Back to Basics: Congenital Nephrogenic Diabetes Insipidus
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CONGENITAL NEPHROGENIC DIABETES INSIPIDUS

Michael A. Linshaw, MD*

Objectives After completing this article, readers should be able to:

1. Recognize the clinical features of congenital nephrogenic diabetes insipidus.
2. Know the different hereditary patterns of nephrogenic diabetes insipidus.
3. Discuss how to evaluate a child who has hypernatremic dehydration in the presence of dilute urine.
4. Describe the nutritional, fluid, and pharmacologic goals of therapy.

Introduction

Diabetes insipidus (DI), the inability under physiologic conditions to concentrate urine adequately, is characterized by the passage of large amounts of very dilute urine, even as the body is threatened with progressive dehydration and circulatory collapse in the presence of severe hypernatremia. Normally, about 10% to 12% of glomerular-filtered volume is reabsorbed along distal nephron vasopressin (ADH)-sensitive sites. Such reabsorption is accomplished by a responsive tubule exposed to ADH that has been secreted by stimulation of osmotic or volume receptors. Both the absence or insufficiency of ADH due to pituitary or hypothalamic dysfunction (central diabetes insipidus [CDI]) or the failure of the kidney to respond adequately to normal or high serum concentrations of ADH (nephrogenic diabetes insipidus [NDI]) can present with similar clinical features, most notably polyuria, polydipsia, and extreme thirst.

The seriousness of such a defect can be illustrated by considering a child who has an actual glomerular filtration rate of 50 mL/min. Failure to reabsorb the expected approximately 5 to 6 mL/min along ADH-sensitive sites would result in the potential loss of 300 to 360 mL/h of fluid or approximately 1 L in 3 hours. With progressive dehydration, the glomerular filtration rate would decline and blunt the fluid loss to some extent, but ensuing volume depletion, hypernatremia from water loss, and renal insufficiency could become life-threatening.

CDI occurs as a result of intracranial lesions; NDI is caused by defects in the renal concentrating process (Table 1). In NDI, congenital X-linked or autosomal inherited forms of DI generally are more severe, although occasional mild phenotypes have been described. This article focuses on congenital nephrogenic diabetes insipidus (CNDI). The family history usually is positive, but generations may be skipped, and cases may occur de novo.

Case Report

A 3,600-g male infant was born following a normal pregnancy and delivery. He was breastfed and appeared healthy, although his height and weight had fallen approximately four growth curves to the 5th percentile by

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4 months of age, at which point he was introduced to formula. He began to vomit several times a day; cried unless given water; soaked 10 to 12 diapers daily; developed hard, pebble-like stools; and was able to suck 12 to 15 wet cloths daily until dry. He took at least 78 oz of fluid a day, with a clear preference for water. Despite dietary changes, he refused solid foods, demanded more water, developed hypernatremic dehydration, and stopped growing. By 8 months of age, his height and weight had fallen well below the 5th percentile.

When referred at 10½ months of age, he was irritable and chronically dehydrated but normotensive. He had dry skin, sunken eyes without skin tenting, slightly moist mucous membranes, and several palpable hard, mobile abdominal masses, presumed to be hard stool. Serum sodium was 155 mEq/L (155 mmol/L), potassium was 5.2 mEq/L (5.2 mmol/L), chloride was 119 mEq/L (119 mmol/L), and bicarbonate was 21 mEq/L (21 mmol/L). Blood urea nitrogen measured 83 mg/dL (29.6 mmol/L), creatinine was 0.8 mg/dL (70.7 mmcmol/L), calcium was 10.4 mg/dL (2.6 mmol/L), and phosphorus was 6.6 mg/dL (2.1 mmol/L). Initial serum and urine osmolalities were 343 and 172 mOsm/L, respectively. After oral rehydration and correction of hypernatremia and azotemia, the patient underwent a water deprivation test. After 12 hours, he had lost 5% of his body weight from persistent polyuria; excreted 326 and 320 mOsm/L, respectively. There was no response to administration of vasopressin. His polyuria continued, and the serum and urine osmolalities rose to 338 and 326 mOsm/L, respectively.

The family preferred to avoid possible adverse effects of pharmacotherapy, and calculations were made to provide adequate calories and water to offset estimated insensible water losses and to allow the relatively low renal solute load to be excreted in urine that had an osmolality of 80 to 120 mOsm/L. Adjustments were made as the child grew. Solid foods were introduced and formula phased out at 15 to 16 months of age. By 24 months of age, his height had reached the 5th percentile, but his weight had increased disproportionately with overzealous feeding. His caloric intake was reduced. (1) With convenient access to water, he regulated his water needs effectively day and night, adjusted well to school, and turned out to be intellectually gifted.

Clinical Features

Children who have CNDI can develop signs in the first weeks after birth, but such signs may not be apparent to parents or practitioners, especially if the baby is breast-feeding, because human milk has a low renal solute load and signs of dehydration may not be appreciated immediately. However, affected infants prefer water, if available, and often are irritable and hard to mollify, demonstrating frequent, almost constant, crying, even in the mother’s arms. They improve dramatically if given water and periodically are febrile without good reason. Clinical findings progress over time, varying with the degree of dehydration (Table 2).

Affected infants have marked polyuria; excrete very dilute urine; develop small, hard, pebble-like stools; fall off growth chart percentiles; and are anxious to suck, although they want to drink, not feed. Given moist towels, they will suck the towels dry. Diapers are saturated, dripping, and heavy and need frequent changing.

Physical findings vary with the degree of dehydration. The serum sodium concentration often is greater than 160 mEq/L (160 mmol/L), with acidosis. The blood urea nitrogen value usually is elevated out of proportion to a high serum creatinine concentration, as is typical of prerenal failure resulting from effective volume depletion. Urine specific gravity or osmolality often is less than 1.005 or 150 mOsm/kg water, respectively, despite hypernatremia.

Mental retardation can result
from repeated episodes of severe hypernatremic dehydration, but is not a fundamental part of the clinical picture. Studies of cognitive function in patients who have CNDI showed that most of the children had normal intelligence. (2)

Large urinary volumes may be associated with nonobstructive hydronephrosis and hydrourerter, sometimes severe. Urinary tract infections, enuresis, daytime incontinence, urinary retention, and traumatic rupture of the urinary tract are potential complications. Dysfunction may be severe enough to resemble a neurogenic bladder. Growth failure is related to inadequate caloric intake because of the constant large fluid intake needed to maintain electrolyte balance. No reliable evidence indicates that growth will be retarded in such children when they are given early and adequate caloric and fluid intake. However, during the early years, before children had ready access to water, extreme diligence was required of caregivers, even with pharmacotherapy, to maintain growth and health.

**Genetic Pathogenesis**

CNDI occurs in X-linked and autosomal recessive and dominant modes of inheritance. Mutations in two different, but functionally related, genes cause clinically similar disease (Table 3). Defects in a gene on the X chromosome encoding the vasopressin receptor 2 (VR2) are carried by females, who can have variable (rarely severe) degrees of polydipsia and polyuria. Males tend to have more serious symptoms. The VR2 is present on basolateral membranes of collecting tubule principal cells. When circulating ADH binds to this receptor, cascading chemical changes (activation of G-protein and adenyl cyclase, generation of cyclic AMP, activation of protein kinase A) ultimately lead to insertion of cytoplasmic water channels (aquaporins) directly into the apical membrane. This occurrence facilitates water reabsorption down an osmotic gradient (see later brief discussion of countercurrent movement of fluid and solutes).

About 90% of children born with CNDI have loss-of-function mutations in the VR2, with more than 180 VR2 gene mutations reported. In most of these mutations, the defective protein is retained in the cellular endoplasmic reticulum and cannot reach the cell membrane. In other mutations, the protein reaches the cell membrane, but cannot bind ADH or activate the G-protein/cyclic AMP chemical cascade.

About 10% of children who have CNDI have defects in the gene encoding the aquaporin 2 (AQP2) ADH-sensitive water channel located on chromosome 12. Most of these patients show autosomal recessive inheritance, with mutant genes causing misfolding of the water channel protein so the channel is trapped in the endoplasmic reticulum, fails to route to the apical membrane, and degrades quickly. Some channel mutations may cause less severe misfolding and may be partly functional, causing less severe polyuria.

In those who have autosomal dominant disease, the least common type of CNDI, the mutation appears to be located in the COOH terminus of the protein. These water channels move to other parts of the cell and are

### Table 3. Pathogenesis and Genetics of Nephrogenic Diabetes Insipidus

<table>
<thead>
<tr>
<th>Mode of Transmission</th>
<th>Gene</th>
<th>Target Site of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-linked</td>
<td>Xq28</td>
<td>Vasopressin 2 Receptor (V2R)</td>
</tr>
<tr>
<td>Autosomal</td>
<td>12q13</td>
<td>Aquaporin 2 (ADH-sensitive) water channel</td>
</tr>
</tbody>
</table>

### Table 2. Clinical Findings in Congenital Nephrogenic Diabetes Insipidus

**Historical Features**
- Failure to thrive
- Extreme thirst
- Unexplained fever
- Irritability
- Constipation
- Impressive polyuria
- Vomiting
- Seizures

**Physical Findings**
- Dry mouth and eyes
- Poor skin turgor
- Sunken eyes and anterior fontanelle
- Mottled skin
- Decreased peripheral pulses
- Low blood pressure
- Multiple abdominal masses/fecaliths

**Laboratory Features**
- Hypernatremia
- Hyperchloremia
- Metabolic acidosis
- Normal potassium concentration
- Hyperuricemia
- High serum and low urine osmolality
retained by lysosomes via the Golgi apparatus, stored in other vesicles, or routed to the basolateral rather than the apical membrane.

Pathophysiology
The Figure illustrates the sequences described in the following section. Fluid filtered at the glomerulus enters the proximal tubule essentially isotonic with serum. Water and solute are reabsorbed isotonically along this segment, but fluid traversing the

Figure. Solute and water transport during the urinary concentrating process. Solid arrows depict active NaCl transport; dashed arrows depict passive transport. Decreased permeability to NaCl, urea, or H2O is illustrated by lack of arrows in the appropriate segment. Low urea permeability in the outer medulla is reflected by lack of arrows for urea, and increased urea permeability from the effect of ADH in the medullary portion of the collecting duct is shown by arrows. Numbers show osmolality in mOsm/kg H2O. Increasing NaCl concentration in the descending limb, caused by removal of H2O from this segment that has low NaCl permeability, is depicted by larger lettering for NaCl. Increasing H2O concentration (dilute urine) in the ascending limb, caused by NaCl transport from this segment that has low H2O permeability, is depicted by larger lettering for H2O. Isotonic reabsorption of NaCl and H2O in proximal and distal tubules to maintain cortical isotonicity is assumed in this illustration. A CCD with its medullary portions from a second nephron (B) is placed between the descending and ascending limbs of nephron A to illustrate more clearly the effect of solute and H2O movement from the CCD on solute and H2O transfer occurring in the limbs. See text for more details. Not illustrated or discussed is a recycling of urea from interstitium to ATL and DTL. ADH=antidiuretic hormone, ATL=ascending thin limb, CCD=cortical collecting duct, DT=distal tubule, DTL=descending thin limb, H2O=water, LH=loop of Henle, NaCl=sodium chloride, PT=proximal tubule, TAL=thick ascending limb.
descending loop of Henle is exposed to an increasing interstitial osmolality largely generated by events occurring in the ascending thick limb. Therefore, it is helpful to consider this tubular segment initially to appreciate development of the corticomedullary osmotic gradient.

The ascending thick limb has an apical membrane Na-K-2Cl cotransporter and an active Na+ pump (basolateral Na+/K+/ATPase). However, its water permeability is low because it lacks water channels. In this segment, salt is reabsorbed in the relative absence of water, resulting in tubular fluid that becomes progressively hypotonic as the surrounding interstitial sodium chloride (NaCl) concentration increases. Fluid reentering the cortex becomes isotonic from continued salt and water reabsorption as it reaches the collecting duct.

In the presence of ADH, the cortical collecting duct is highly permeant to water, but relatively nonpermeant to urea. Therefore, fluid descending the collecting duct loses water osmotically (from a high interstitial NaCl content generated by the thick ascending limb), but the urea concentration increases. By contrast, the medullary collecting duct is highly permeant to both urea and water because it also lacks water channels. Therefore, as fluid enters the thin ascending limb and heads toward the cortex, the interstitial salt concentration is decreasing, favoring reabsorption of salt.

Water does not leave this segment effectively. Lack of water channels accounts for the eventual hypotonicity of urine as it leaves the ascending loop of Henle. However, because of ADH-induced high water and urea permeability of medullary collecting ducts, equilibration of osmolality results in a final urine that has a concentration similar to that of fluid at the bend of the loop of Henle and the deep medullary interstitium. This process translates to a roughly fourfold increase (multiplication) in urinary osmolality, from approximately 300 mOsm/kg in the cortex to approximately 1,200 mOsm/kg or more at the medullary papillary tip by the time a child reaches 1 to 2 years of age.

In older children and adults, approximately 50% of the urinary osmoles are from urea and 50% from NaCl. The urea contribution is considerably less in infants. It is largely in the collecting ducts where the consequences of CNDI are manifest. Reabsorption of the roughly 10% of filtrate handled by this segment depends on the presence of ADH and the ability of collecting tubules to respond to it. In CNDI, hypothalamic synthesis, posterior pituitary storage, and release of ADH are intact, but end-organ resistance to ADH makes the kidney unable to reabsorb adequate water to maintain electrolyte and fluid balance. Mutational defects in the vasopressin receptor (VR2) on the basolateral membrane of collecting duct principal cells, defects in the translation of information once the receptor is stimulated, or a mutational defect in the apical membrane water channel (AQP2) can lead to impaired ability to reabsorb water. The patient in the case report could lose substantial circulating volume and become severely dehydrated quickly.

**Diagnosis**

In the presence of dehydration or hypernatremia, urine should be concentrated and low in volume. Polyuria, dilute urine, and mildly low or low-normal serum sodium concentration are suggestive of psychogenic or maternogenic excessive water intake, but polyuria and dilute urine together with high serum sodium concentration and osmolality indicate lack of, or resistance to, ADH. Acquired forms of NDI rarely cause the degree of polyuria and hypernatremia associated with true CNDI.

Once DI is strongly suspected, a careful water deprivation test should be conducted. One approach is summarized in Table 4. A normal response to water restriction or ADH is a urine osmolality \(\geq 450\) mOsm/kg water and a urine-to-plasma osmolar ratio of \(\approx 1.5\) (usually much more). The response to ADH is blunted in
transient response to ADH. There even may be the urine osmolality not be as severe (urine osmolality 6 to 12 months or even later and may tend to become noticeable after dominance form, the clinical expression usually does not exceed approximately 200 mOsm/kg water. In the dominant forms, polyuria and polydipsia are generally not exceeding approximately 200 mOsm/kg water. In the dominant form, the clinical expression tends to become noticeable after 6 to 12 months or even later and may not be as severe (urine osmolality may be higher). There even may be a transient response to ADH.

Treatment
Treatment is designed to provide: 1) sufficient water to maintain normal electrolytes, 2) low renal solute load to minimize water loss, and 3) adequate calories to support growth. Pharmacotherapy usually is needed.

Water
Infants who have CNDI require a constant supply of water, which should be provided every 2 hours, day and night. When able to retrieve and hold a bottle of water, the infant’s lifetime remains an available bottle of water. There is essentially no risk in providing excess water because there is no problem diluting the urine. Water intake must replace urine output and insensible loss plus water for growth. When provided, the infant drinks what is needed, as will a child who has ready access to a water faucet. It is critical to realize that affected children need multiple liters of fluid a day. Even infants may need 2 to 3 L or more daily.

Renal Solute Load
Because solutes require urinary water for excretion, the more the kidney concentrates urine (the greater the urinary osmolality), the more solutes can be excreted in a given volume. If urine concentrates to 1,000 mOsm/kg of water (normal), the kidney can excrete a solute load of 300 mOsm in 300 mL of urine. However, if urine concentrates only to 100 mOsm/kg of water, excreting 300 mOsm requires 3 L of urine. A huge fluid intake is needed to offset such loss. Therefore, formula for infants who have CNDI should contain adequate calories for growth and minimal solute for excretion by the kidney.

The potential renal solute load, as reviewed by Fomon and Ziegler in 1999, (3) refers to solutes—primarily dietary nitrogen and electrolytes—excreted in urine and not incorporated into new tissue or excreted by nonrenal routes. For clinical purposes, re-

Table 4. Diagnostic Approach

1. Admit to hospital: severe dehydration can occur during water deprivation without careful monitoring.
2. Make sure the patient is adequately hydrated and has normal electrolytes before starting the test.
3. Start the water restriction after breakfast and after the child voids or wets a fresh diaper.
4. Collect baseline specimens of urine and blood for measurement of electrolytes and osmolality.
5. Weigh every 2 h, follow blood pressure and pulse rate, and do not allow more than 3% to 5% dehydration (weight loss).
6. Check each urine specimen for specific gravity (SG) by using a refractometer because the dipstick is not sufficiently accurate. Also, record osmolality and volume (weigh the diaper if an infant).
7. Check serum electrolytes and osmolality at 4 h and again every 2 h as needed.
8. If urine SG reaches ≥1,015 or osmolality ≥500 mOsm/kg water in an infant or ≥1,020 or osmolality ≥600 mOsm/kg water, stop the test and measure blood electrolytes and osmolality. The patient is not likely to have chronic nephrogenic diabetes insipidus. Although a 6-month-old infant usually can concentrate the urine to ≥1,000 mOsm/kg water, the maximally concentrating ability of an infant a few weeks old is closer to 500 to 550 mOsm/kg water.
9. If serum sodium concentration is ≥150 mEq/L (150 mmol/L) or osmolality is ≥300 mOsm/kg water or if weight decreases by 3% to 5%, stop the test and administer 1-desamino-9-D-arginine vasopressin (dDAVP) after obtaining blood for measurement of electrolytes, osmolality, and plasma antidiuretic hormone.
10. Limit the water deprivation to 8 to 12 h (4 to 6 h in an infant) to avoid dangerous dehydration and allow food at an appropriate time. A standard water deprivation test is 18 h, but not in a patient strongly suspected of having true diabetes insipidus.
11. If polyuria persists with dilute urine, administer intranasal dDAVP or desmopressin acetate in appropriate dose (10 mcg for infants, 20 mcg for older children). Replace urine volume thereafter with an equal amount of water to avoid further dehydration, and check urinary concentration and blood electrolytes and osmolality in 4 h (2 h in infants).
12. If there is uncertainty about nasal absorption of dDAVP, vasopressin can be administered intravenously in a dose 10% of the nasal dose (1 mcg in infants and 2 mcg in older children).
nal solute load is composed of urea (from protein), sodium (Na), potassium (K), chloride (Cl), and phosphorus (P). Potential renal solute load in mOsm is quantified by adding the solute load of protein (generally about 4 mOsm/g protein ingested, mostly as urea) to that of Na, K, and Cl in milliequivalents (mEq) and P in mOsm.

The available P is considered to be total P content of milk-based formula and approximately two thirds of soy-based formula because about one third of soy formula P is not absorbed by the bowel. If protein intake is unknown, the clinician can divide the total milligrams of urinary intake by 28 because there are 28 mg of N per millimole (mM) of nitrogen by 28 because there are divide the total milligrams of urinary intake is unknown, the clinician can divide the total milligrams of urinary nitrogen by 28 because there are 28 mg of N per millimole (mM) of urea, and most of the urinary N is excreted as urea. The formula is:

Potential renal solute load = urinary N/28 + Na + K + Cl + available P
(all in mOsm or mM)

For Na, K, and Cl, the number of mOsm equals the number of mEq, respectively. To convert mg to mOsm, divide mg of Na by 23, mg of Cl by 35.5, and mg of K by 39. The mOsm content from P can be calculated by dividing the total number of mg by 31. Fomon and Ziegler estimate potential renal solute load to be 93 mOsm/L or 14 mOsm/100 kcal for human milk, 135 mOsm/L or 20 mOsm/100 kcal for milk-based formula, and 160 mOsm/L or 24 mOsm/100 kcal for one soy formula. (3) An estimate for a second soy formula is slightly higher. A potential renal solute load of 20 to 26 mOsm/100 kcal should be safe, although more can be tolerated if enough water is given. The infant who has CNDI needs the lowest renal solute load that supports normal growth and electrolyte balance.

**Pharmacotherapy**

Several agents in varying combinations may lower urine output, thereby decreasing water needs and facilitating greater caloric intake. Adverse effects of these agents are not common, but must be kept in mind with long-term use of drug therapy (Table 5).

For more than 40 years, thiazides have been known to decrease urine output, paradoxically, in DI. The explanation has been that thiazide decreases Na reabsorption along the distal nephron, leading to additional volume depletion, a decrease in filtration rate, an increase in reabsorption of filtrate along the proximal tubule, and a resultant decreased delivery of filtrate to a defective more distal reabsorptive site. A problem with this explanation is that children who have severe polyuria often are dehydrated with prerenal failure and already should have enhanced this “thiazide-type” response. Nevertheless, they continue to have marked polyuria and progressive dehydration.

Recently, in lithium-induced NDI (a model associated with downregulation of AQP2), thiazide appeared to upregulate both AQP2 and a distal epithelial sodium channel. A similar effect in CNDI could facilitate movement of aquaporin to apical membranes, enhancing the activity of potentially functional water channels. Note that although salt restriction may add to the thiazide effect, stringent salt restriction can cause some children to rebel and receive inadequate caloric intake. A combination of thiazides with amiloride or indomethacin is more effective than thiazide alone in decreasing urine output, but none of these agents reduces urine output to normal, and large quantities of water usually still are needed.

Amiloride, a diuretic that blocks the epithelial Na channel along the cortical collecting tubule, provides additional natriuresis and can offset thiazide-induced hypokalemia through its K-sparing effect. It generally is well tolerated.

Prostaglandins have an inhibitory effect on ADH-stimulated osmotic water permeability of cortical collecting tubules, probably by downregulating AQP2 expression. Indomethacin, a nonspecific cyclo-oxygenase inhibitor, decreases prostaglandin synthesis, attenuates the ADH-inhibiting effect of prostaglandin, and has been used effectively with thiazides to reduce urine output in patients who have NDI. There is evidence that indomethacin increases

**Table 5. Dose and Adverse Effects of Commonly Used Drugs**

<table>
<thead>
<tr>
<th>Thiazide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrochlorothiazide: 1 to 3 mg/kg per day bid</td>
</tr>
<tr>
<td>Hypokalemia</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Alkalosis</td>
</tr>
<tr>
<td>Hypercalcemia</td>
</tr>
<tr>
<td>Hyperglycemia</td>
</tr>
<tr>
<td>Hyperuricemia</td>
</tr>
<tr>
<td>Hepatitis</td>
</tr>
<tr>
<td>Intestinal symptoms</td>
</tr>
<tr>
<td>Bone marrow suppression</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Amiloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg/1.73 m² per day bid-tid</td>
</tr>
<tr>
<td>Hypokalemia</td>
</tr>
<tr>
<td>Headaches</td>
</tr>
<tr>
<td>Gastrointestinal discomfort</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indomethacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 to 2.5 mg/kg per day tid</td>
</tr>
<tr>
<td>Gastrointestinal discomfort</td>
</tr>
<tr>
<td>Headaches</td>
</tr>
<tr>
<td>Renal toxicity</td>
</tr>
<tr>
<td>Hematopoietic adverse effects</td>
</tr>
</tbody>
</table>

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the shuttling of AQP2 channels to the apical membrane of collecting ducts. A more specific cyclooxygenase 2 inhibitor, rofecoxib, has been useful in reducing polyuria in patients who have NDI, but has been associated with cardiac ischemia and potentially is renal toxic. Its use in NDI should be curtailed until questions of its safety are settled.

Although CNDI, in contrast to DI, is resistant to ADH, some patients who have CNDI have a mild phenotype or, even if they have significant polyuria and polydipsia, actually respond to ADH. For example, a family having autosomal recessive CNDI was found to have a valine-to-methionine alteration at amino acid #168 in a transmembrane domain of the AQP2 water channel. This mutation caused marked polyuria and thirst in homozygotes, but 1-desamino-9-D-arginine vasopressin (dDAVP), although causing only modest improvement in urine osmolality, resulted in a subjective improvement in polyuria and thirst. In such patients, the mutant water channel may be partly functional and more able to route to its target apical membrane after ADH.

Some patients who have mutant VP2 receptor proteins also show some response to dDAVP. The type of mutation may dictate the severity of disease and the potential for some response to ADH. Therefore, some children who have CNDI may benefit from larger or more frequent doses of dDAVP. A reasonable starting dose is 5 to 30 mcg/d given one to three times daily, titrating to lessen thirst and polyuria.

Newer Considerations

The clarification of intracellular and molecular processes may open the way for more specifically directed therapy. For example, activating cGMP kinase may allow for phosphorylation of AQP2 when cAMP fails to be activated in X-linked disease. Moreover, pharmacologic chaperone molecules may be able to correct the conformation of misfolded proteins retained in the endoplasmic reticulum and help move certain types of potentially functional VR2 or AQP2 mutations to their more appropriate intracellular sites of action. Thus, defining a specific genetic mutational defect eventually may help in the therapy of individual patients.

References


Suggested Reading

### PIR Quiz

Quiz also available online at www.pedsinreview.org.

5. In the first weeks after birth, breastfeeding infants who have congenital nephrogenic diabetes insipidus (CNDI) are most likely to present with:
   - A. Developmental delay.
   - B. Diarrhea.
   - C. Hypothermia.
   - D. Incessant crying.
   - E. Linear growth failure.

6. Diabetes insipidus (DI) is most reliably differentiated from psychogenic excessive water intake (PEWI) by a history of:
   - A. Diarrhea in DI.
   - B. Hypernatremia.
   - C. Pale urine in DI.
   - D. Pale urine in PEWI.
   - E. Polyphagia in DI.

7. The most likely effect to occur during a water deprivation test in a patient who has a complete form of DI is:
   - A. Significant decrease in serum osmolality.
   - B. Significant decrease in urine osmolality.
   - C. Significant increase in serum osmolality.
   - D. Significant increase in urine osmolality.
   - E. Unchanged serum osmolality.

8. For a patient who has autosomal recessive CNDI, the administration of vasopressin during a water deprivation test will result in:
   - A. Significantly higher serum osmolality.
   - B. Significantly higher urine osmolality.
   - C. Significantly lower serum osmolality.
   - D. Significantly lower urine osmolality.
   - E. Unchanged urine osmolality.

9. When treating CNDI, in addition to assuring ready access to water and supplying appropriate pharmacotherapy, careful attention to renal solute load and caloric intake is indispensable. The ratio of renal solute load to calories (mOsm/kcal) in a diet that is most appropriate for an infant who has CNDI is:
   - A. <14 mOsm/100 kcal.
   - B. 14 to 26 mOsm/100 kcal.
   - C. 27 to 50 mOsm/100 kcal.
   - D. 51 to 75 mOsm/100 kcal.
   - E. >76 mOsm/100 kcal.