Nephrogenic diabetes insipidus in children (Review)

CARMEN DUICU[1], ANA MARIA PITEA[1], OANA MARIA SĂSĂRAN[2], IULIA COZEA[1], LIDIA MAN[1] and CLAUDIA BĂNESCU[3]

Departments of [1]Pediatrics, [2]Pediatric Cardiology and [3]Genetics, 'George Emil Palade' University of Medicine, Pharmacy, Sciences and Technology, 540142 Târgu Mureş, Romania

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Abstract. Nephrogenic diabetes insipidus (NDI) is characterized by impaired urinary concentrating ability, despite normal or elevated plasma concentrations of the antidiuretic hormone, arginine vasopressin (AVP). NDI can be inherited or acquired. NDI can result from genetic abnormalities, such as mutations in the vasopressin V2 receptor (*AVPR2*) or the aquaporin-2 (AQP2) water channel, or acquired causes, such as chronic lithium therapy. Congenital NDI is a rare condition. Mutations in *AVPR2* are responsible for approximately 90% of patients with congenital NDI, and they have an X-linked pattern of inheritance. In approximately 10% of patients, congenital NDI has an autosomal recessive or dominant pattern of inheritance with mutations in the *AQP2* gene. In 2% of cases, the genetic cause is unknown. The main symptoms at presentation include growth retardation, vomiting or feeding concerns, polyuria plus polydipsia, and dehydration. Without treatment, most patients fail to grow normally, and present with associated constipation, urological complication, megacystis, trabeculated bladder, hydroureter, hydronephrosis, and mental retardation. Treatment of NDI consist of sufficient water intake, low-sodium diet, diuretic thiazide, sometimes in combination with a cyclooxygenase (COX) inhibitor (indomethacin) or nonsteroidal anti-inflammatory drugs (NSAIDs), or hydrochlorothiazide in combination with amiloride. Some authors note a generally favorable long-term outcome and an apparent loss of efficacy of medical treatment during school age.

Correspondence to: Dr Carmen Duicu, Department of Pediatrics, 'George Emil Palade' University of Medicine, Pharmacy, Sciences and Technology, 38 Gheorghe Marinescu Street, 540142 Târgu Mureş, Romania
E-mail: duicucarmen@yahoo.com

Abbreviations: AQP2, aquaporin-2; AVP, arginine vasopressin; AVPR2, vasopressin V2 receptor; CDI, central diabetes insipidus; COX, cyclooxygenase; NDI, nephrogenic diabetes insipidus; NSAIDs, nonsteroidal anti-inflammatory drugs; PRSL, potential renal solute load; PSA, potassium-sparing agents; UOP, urine output; FENa, fractional excretion of sodium

Key words: nephrogenic diabetes insipidus, children, polyuria, polydipsia, nephrogen, inherited

Contents

1. Introduction

Nephrogenic diabetes insipidus (NDI) can be inherited or acquired. NDI is characterized by a lack of ability to concentrate urine regardless of normal or increased plasma concentrations of the antidiuretic hormone, namely arginine vasopressin (AVP). This incapacity of the late distal tubules and collecting ducts to respond to AVP results in defective urine concentration causing polyuria and polydipsia, leading to severe dehydration and electrolyte imbalance (hypernatremia and hyperchloremia) (1,2).

In the last two decades, major research endeavors have been conducted in the attempt to understand NDI at the genetic, cellular, molecular, and biological levels and to propose new therapeutic strategies for NDI (3).

In the pediatric population, NDI is more frequent than central diabetes insipidus (CDI) (4). In children, both forms of NDI, hereditary (congenital) and acquired, are encountered. Congenital NDI is a result of a mutation in vasopressin V2 receptor (*AVPR2*) or aquaporin-2 (*AQP2*) genes. The *AVPR* gene encodes the vasopressin V2 receptor while *AQP2* encodes the aquaporin-2 (AQP2) water channel. X-linked NDI represents 90% of congenital cases with an incidence of 4 cases in 1 million male births. In the remaining 10% of cases, congenital NDI has an autosomal dominant or recessive inheritance pattern with mutations in the aquaporin-2 (*AQP2*) gene (2,3-7). The inherited form of NDI is less frequent in children. Only a few clinical data on long-term outcomes exist (8).

The first report of the *AVPR2* gene was presented in 1992 (9), while its association with NDI was documented in the same year by van den Ouweland *et al* (10). To date, around 280 mutations in the *AVPR2* gene in association with NDI have been reported (Human Gene Mutation Database) (11). Mutations in the *AVPR2* gene leading to X-linked NDI can be classified as a 'loss-of-function' mutation.

In humans, the *AQP2* gene encodes a 271-amino acid protein and is mapped on chromosome 12q13. Up to now, 65 mutations in the *AQP2* gene have been described to cause NDI (11). Severe forms of NDI are a consequence of *AQP2* mutation or loss-of-function of *AQP2* (12).

Significant variability has been observed in the severity of the disease. The clinical appearance varies widely from mild symptoms to severe neurological manifestations (3). The hereditary forms are more severe than acquired forms. In these forms, symptoms usually appear shortly after birth leading to early diagnosis within the first year of life (3).

The cardinal clinical manifestations of the disease are polyuria with hyposthenuria and polydipsia. In children, a urine output (UOP) >2 liters/m^2/day defines polyuria (6,13). This may be evaluated also as UOP/body weight (ml/kg/day) that differs by the age of a child as listed in Table I (6). In extremely severe forms, a UOP of 1 liter of urine every hour may be recorded (14).

In infants and toddlers, the main symptoms at presentation are growth retardation, vomiting or poor feeding, retching, unexplained fever, lethargy or irritability, excessive thirst (polydipsia), excessive urine production (polyuria), excessive urination during the night (nocturia), or bedwetting at night (nocturnal enuresis), potentially severe or life-threatening dehydration and electrolyte imbalance (hypernatremia and hyperchloremia) (4,7,15,16).

An inappropriate weight gain and linear or downward growth are encountered in these children due to their preference for water that results in reduced intake of nutrients. Some authors stated that DI should be included in the pediatric list of differential diagnosis of failure to thrive or growth retardation (17). Sometimes, growth hormone deficiency is also encountered in these children (6).

Without treatment, most patients will fail to grow normally, and present with associated constipation, urological complications such as megacystis, trabeculated bladder, hydroureter, and hydronephrosis, urinary tract infections, enuresis, chronic kidney disease, or rarely urinous peritonitis (1,16,18,19).

Irreversible brain damage and cognitive deficit secondary to electrolyte imbalances may be present. These children may also present psychological and/or behavioral problems because of the continued need for drinking and frequent voiding. Furthermore, seizures and cerebral calcifications have been reported (8,16,19). An influenced life-quality and reduced ability to participate in social activities are noted (18).

In some cases, clinical features may not be so severe and they are underestimated. Teenagers and young persons with NDI may also develop postural hypotension (20-22).

Acquired NDI, found more frequently in adults, is a result of electrolyte disturbance, kidney disease, or a side effect of pharmacological treatments. Almost 30 agents are considered to be the cause of drug-induced NDI, including psychotropic, chemotherapeutic, and antimicrobial agents. NDI can be acquired at any time (2,3,5,6). A particular group of NDI is represented by those who do not have acquired NDI but, rather, NDI due to secondary genetic disease, similar to patients with renal disorders as well as in the context of autoimmune disease (Sjögren's syndrome) (13,23). A list of potential etiologies of acquired and secondary NDI is presented in Table II.

2. Diagnosis

The suspicion of NDI is based upon the identification of characteristic symptoms, specifically polyuria and polydipsia. A complete clinical assessment, detailed case history, and family medical history, as well as specific tests, are necessary to confirm the diagnosis.

In neonates and infants, the main theme should be early phenotypic and genetic recognition. Therefore, in the presence of mild fever, feeding intolerance, irritability and later, an increased appetite (polydipsia), polyuria plus modified laboratory tests (persistent hypernatremia, increased plasma osmolality, low urine osmolality, low FENa levels) as well as a positive family history, inherited NDI should be suspected (13,23,24).

3. Clinical testing and workup

Blood, urine samples, and urine collection for 24 h are necessary for diagnosis. The disease is characterized by high plasmatic osmolality and low urinary osmolality. When diabetes insipidus (DI) is suspected, laboratory workup should include: Early morning measurements of serum electrolytes (sodium, potassium, calcium), glucose, creatinine, and blood urea nitrogen, serum osmolality, urine osmolality, urine analysis, and antidiuretic hormone level (6).

A cardinal finding in all cases of DI is urine concentration defect. Also, urine analysis displays a hyposthenuric gravity of 1,000.

A water deprivation test may be required to differentiate between the various causes of DI or to distinguish between individuals with complete or partial NDI. The water deprivation test is the gold standard in differentiating between NDI, central DI, and compulsive water drinking or psychogenic polydipsia (6), but dehydration tests are often unnecessary and could be dangerous if plasma sodium is higher than 146 mEq/l. If concomitant hypernatremia and hyposthenuria are present the water deprivation test is not required (25).

Dilute urine with an osmolality of <200 mOsm/kg and serum osmolality >300 mOsm/kg is a diagnostic indicator for NDI (6,26). In addition, the vasopressin or 1-deamino-8D-arginine vasopressin (dDAVP) test is necessary to differentiate between CDI and NDI (19). NDI is characterized by a lack of response to the vasopressin test (low urine osmolality <200 mOsm/kg H_2O and low urine gravity). Summary of laboratory results characteristic for NDI are: UOP >4 ml/kg/h, serum sodium >170 mmol/l, serum osmolality >300 mOsm/kg, urine osmolality <300 mOsm/kg, and a urine specific gravity <1,005 (23).

High plasma vasopressin levels indicate NDI while lower levels indicate CDI. Due to the short half-life of AVP, it makes it difficult to be measured (23). Copeptin (CT-proAVP) has proven to be a more stable marker of AVP (23). Therefore copeptin levels may be measured as a further confirmation of the diagnosis. Some authors have doubts regarding the usefulness of this test in the differential diagnosis of DI (3), but it may differentiate it from primary polydipsia (24).

The ultrasound assessment is required to rule out primary renal disorders and to detect any pelvis, ureter, or bladder abnormalities (1). Periodic long-term nephrologic and

Table I. Urinary output to assess polyuria (according to age).

Age groups	Diuresis (ml/kg/day)
Neonates	150
Up to 2 years	100-110
Older children (>2 years)	40-50

ultrasound monitoring should be performed as aproximately 50% of cases may develop flow uropathy, ensuring early detection of urological abnormalities (8). An up-to-date study found a high incidence of urologic complications (one-third of cases), and chronic kidney disease stage 2 or higher (>25% of cases) in children with congenital NDI (16).

Adequate therapy can lead to an improvement in renal tract dilation even after a short period (8).

In all cases with a history of family DI, a genetic investigation should be performed. Neonates or infants presenting with DI symptoms should be checked for mutations in either the *AVPR2* or *AQP2* genes. In inherited forms of NDI, genetic counseling should be offered for affected individuals and their families. A known gene mutation allows early diagnosis by prenatal genetic testing for subsequent pregnancies and genetic counseling for family members of cases with NDI (8,27,28). Although the majority of NDI patients have mutations in the previously discussed gene, nearly 2% do not, and the genetic cause of NDI in these patients is not known (14).

4. Treatment

Lifestyle and dietary management. Inherited NDI is difficult to treat. A multidisciplinary team (pediatrician, nephrologist, endocrinologist, and nutritionist) is required to supervise a child with NDI (2,16).

Management of NDI is challenging with available symptomatic treatment, based on low-solute diet, diuretics, and prostaglandin inhibitors, as they simply reduce symptoms and complications. Recent potential therapies that may improve the management of these patients have been proposed (3,7,15).

NDI management starts with teaching the patient and caregivers about the disease and its therapies. The therapeutic aims are to reduce polyuria and polydipsia so that the patient has normal growth and a normal lifestyle (8).

Dehydration and electrolyte disorders must be avoided. Proper hydration by adequate water intake is required for patients with NDI. Therefore, free access to water should be provided, this being a challenge in infants and toddlers. It is crucial in the case of inadequate water supply or intake, febrile illness or gastroenteritis, hot weather, episodic losses of free water, or in the case of surgery (7).

In the case of persistent growth failure and no evidence of catch-up growth, the indication for tube feeding or gastrostomy should be considered (8,16).

For constipation, a regular intake of laxatives should be prescribed for these patients (7).

When appropriate treatment is initiated in time, most children with NDI will recover their initial weight loss while urine output is decreased. Early recognition and treatment assure normal intelligence and development. Lejarraga *et al* reported in their paper a favorable response to treatment consistent with catch-up growth (17).

In addition, a recent study reported improvement in dilation of the urinary tract with early treatment of NDI (1).

In the case of inappropriate oral intake and hypernatremia, losses should be replaced with glucose 5% in water or intravenous hypo-osmolar fluids concerning the patient's serum osmolality (20). The fluid replacement should be given slowly, trying to reduce serum sodium by 0.5 mEq/l (0.5 mmol/l) every hour and to prevent hyperglycemia, volume overload, brain edema, and rapid correction of hypernatremia. Admittance in intensive care units should be considered to provide careful monitoring (29).

Currently, there is no specific therapy to cure the disease (12,14). Management of NDI can be difficult with only available symptomatic treatment, and it consists of a low-solute (low-salt and low-protein) diet, solute-free fluid intake as well as the use of diuretics and NSAIDs. Additional UOP reduction can be obtained with low-protein restriction (2.0 g/kg per day), but this protein restriction could worsen growth deficiency (1,6). To counteract this deficiency, high calorie foods providing a high caloric value should be recommended. Contrary to this, some authors propose a normal protein diet (2.0-2.5 g/kg per day) (17). As a protein intake of 3 g/kg/day provides around 12 mOsm/kg/day a strictly restricted salt intake is vital in such cases (15).

A diet with an increased calorie to osmolality ratio associated with decreased Na intake (<1 mEq/kg/24 h) is recommended (25). Some authors proposed a regimen of about 15 mOsm/kg/day (15).

In infants, a low-solute diet such as breast milk or low-solute formula is recommended. This diet will enhance the antidiuretic effect of a specific therapy. It is well known that breast milk has a 20-30% lower-solute load compared to standard infant formula but despite all proven valuable advantages, not all infants may benefit from breastfeeding (30). Different potential renal solute loads (PRSLs) for different types of infant formulas are presented in Table III. The addition of protein increases the renal solute load (RSL). PRSL for cow milk is about 3.3 times higher than human milk; for milk-based formulas 1.5-2 times higher while for low-fat and skim milk, 3.5 times higher. Goat's milk has a higher RSL compared to cow's milk. According to Ziegler and Fomon, the maximum PRSL for standard infant formula should be 221 mOsmol/l or 33 mOsmol/100 kcal for healthy infants (31). PRSL represents an important factor in maintaining water balance. The urinary output should be 1.5-2 times the PRSL to ensure optimal kidney function. PRSL has to be calculated in special cases, for diverse food according to a formula proposed by Ziegler and Fomon (31): PRSL (mOsmol/l)= N/28+ mEq/l(Na+Cl+K+P), where N is the dietary nitrogen expressed in milligrams (and N/28 is mmol nitrogenous solutes), or the formula proposed by Nevin-Folino and Miller: PRSL=(4 x protein g/l)+mEq/l(Na+K+Cl) (32).

Pharmaceutical treatments. The approved pharmacologic therapy consists of thiazide diuretics plus potassium sparring agents (amiloride) or prostaglandin inhibitors (indomethacin) (6,7,20,22). Common NSAIDs used in NDI are ibuprofen

Table II. Causes of acquired forms of NDI and secondary NDI.

Drugs	Antibiotic/antifungal/ antiviral therapy	Antineoplastic agents	Metabolic imbalances	Inherited disease/autoimmune disease
Lithium	Demeclocycline	Ifosfamide	Hypokalemia	Acute/chronic renal failure
Orlistat	Ofloxacin	Cisplatin	Hypercalcemia	Urinary tract obstruction
Methoxyflurane	Didanosine	Vinblastine		Sickle cell disease
Colchicine	Cidofovir	Cyclophosphamide		Renal amyloidosis
Sulfonylureas	Foscarnet			Sjögren's syndrome
	Amphotericin B			Cystinosis Bartter syndrome (type 1 and type 2)
				Familial hypomagnesemia with hypercalciuria
				Nephrocalcinosis/cystic kidney disorders: Autosomal dominant polycystic kidney disease/medullary cystic kidney disease
				Bardet-Biedl syndrome, nephronophthisis

NDI, nephrogenic diabetes insipidus.

Table III. RSL for different types of infant formula.

Type of milk feeding	RSL (mOsm/l)
Breast milk	93
Standard formula	135-177
Anti-reflux formula	153
Cow's milk	308
Standard hypoallergenic formula	171
Lactose reduced formula	130-140
Soy-based infant formula	155-160
Preterm baby formula	188-240
Preterm post-discharge formula	188
Amino acid-based formula	194-252
Extensively hydrolyzed protein formula	169-180
Special formula (low mineral content; for impaired renal function)	124-128

RSL, renal solute load.

and indomethacin. The last drug appears to have a superior effect when compared with ibuprofen (2). Ibuprofen may be used in case of difficulties with indomethacin availability. However, these remedies only ameliorate the symptoms of NDI (1,12,18). The treatment aims to reduce the urine outputand polydipsia and thus to restore the intake of appropriate nutrients. Close monitoring and medical follow-up are necessary to recognize and to prevent side effects of these drugs. Pediatric doses and side effects are listed in Table IV. In the beginning, UOP may be decreased using thiazide diuretics and a low-sodium diet (1 mmol/kg/day or to ≤100 mEq/day (2.3 g sodium) or severely sodium-restricted diet (9 mEq/day) (26,31).

Indomethacin, a nonselective cyclooxygenase (COX) inhibitor, in combination with the diuretic thiazide efficiently decreases the UOP more than thiazides alone (2,6). Moreover, the efficiency in UOP reduction for indomethacin is up to 25-50% (2).

The side effects of NSAIDs can be controlled if administered with food or with a proton pump inhibitor, especially for long-term use. Usually, a combination of hydrochlorothiazide and amiloride is recommended, with fewer side effects. Amiloride is necessary to manage the side effects of thiazide diuretics. A new thiazide drug, bendroflumethiazide has been used, with good results (8).

A recent large cohort study confirmed once again that thiazides and potassium-sparing agents (PSAs) are the most commonly used drugs for NDI (74 and 67% respectively). The same study confirmed that thiazides and PSAs represent the most frequent combination therapy (33%), followed by a thiazide plus PSA and NSAID (17%), or thiazide and NSAID (15%), and rarely PSA with NSAID (3%) (16). The same study proposed, as first-line treatment, thiazides in combination with amiloride, with the later addition of NSAID (16).

Selective inhibitors of COX-2 (colecoxib) may be beneficial in patients who can not tolerate indomethacin (7).

All of these drugs prove useful but in addition to a low-solute diet (21).

In situations when the patients do not tolerate common drugs or the results are not adequate, then alternate methods of treatment must be considered. With adequate therapy, a substantial reduction in urine volume, and improvement of dilation is observed (1). Also, severe intellectual impairment can be prevented with adequate treatment (8). Adequate therapy can lead to an improvement in renal tract dilation even after a short period (8).

Currently, treatment for NDI is rather supportive being designed to provide good symptom control and to delay or prevent its many complications (growth failure and mental retardation). A recent study brought to light that there is a reduction in conventional treatment efficiency during school-age (8).

Table IV. Medical treatment options for NDI.

Drug	Dose	No. of doses/day	Side effects
Hydrochlorothiazide	1-3 mg/kg/day	2-3	Hypokalemia Hyperuricemia
Chlorothiazide	10 mg/kg/day	2-3	Hypokalemia Hyperuricemia Hypercalcemia
Bendroflumethiazide	0.08-0.1 mg/kg	2	Hypokalemia Hyperuricemia Hypercalcemia
Amiloride	0.3-0.6 mg/kg/day or 20 mg/1.73 m^2/day	2	Abdominal pain Hyperkalemia
Indomethacin	0.75-2 mg/kg/day	3	Abdominal pain Gastric bleeding
Ibuprofen	20-25 mg/kg/day	2-3	Abdominal pain Gastric bleeding

NDI, nephrogenic diabetes insipidus.

Recent studies discuss new potential therapies for treating patients with NDI. Some of these drugs (metformin, sildenafil, simvastatin, clopidogrel) are commercially available as they are in use for other diseases, where they have excellent safety records. Even if these treatments do not normalize urine output in NDI patients, they seem to represent a therapeutic option, especially in those who have weak responses to common therapies. Some NDI patients may experience a significant reduction in UOP that would result in a remarkable improvement in their life quality and reduce the risk of severe dehydration (14). Recent research appears in contrast to earlier reports and found that only simvastatin influenced urine osmolality, but only in healthy volunteers. These findings should be validated in patients with NDI as well (33). Sildenafil may represent an alternative agent to standard therapy in the treatment of inherited NDI resistant (34). Demopressin may be effective in partial nephrogenic DI cases (35).

New targeted therapeutic molecules have been investigated and proposed to improve the treatment of congenital NDI, but none have proven efficient or reached clinical application yet. The new proposed therapies try to restore the accuracy of protein folding, as several mutations in the *AVPR2/AQP2* gene do not lead to a complete loss of function. For the remaining *AVPR2/AQP2* gene mutation, gene therapy may be the only possible therapeutic strategy (7). Latest therapeutical strategies include chemical chaperones, molecular chaperones, pharmacological chaperones or vaptans; and nonpeptide AVPR2 agonists (7,35,36). Chemical chaperons try to correct the folding of proteins, pharmacological chaperones or vaptans aid to restore receptor plasma membrane expression with effects linked by their affinity for AVPR2 and the *AVPR2* mutation type and site (7,37,38). Other therapeutic strategies are medications that bypass AVPR2 such as statins, cGMP phosphodiesterase inhibitors (sildenafil), sodium nitroprusside, secretin, calcitonin, and prostaglandin receptor agonists (1,12,20). In the future, gene therapy may represent a treatment option for the congenital forms of NDI (26).

Further studies are needed to investigate the dose-effect of different research drugs, duration of treatment, and safety for use in children.

5. Concluding remarks

Despite the lack of curative treatment for inherited NDI, early diet and symptomatic treatment have beneficial effects in providing favorable growth, neurological development, and long-term outcome for these patients. Until new targeted therapies for patients with NDI become available, a global effort is necessary to ensure an early diagnostic and better clinical management of these patients.

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Authors' information

Dr Carmen Duicu: https://orcid.org/0000-0002-8056-1339.

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