Diabetes Insipidus

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Diabetes insipidus (DI) is characterized by polydipsia and polyuria with a dilute urine having a specific gravity less than 1.010, hypernatremia, and dehydration. It results either from a deficiency of arginine vasopressin (AVP), termed *central DI (CDI)*, or from renal resistance to the action of AVP, called *nephrogenic DI (NDI)*. The prevalence of DI is 1:25,000, with fewer than 10% of cases from hereditary forms. Intact thirst protects self-sufficient patients against severe hypernatremic dehydration, putting infants and neurologically compromised patients more at risk for clinically significant dehydration.

Water balance is tightly regulated by AVP, which stimulates both water reabsorption by the kidneys and the ingestion of water in response to thirst. AVP is principally synthesized in the hypothalamic paraventricular, and supra-optic nuclei, and then is stored in the posterior pituitary before it is secreted into the systemic circulation in response to increasing plasma osmolality. In the kidneys, AVP, through binding to the vasopressin V2 receptor in the basolateral membrane of the collecting ducts, activates a series of reactions that allows water to move freely across an osmotic gradient back from a relatively dilute urine into the systemic circulation in response to the plasma's rising osmolality.

Decreased production or release of AVP results in CDI, which can present at any age. Underlying mechanisms of CDI include mutations in the *AVP* gene, anatomical hypothalamic or pituitary defects, trauma, neoplasms, infections, autoimmune disease, or infiltrative processes affecting the AVP neurons or fiber tracts (Table 1). Familial, autosomal dominant CDI results from any of multiple different mutations in the coding region of the *AVP* gene, with variable severity within a family, and it usually presents after the first year after birth. Another cause of genetically acquired CDI is Wolfram syndrome, a rare autosomal dominant disorder characterized by diabetes mellitus, CDI, optic nerve atrophy, and sensorineural hearing loss. CDI may also manifest as a component of septo-optic dysplasia, which includes optic nerve hypoplasia, an abnormal septum pellucidum, and pituitary hormone deficiencies. CDI associated with septo-optic dysplasia puts patients at particular risk for dehydration due to dysfunction of the osmo-regulated thirst mechanism. Slightly more than half of patients with a craniopharyngioma have accompanying CDI, either before or, particularly, after resection. Typically, a triphasic response follows neurosurgery, with CDI first manifesting 1 to 2 days postoperatively, giving way to the syndrome of inappropriate antidiuretic hormone 2 to 10 days postoperatively, and then converting back to CDI, either transiently or permanently.

Absent response to AVP in the kidneys results in NDI, which can be genetic or acquired (Table 1). The genetic causes, which are rare, commonly present in childhood. Congenital X-linked NDI results from an inactivating mutation of the vasopressin V2 receptor and accounts for 90% of inherited NDI. In boys, it usually presents in the first few weeks after birth, but, based on X-chromosome

inactivation, it may affect girls later in life with dehydration, vomiting, growth failure, polyuria, and polydipsia. Much rarer is congenital autosomal NDI, which can be dominant or recessive. More commonly, NDI is acquired, often as an adverse effect of a variety of medications (amphotericin, cisplatin, clozapine, cyclophosphamide, demeclocycline, foscarnet, furosemide, ifosfamide, lithium, methicillin, rifampin, vinblastine). Other causes of acquired NDI include chronic renal failure, polycystic kidney disease, Sjogren syndrome, and sickle cell disease, all of which can cause a tubulopathy that interferes with renal concentrating ability. For patients with sickle cell disease or sickle cell trait, sickling and ischemia in the vasa recta may lead to a decrease in the osmotic gradient between the collecting ducts and medullary interstitium, resulting in impaired free water reabsorption and limited ability to concentrate urine.

Another form of DI is gestational DI, which has an incidence of approximately 4:100,000 pregnancies. Vasopressinase, which metabolizes AVP, is produced by the placenta and cleared by the liver; pregnant women with preeclampsia or liver dysfunction have increased vasopressinase activity, causing a decrease in circulating AVP. Gestational DI typically resolves 4 to 6 weeks after delivery but may require treatment with 1-desamino-8-D-arginine vasopressin (desmopressin acetate, DDAVP) until then.

For a patient with suspected DI, for example a child with secondary enuresis, the first step in diagnosis is to confirm polyuria, which is classically defined as urine output greater than 4 to 5 mL/kg per hour. Polyuria in children has been more specifically defined as greater than 150 mL/kg per day in neonates, 100 to 110 mL/kg per day in children up to age 2 years, and 40 to 50 mL/kg per day in older children. Once polyuria has been confirmed, the following laboratory tests should be collected: serum osmolality, sodium, potassium, glucose, calcium, and blood urea nitrogen, and urine specific gravity and osmolality. A serum osmolality greater than 300 mOsm/kg with a urine osmolality less than 300 mOsm/kg confirms a diagnosis of DI (Table 2). If the diagnosis is uncertain, a water deprivation test should be performed for 3 to 10 hours in a medical setting. Compared with patients with DI who cannot concentrate their urine, patients with primary

TABLE 1. Causes of Diabetes Insipidus (DI)

CENTRAL DI	NEPHROGENIC DI
Autoimmune disease: lymphocytic hypophysitis	**Electrolyte disturbances:** hypokalemia, hypercalcemia, hypocalciuria
AVP gene mutations: autosomal dominant central DI, Wolfram syndrome	**Genetic mutations:** X-linked nephrogenic DI (inactivating mutation of the vasopressin V2 receptor), autosomal nephrogenic DI (aquaporin 2 channel mutations)
Drug induced: β-adrenergic agents, ethanol, halothane, phenytoin, opioid antagonists	**Medications:** amphotericin, cisplatin, clozapine, cyclophosphamide, demeclocycline, foscarnet, furosemide, ifosfamide, lithium, methicillin, rifampin, vinblastine
Infections: congenital cytomegalovirus, encephalitis, intracranial abscess, meningitis, syphilis, toxoplasmosis, tuberculosis	**Tubulopathy:** amyloidosis, chronic renal failure, polycystic kidney disease, sickle cell disease, Sjogren syndrome
Infiltrative processes: Langerhans cell histiocytosis, sarcoidosis	
Neoplasms: craniopharyngioma, germinoma, lymphoma, metastases, optic glioma	
Structural: pituitary hypoplasia, septo-optic dysplasia	
Traumatic: after head trauma, intracranial hemorrhage, neurosurgery	

polydipsia, which is excessive water intake often in the setting of psychiatric disorders or developmental delay, usually have appropriately concentrated urine in the setting of water deprivation. However, excessive water intake over time suppresses AVP production and reduces renal concentrating ability, making it difficult to distinguish primary polydipsia from NDI.

Once a diagnosis of DI is confirmed, vasopressin should be given subcutaneously to help distinguish between CDI and NDI. A patient with CDI will usually respond to vasopressin quickly with decreased urine output and increased urine osmolality, whereas a patient with NDI will not. Plasma vasopressin levels may be useful in distinguishing NDI from CDI, with higher levels indicating NDI and lower levels CDI. Unfortunately, AVP has a short half-life and is difficult to measure. More recently, copeptin (a C-terminal part of the AVP precursor) has proved to be more stable than AVP, and its levels correlate with AVP levels. For patients with CDI, magnetic resonance imaging is recommended to examine the pituitary stalk for structural causes. Absence of the posterior pituitary gland, demonstrated radiographically as a bright spot, is typically found, although it is not helpful in distinguishing CDI from NDI: the bright spot may be diminished or absent in both forms. In NDI, this finding is thought to be from chronic hypersecretion of AVP and diminished AVP stores. However, the bright spot is absent in 10% of all newborn children, and its absence is not required for the diagnosis of DI. Patients diagnosed as having CDI should also be screened for deficits in anterior pituitary hormones, including thyrotropin, adrenocorticotropic hormone, and growth hormone, and for hypogonadotropic hypogonadism.

Treatment of DI depends on whether the patient has CDI or NDI. For CDI, oral DDAVP is typically used, in preference to intranasal therapy, every 8 to 12 hours, allowing for at least an hour without the antidiuretic effect for excess water to be excreted. The most common adverse effect of DDAVP is hyponatremia. Intranasal DDAVP is more difficult to titrate and can lead to eye irritation, headaches, dizziness, rhinitis, epistaxis, coughing, and flushing. Caution should be taken when giving DDAVP to babies and postoperative patients given the risk of hyponatremia and water intoxication. Infants with CDI can be managed with thiazide diuretics, which have a paradoxical antidiuretic effect in DI, until they make the transition to a solid diet; they should be monitored for hypokalemia or be given amiloride to preserve potassium. NDI is difficult to treat, other than by eliminating its underlying cause. Congenital NDI is treated with foods with a high ratio of calories to osmotic load. In consultation with nephrology, thiazide diuretics, possibly in combination with amiloride or indomethacin, may also be used to reduce urine output.

Complications from DI result from increased water intake, leading to hydroureter, nonobstructive hydronephrosis, megabladder, and hyperfluorosis. Although the mechanism is unclear, decreased bone density has also been reported in patients with CDI. Patients with congenital NDI may have developmental delays from repeated episodes of dehydration and hyponatremia, as well as cerebral calcifications thought to be secondary to high circulating AVP levels.

TABLE 2. **Interpreting Laboratory Results**

DIAGNOSIS	URINE VOLUME, mL/kg per hour	SERUM SODIUM, mEq/L	SERUM OSMOLARITY, mOsm/kg	URINE SPECIFIC GRAVITY	URINE OSMOLALITY, mOsm/kg
Normal	1–4	135–145	280	1.010–1.030	50–1400
Central DI	>4	>145	>300	<1.010	<300
Nephrogenic DI	>4	>170	>300	<1.005	<300
Primary polydipsia	May be >4	135–145	<280	<1.020	<300

DI=diabetes insipidus.

Fundamental to an understanding of DI is appreciating how different CDI and NDI are in their clinical course and treatment.

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COMMENT: Why would thiazide diuretics help diminish urine output in both NDI and CDI? At first glance that certainly does seem paradoxical. Although the mechanism is not fully understood, experimental evidence provides some probable answers. A known effect of thiazide diuretics is that they produce volume depletion, which may then induce increased absorption of water and salt in the proximal tubule; with less water and salt reaching the distal nephron, urine output is diminished. Another factor may be sodium load. Particularly with NDI, solute concentration is an important contributor to urine output, which is why relative salt restriction (a diet low in sodium with a high ratio of calories to osmotic load) is helpful in management. An adverse effect of thiazide diuretics is hyponatremia from decreased sodium reabsorption at the distal convoluted tubule. The effect is a lower solute load delivered to the kidneys and, thus, in NDI a fall in urine volume.

Yes, apparent paradoxes can be interesting.

– Henry M. Adam, MD
Associate Editor, *In Brief*

Correction

An error in terminology appeared in the print version of the January 2020 In Brief "The Glycogen Storage Disorders" (Marion RW, Paljevic E. *Pediatr Rev.* 2020;41(1):41–44; DOI: 10.1542/pir.2018-0146). The 3 mentions of "glycolysis" on the article's first page should read "glycogenolysis." The online version of the article has been corrected, and a correction notice has been posted with the online version of the article. The journal regrets the error.

ANSWER KEY FOR FEBRUARY 2020 PEDIATRICS IN REVIEW
Medical Child Abuse and Medical Neglect: 1. C; 2. B; 3. A; 4. C; 5. D.
Marijuana Use and Potential Implications of Marijuana Legalization: 1. B; 2. B; 3. D; 4. A; 5. E.
Intimate Partner Violence in the Adolescent: 1. D; 2. E; 3. D; 4. A; 5. A.