Nephrogenic Diabetes Insipidus

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KEYWORDS

• Nephrogenic diabetes insipidus • Polyuria • Vasopressin • Polydipsia • Aquaporin

KEY POINTS

- Nephrogenic diabetes insipidus (NDI) is due to failure of the kidneys to respond to vasopressin, resulting in increased excretion of dilute urine.
- NDI can be congenital (AVPR2 or AQP2 mutations) or acquired.
- Low-solute diet, thiazide ± amiloride diuretics, and prostaglandin inhibitors are currently the mainstay of NDI treatment.
- Novel therapies for NDI, including molecular chaperones, are under investigation in animal models, but there are limited data in clinical studies.

Nephrogenic diabetes insipidus (NDI), the clinical triad of polyuria, polydipsia, and hypernatremia,[1] results from the physiologic inability to concentrate urine due to failure of the kidneys to respond to antidiuretic hormone (ADH; and also named arginine vasopressin or AVP), resulting in increased excretion of dilute urine. This review focuses on the diagnosis of NDI, the various causes, treatment options, and future perspectives.

PATHOPHYSIOLOGY

Vasopressin is produced by the paraventricular and supraoptic nuclei of the hypothalamus and is then secreted from the posterior pituitary gland, in response to elevations in plasma osmolality or hypovolemia. The osmotic threshold for ADH or vasopressin release is a plasma osmolality of about 280 to 290 mOsmol/kg[2]. Above this threshold, there is a progressive increase in vasopressin secretion.

The target of vasopressin is the V2 receptors (V2R) located at the basolateral membrane of the principal cells of the collecting duct, which is the site of renal water handling for regulation of approximately 10% of the glomerular filtrate. Once bound, intracellular production of cyclic adenosine monophosphatase (cAMP) increases,

Disclosure Statement: There are no financial conflicts of interests to disclose.
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Pediatr Clin N Am 66 (2019) 227–234
https://doi.org/10.1016/j.pcl.2018.09.006 **pediatric.theclinics.com**

activating cAMP-dependent protein kinase. This activation leads to phosphorylation and trafficking of the aquaporin channel (AQP2), followed by insertion of AQP2 along the apical cell membrane of the collecting duct, thereby allowing water to enter the cell (Fig. 1).[2]

NDI is caused by renal insensitivity to vasopressin, resulting in large volumes of dilute urine with secondary polydipsia. Primary and secondary forms of NDI exist. Congenital defects are more common at the site of the V2R than the AQP2 channel. Acquired NDI is associated with electrolyte abnormalities, obstructive uropathy, and numerous drugs, most commonly lithium[3,4] (Table 1).

DIAGNOSIS

History

NDI must be high on the differential for an infant with frequent wet and heavy diapers. Children with NDI display marked thirst especially for cold water. Infants are often found drinking bathwater or sucking on wet washcloths and may even refuse food and milk or formula in preference of water. Patients with primary NDI will usually present in the first year of life, mostly boys, with failure to thrive and vomiting. In contrast, acquired NDI is much more common in adults than primary NDI.

The definition of polyuria is age specific, and several cutoffs have been defined based on age (Table 2): greater than 150 mL/kg/d for neonates, 100 to 110 mL/kg/d in children up to age 2, and 40 to 50 mL/kg/d in older children.[5] However, children with NDI may present in a state of dehydration and may not have such high urine output.

Laboratory Evaluation

A first morning-specific gravity may be used to estimate the renal concentrating ability. First morning urine sample can be used as a screening test in some polyuric patients, because a concentrated first morning urine (urine specific gravity 1.030) excludes NDI.

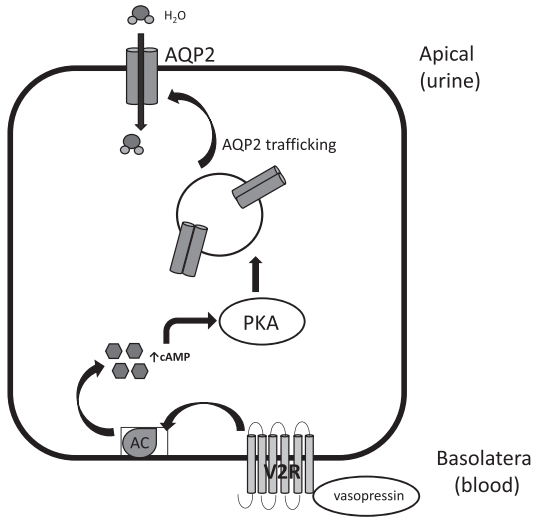

Fig. 1. Mechanism of urine concentration by vasopressin in the collecting duct. Vasopressin binds to V2R, which stimulates a signaling cascade that leads to the insertion of AQP2 channels in the apical side and allows water reabsorption. AC, adenylyl cyclase; PKA, protein kinase.

Table 1
Causes of nephrogenic diabetes insipidus

Congenital	Acquired
X-linked NDI- Xq28 encoding AVPR2 (arginine vasopressin receptor 2)	Antimicrobials: foscarnet, aminoglycoside, methicillin, rifampin
Autosomal recessive NDI- Ch12q13 encoding AQP2	Electrolyte abnormalities: hypokalemia, hypercalcemia, hypercalciuria
	Renal parenchyma disorders, obstructive uropathy
	Other drugs: *lithium*, furosemide, colchicine, cisplatin, isophosphamide, vinblastine
	Systemic disorders: amyloidosis, sarcoidosis, sickle cell disease and trait, Sjögren syndrome

However, specific gravity may be elevated by the presence of proteinuria and glucosuria. Laboratory evaluation must also include serum osmolality and urine osmolality. As hypokalemia and hypercalcemia can be underlying causes for secondary NDI, serum chemistry is also necessary. Diabetes insipidus (DI) is associated with urine that is inappropriately dilute with a urine osmolality less than 300 mOsm/kg in the setting of a serum osmolality greater than 300 mOsm/kg.

A water-deprivation test can be used to establish the diagnosis of NDI if serum osmolality is less than 300 mOsm/kg. If serum osmolality is greater than 300 mOsm/kg in a child with polyuria, the water deprivation test is unnecessary and can potentially be harmful. In these cases, DDAVP (D-amino D-arginine vasopressin) test should be performed to differentiate between central and NDI.

The aim of the water deprivation test is to induce mild dehydration and challenge the kidney to preserve water. This test should be performed in a controlled environment with medical staff and access to frequent laboratory monitoring (**Fig. 2**).[4,6] The test must be stopped if the patient develops greater than 5% loss of body weight or develops any symptoms of hypovolemia. If urine osmolality is greater than 1000 mOsm/kg once or more than 600 mOsm/kg for 2 voids, then the test must be stopped because the patient does not have DI.[3] If the patient has serum osmolality greater than 300 mOsm/kg and urine osmolality is less than 600 mOsm/kg, the child meets criteria of DI and should be given DDAVP to differentiate between central and NDI. A urine osmolality less than 300 mOsm/kg after DDAVP is consistent with NDI.

GENETICS

AVPR2 Mutations

Most cases of primary NDI (90%) is the result of loss-of-function mutation to the V2R, which is encoded by the AVPR2 gene. The gene is located on chromosome region Xq28, and the mode of inheritance is X-linked recessive. Therefore, most patients with NDI are boys, but, as a result of skewed X-inactivation, girls can be affected

Table 2
Definition of polyuria based on age

Age	Urine Output, mL/kg/d
Neonates	>150
Children up to 2 y old	100–110
Older than 2 y	40–50

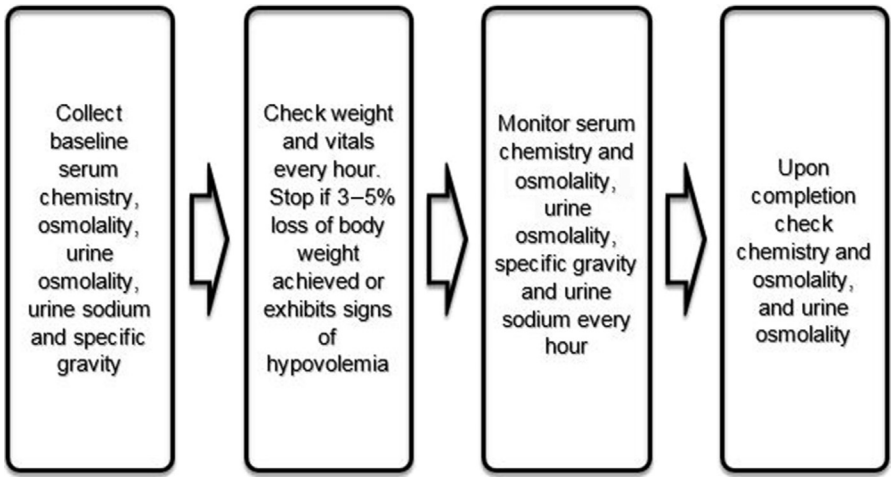

Fig. 2. Water deprivation test. Duration of test: 7 hours in children; 4 hours in infants.

with variable degrees of polyuria and polydipsia. X-linked recessive NDI occurs in about one in 250,000 boys.

AQP2 Mutations

In approximately 10% of patients, congenital NDI is due to loss-of-function mutations in the AQP2 gene, located on chromosome 12. The mode of inheritance is usually autosomal recessive, although a few mutations have been described as autosomal dominant.

Acquired Nephrogenic Diabetes Insipidus

Secondary forms of NDI can be a result of primary disorders, which affect tubular function, such as nephronophthisis, Bartter syndrome, or apparent mineralocorticoid excess. Tubular dysfunction often results in hypokalemia and hypercalciuria, both of which can also be causes of NDI and associated with decreased AQP2 expression.[7] Hypercalciuria can affect the calcium-sensing receptor on the luminal side of the collecting duct and alter AQP2 trafficking, resulting in a urinary concentration defect.[8,9] Other electrolyte abnormalities that can result in NDI include hypercalcemia (Ca >11 mg/dL), and although the mechanism is not completely understood, this may also be associated with activation of the calcium-sensing receptor in the thick ascending limb of the loop of Henle (LOH), thereby reducing sodium reabsorption and calcium reabsorption in the LOH, impairing the medullary osmotic gradient needed for urinary concentration.[10]

Other secondary forms of NDI include obstructive uropathy, which results in downregulation of AQP2 expression. In unilateral obstruction, AQP2 reduction is seen only in the obstructed kidney in animal studies.[11] Downregulation of AQP2 expression can persist up to 30 days after relief of obstruction, which can explain the slow recovery from postobstructive diuresis.[11,12]

Numerous drugs can be responsible for acquired NDI, as listed in **Table 1**. Lithium treatment is the predominant cause of acquired NDI. Lithium enters the cell through epithelial sodium channels (ENaC) with limited transport out of the cells, causing accumulation of intracellular lithium. The exact mechanism of lithium toxicity is

incompletely understood, but data suggest that lithium inhibits adenylyl cyclase in the collecting duct, causing downregulation of AQP2 and diminished water reabsorption.[13] In animal studies, chronic lithium treatment led to epithelial remodeling in the collecting duct and a reduction in principal cells.[14]

Partial Nephrogenic Diabetes Insipidus

Some patients with congenital NDI have a mild phenotype; they present after infancy with normal development, and with symptoms of polyuria or enuresis. Evaluation typically reveals intermediate urine osmolality after DDAVP administration (greater than plasma osmolality, but <800 mOsm/kg), suggestive of partial NDI. However, children less than 3 years of age may not be able to maximally concentrate their urine yet, and values between 500 and 800 mOsm/kg can be physiologic.

Patients with partial NDI typically carry mutations that result in partial function of either AVPR2 or AQP2. More recently, Mamenko and colleagues[15] identified a novel mutation in the STIM1 (stream interaction molecule) gene, and a novel physiologic mechanism via calcium signaling, which results in partial NDI. STIM1 encodes the endoplasmic reticulum (ER) calcium sensor that triggers store-operative calcium entry, which is the mechanism by which ER calcium depletion can lead to prolonged calcium influx to drive changes in cellular processes.[16] STIM1 mutation was associated with decreased intracellular calcium levels, and failure of vasopressin to induce a sustained intracellular calcium mobilization in the collecting ducts, resulting in decreased AQP2 abundance. Animals with STIM1 mutation developed polyuria, polydipsia, elevated serum osmolality, dilute urine, and elevated vasopressin levels.[15]

TREATMENT

General Aspects of Treatment

Treatment of a patient with NDI can be most difficult during infancy, when children are dependent on their caregivers for adequate hydration. Fluids should be offered every 2 hours; feeding per nasogastric or gastrostomy tube is often helpful overnight. When requiring intravenous fluids, hypotonic fluids (1/4 isotonic or 0.22%) are usually appropriate due to ongoing urinary losses of essentially pure water; replacement fluids with higher osmolality than urine osmolality will worsen hypernatremia. For example, in a patient with NDI that has a maximum urine osmolality of 100 mOsm/kg and receives 0.45% saline (which has an osmolality of 154 mOsm/kg = 77 mOsm sodium and 77 mOsm chloride), the patient will need to void 1.54 L of urine for each liter of 0.45% saline received to excrete the osmotic load. Therefore, in patients with NDI, the administration of fluids that are hypertonic as compared with urine (but hypotonic to plasma) can lead to hypernatremic dehydration. However, if there are increased salt losses (ie, diarrhea) or if hypotonic fluids are administered at a rate that is higher than the urine losses, hyponatremia could occur. Isotonic fluids should only be administered for acute intravascular volume expansion in hypovolemic shock, requiring normal saline boluses. Otherwise, 0.9% saline will result in excess sodium chloride administration and worsen hypernatremia.

Low-Solute Diet

Another important component in the treatment of patients with NDI is a reduction of osmotic load, which consists of dietary restriction of proteins and sodium, with the goal of reducing the amount of protein metabolites and sodium to be excreted by the kidney. When urine osmolality is fixed in patients with NDI, urine output is determined by osmotic load or solute excretion, and therefore, the use of a

low-salt, low-protein diet can decrease urine output. In children, minimizing the osmotic load, while providing the recommended caloric and protein intake to enable normal growth and development, can be challenging. A typical Western diet contains an osmotic load of about 800 mOsm per day. An individual with a urine osmolality of 800 mOsm/kg only needs 1 L of water to excrete that load. However, a patient with NDI and a maximum urine osmolality of 100 mOsm/kg needs to void at least 8 L of water for excretion. In addition, 1 g of table salt (17 mmol of sodium) contains an osmotic load of 34 mOsm (17 mOsm sodium and 17 mOsm of chloride). In a patient with NDI and a urine osmolality of 100 mOsm/kg, each gram of table salt increases urine output by 340 mL. A recommended dietary intake for a child with NDI would be an osmotic load of 15 mOsm/kg/d. A child with NDI and fixed urine osmolality of 100 mOsm/kg will need a fluid intake of 150 mL/kg/d to excrete that solute load.

DIURETICS

Thiazides

The use of diuretics in polyuric disorders seems counterintuitive. Thiazides block the sodium-chloride cotransporter (NCC) in the distal convoluted tubule and thus increase sodium concentration and urine osmolality. This increase in salt losses decreases the intravascular volume further, increases an already activated renin-angiotensin-aldosterone system, and decreases the volume of glomerular filtrate. As a result, sodium and water reabsorption increases in the proximal tubule, thereby decreasing volume delivery to the distal nephron and decreasing amount of tubular fluid available to become urine. Thiazides are often the initial medication treatment of NDI, typically hydrochlorothiaze at 2 to 4 mg/kg/d divided in 2 doses. In conjunction with low-solute diet, thiazide diuretics can decrease urine output by as much as 70%.[17]

Amiloride

Hypokalemia is a common complication of thiazide administration, but supplementation with potassium salts increases the osmotic load. Therefore, the combination of thiazide with a potassium-sparing diuretic can be used, amiloride 0.1 to 0.3 mg/kg/d. Amiloride blocks the ENaC, decreasing sodium reabsorption and increasing urine osmolality. Amiloride is also beneficial with lithium-induced NDI, by blocking ENaC, through which lithium enters the cell.

PROSTAGLANDIN SYNTHESIS INHIBITORS

Inhibitors of prostaglandin synthesis, such as indomethacin (1–3 mg/kg/d in 3 to 4 divided doses), can be used in the treatment of NDI. The exact mechanism remains to be elucidated, but typically prostaglandin inhibitors minimize urinary losses by decreasing glomerular filtration rate (GFR), and renal function must be monitored closely. However, experiments in animals and humans suggest that indomethacin increases urine osmolality and reduces water diuresis without affecting GFR and may be independent of vasopressin.[18] Some evidence suggests that binding of prostaglandin E2 to basolateral prostaglandin receptors may inhibit adenylyl cyclase and the shuttling of AQP2 to the apical membrane,[18] thereby reducing water diuresis.[18,19]

Indomethacin can reduce urine output by 25% to 50% more than thiazides alone,[17] but use must be monitored carefully, especially when first initiated. Indomethacin, especially with concomitant use of thiazide, can cause rapid lowering of serum sodium and hyponatremic seizures.[20] Other side effects of indomethacin include abdominal pain or gastric bleeding, which can be reduced with the use of H2 blocker or proton pump inhibitor.

NOVEL TREATMENTS

Acetazolamide/Lithium-Induced Nephrogenic Diabetes Insipidus

Discontinuation of lithium therapy can resolve the symptoms of NDI, but this is usually not an option because the beneficial effects of lithium on the psychiatric condition outweigh the complications of NDI on quality of life. In addition to the treatment options previously discussed, recent studies suggest the potential use of acetazolamide for lithium-induced NDI. Thiazides, which inhibit the NCC and are derived from carbonic anhydrase, still reduced polyuria in mice lacking NCC with lithium-induced NDI, suggesting that an additional antidiuretic effect of thiazides may be due to carbonic anhydrase inhibition.[21] In an animal model of lithium-induced NDI, acetazolamide was as effective as thiazide/amiloride in reducing polyuria, increasing urine osmolality and increasing AQP2 abundance, but with fewer side effects. The thiazide/amiloride-treated mice developed hyponatremia, hyperkalemia, hypercalcemia, metabolic acidosis, and increased serum lithium concentrations, which were not observed in the acetazolamide-treated mice.[21,22] Reduction in polyuria after acetazolamide treatment was partially caused by a tubular-glomerular feedback response and reduced GFR. Case reports in adult patients with lithium-induced NDI have shown promising results with acetazolamide treatment: decreased urine output, increased urine osmolality without major side effects,[23] but further studies are still needed to assess the safety of acetazolamide, especially in patients with reduced GFR.

FUTURE PERSPECTIVES

Molecular Chaperones

Multiple novel therapies, including mutation-specific treatment, are being examined to improve NDI treatment. Most mutations identified in the AVPR2 gene lead to the improper folding of V2R with entrapment in the ER and preventing their function at the plasma membrane. Retention of V2R is dependent on ER calcium stores for optimal function. By inhibiting the sarcoplasmic calcium pump and depleting ER calcium stores, the mutated V2R can overcome entrapment, as demonstrated in vitro.[24] Other promising treatments that have been successful in vitro include the use of molecular chaperones, or AVPR2-receptor antagonists, that can bind to the mutated V2R, and induce proper folding of the receptor, leading to release from the ER.[24–26] The use of this receptor ligand, or pharmacologic chaperone, has been studied in small trials in vivo. Although the reduction in urine output and increase in urine osmolality were modest,[25] the potential use of a targeted, mutation-specific therapy for patients with congenital NDI appears promising.

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