diagnosis, but it is not routinely available and should not delay clinical decision-making. Genetic testing for *AVPR2* or *AQP2* variants confirms the diagnosis of congenital NDI (5,7,12).

Identifying polyuria in neonates can be particularly difficult, especially in the context of poor weight gain. While gastroesophageal reflux disease (GERD) is a common differential diagnosis in infants with poor weight gain, it is not a cause of polyuria. Therefore, it is crucial to distinguish between poor weight gain related to feeding issues and that due to pathological water loss. Other causes of neonatal polyuria to consider include uncontrolled diabetes mellitus, central diabetes insipidus, post-obstructive diuresis, Bartter syndrome, osmotic diuresis due to hyperglycemia or hypercalcemia, and increased intake of fluids.

Management Strategies

Management aims to correct dehydration, maintain electrolyte balance, and reduce polyuria. Initial treatment involves rehydration with oral or intravenous fluids and correction of electrolyte abnormalities (6,8). The use of free water via a nasogastric tube helps balance more complex cases, as was the situation with

this patient. Thiazide diuretics, amiloride, and nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce urinary output by enhancing water reabsorption in proximal and distal tubules (6,9).

In this case, oral hydrochlorothiazide therapy combined with a low-salt diet was initiated immediately after diagnosis, leading to normalization of urine volume and laboratory parameters.

Nutritional management is essential to reduce renal osmotic load and consequently minimize urine output. Since maximal urine osmolality is impaired in NDI, urinary volume is mainly dependent on solute intake — particularly dietary salt and protein. During infancy, feeds should provide a low renal osmotic load (around 15 mOsm/kg/day) to reduce polyuria, support feed tolerance, and promote growth. A simplified formula is commonly used in clinical practice to estimate the renal osmolar load:

Renal osmolar load (mOsm) = [Protein intake (g) × 4] + [2 × (Na^+ + K^+ in mmol)] (12).

Beyond infancy, salt control can be gradually relaxed, moving toward a reduced-salt or "no added salt" diet by the age of 2 years. Strict salt restriction is not required and may impair growth, as sodium plays a key role in cellular proliferation, protein synthesis, and overall development. Salt tolerance varies individually and is often self-regulated by the child to avoid complications such as polyuria or nocturnal enuresis.

Protein intake should meet the recommended daily allowance to support normal growth. Excessive restriction should be avoided as it may compromise nutrition; however, in children with problematic polyuria, a moderate adjustment toward the theoretical minimum protein requirement (based on age or height-age) may be beneficial (12).

Though typically classified as diuretics, thiazides paradoxically reduce polyuria in NDI by inducing mild hypovolemia, which enhances proximal tubular reabsorption of sodium and water via aquaporin-1 (AQP1).

Amiloride is not a first-line treatment but can be added when thiazide-induced hypokalemia occurs. It enhances proximal sodium and water reabsorption similar to thiazides and helps reduce potassium loss.

Prostaglandin synthesis inhibitors—such as indomethacin—not only enhance water permeability and reabsorption in the collecting duct by reducing prostaglandin interference, but also promote proximal sodium and water reabsorption through inhibition of COX-1 and COX-2 pathways. These dual effects contribute to the overall reduction in polyuria.

In summary, both amiloride and NSAIDs can potentiate the effect of thiazides by increasing proximal sodium reabsorption and thereby reducing polyuria (1, 9, 10).

New therapies are currently under investigation, including gene therapy, pharmacological chaperones, and cell-based therapies (11). Advances in genomic sequencing and precision medicine may enable individualized treatment approaches based on the patient's specific genetic variant profile (11).

Ongoing monitoring of growth parameters, urine output, fluid intake, electrolyte levels, kidney function, and renal ultrasound to rule out urinary tract dilatation is essential to assess treatment efficacy and adjust management accordingly.

Prognosis

Compliance with treatment and regular follow-up visits are essential for managing congenital nephrogenic diabetes insipidus (NDI). This condition can lead to significant challenges, including dehydration and electrolyte imbalances, which may impair growth and neurodevelopment, particularly in early childhood.

Lifelong management is often required, as current treatments primarily aim to reduce polyuria and maintain fluid and electrolyte balance rather than correct the underlying defect in water reabsorption. However, it should be noted that pharmacological treatment—typically with thiazide diuretics, amiloride, and NSAIDs—may be tapered or discontinued over time, especially as children become better able to regulate their own fluid intake and avoid dehydration.

Close medical supervision remains important to detect and prevent potential complications, such as urinary tract dilatation due to chronic high urinary flow rates.

By adopting a proactive, age-adapted management strategy and ensuring continuous monitoring, caregivers and healthcare providers can support optimal long-term outcomes for children with congenital NDI

Conclusion

Congenital nephrogenic diabetes insipidus is a rare genetic disorder characterized by impaired renal response to vasopressin, leading to polyuria, polydipsia, and electrolyte imbalances. Early diagnosis, appropriate management, and long-term follow-up are crucial to improve outcomes and quality of life of affected individuals. This clinical case supports the pathogenic significance of a hemizygous A>C transition at nucleotide 610, resulting in a missense Thr204Pro variant in the *AVPR2* gene.

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