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OBJECTIVES

After completing this article, readers should be able to:

1. **Describe the simple test that will establish the diagnosis of diabetes insipidus.**
2. **Explain how to differentiate central diabetes insipidus from nephrogenic diabetes insipidus and compulsive water drinking.**
3. **Delineate the inheritance pattern of central diabetes insipidus and nephrogenic diabetes insipidus.**
4. **Describe the treatments of choice for central diabetes insipidus and nephrogenic diabetes insipidus.**

Definition and Epidemiology

Polydipsia and polyuria with dilute urine, hypernatremia, and dehydration are the hallmarks of diabetes insipidus in infants and children. Patients who have diabetes insipidus are unable to conserve water and can become severely dehydrated when deprived of water. The polyuria exceeds 5 mL/kg per hour of dilute urine, with a documented specific gravity of less than 1.010. The hypernatremia is evidenced by a serum sodium concentration in excess of 145 mmol/L (145 mEq/L).

Three conditions give rise to polydipsia and polyuria. The most common condition is central or neurogenic diabetes insipidus related to a deficiency of vasopressin. Less common is nephrogenic diabetes insipidus, including the X-linked recessive, autosomal recessive, and autosomal dominant types due to renal tubular resistance to vasopressin. Finally, these conditions can occur in the compulsive water drinker who demonstrates physiologic inhibition of vasopressin secretion.

The incidence of diabetes insipidus in the general population is 3 in 100,000, with a slightly higher incidence among males (60%). X-linked nephrogenic diabetes insipidus is very rare, with arginine vasopressin receptor$_2$ (AVPR$_2$) gene mutations among males estimated to be 4 in 1,000,000. The incidence of compulsive water drinking is unknown, but there appears to be a female predisposition (80%). Although the compulsive water drinker commonly presents in the third decade of life, cases have been described in patients from 8 to 18 years of age. Compulsive water drinking is encountered in 10% to 40% of patients who have schizophrenia.

Pathophysiology

The secretion of antidiuretic hormone, arginine vasopressin (AVP), from the posterior pituitary gland is regulated by paraventricular and supraoptic nuclei. AVP acts at the target site of the cortical collecting duct of the kidneys (Fig. 1A). At the basal lateral membrane of the cortical collecting duct (Fig. 1B), AVP binds to a vasopressin$_2$ receptor, which links with G protein and adenylate cyclase to produce cyclic AMP. Protein kinase A subsequently is stimulated and acts to promote aquaporin$_2$ (AQP$_2$) in recycling vesicles. In the presence of AVP, exocytic insertion of AQP$_2$ protein at the apical surface of the cortical tubular cells allows water to enter the cell. In the absence of AVP, AQP$_2$ protein is retrieved by endocytic retrieval mechanisms and returned to the recycling vesicle. Destruction of the posterior pituitary gland by tumors or trauma results in a deficiency of vasopressin and the development of central diabetes insipidus. Nephrogenic diabetes insipidus arises from end-organ resistance to vasopressin, either from a receptor defect or from medications and other agents that interfere with the AQP$_2$ transport of water.

Pathogenesis

Central diabetes insipidus may be either idiopathic or due to neurogenic causes (Table 1). Approximately 29% of central diabetes insipidus in children is idiopathic (isolated or familial) compared with 25% in adults. Primary brain tumors of the hypophyseal fossa result in central diabetes insipidus in 50% of children and 30% of adults. Head trauma to the posterior pituitary gland accounts for 2% of cases in children and 17% in adults. Among adults, 9% of central diabetes insipidus results from inadvertent neurosurgical destruction of the posterior pituitary gland, 8% from metastatic carcinoma, and 6% from intracranial hemorrhage and hypoxia. The postinfectious disease process and histiocytosis X cause central diabetes insipidus in 2% and 16% of children, respectively.

The mode of inheritance of idiopathic central diabetes insipidus may be autosomal dominant or autosomal recessive (Table 2). The autosomal dominant type usually presents after 1 year of age, and the molecular defect is a prepro-AVP$_2$ gene mutation. Central diabetes insipidus inherited by autosomal recessive traits are due to a mitochondrial deletion of 4p16 and usually occurs in children younger than 1 year of age. Nephrogenic diabetes insipidus

ABBREVIATIONS

AVP:	arginine vasopressin
AQP$_2$:	aquaporin$_2$
AVPR$_2$:	arginine vasopressin receptor$_2$
DDAVP:	1-desamino-8-D-arginine vasopressin

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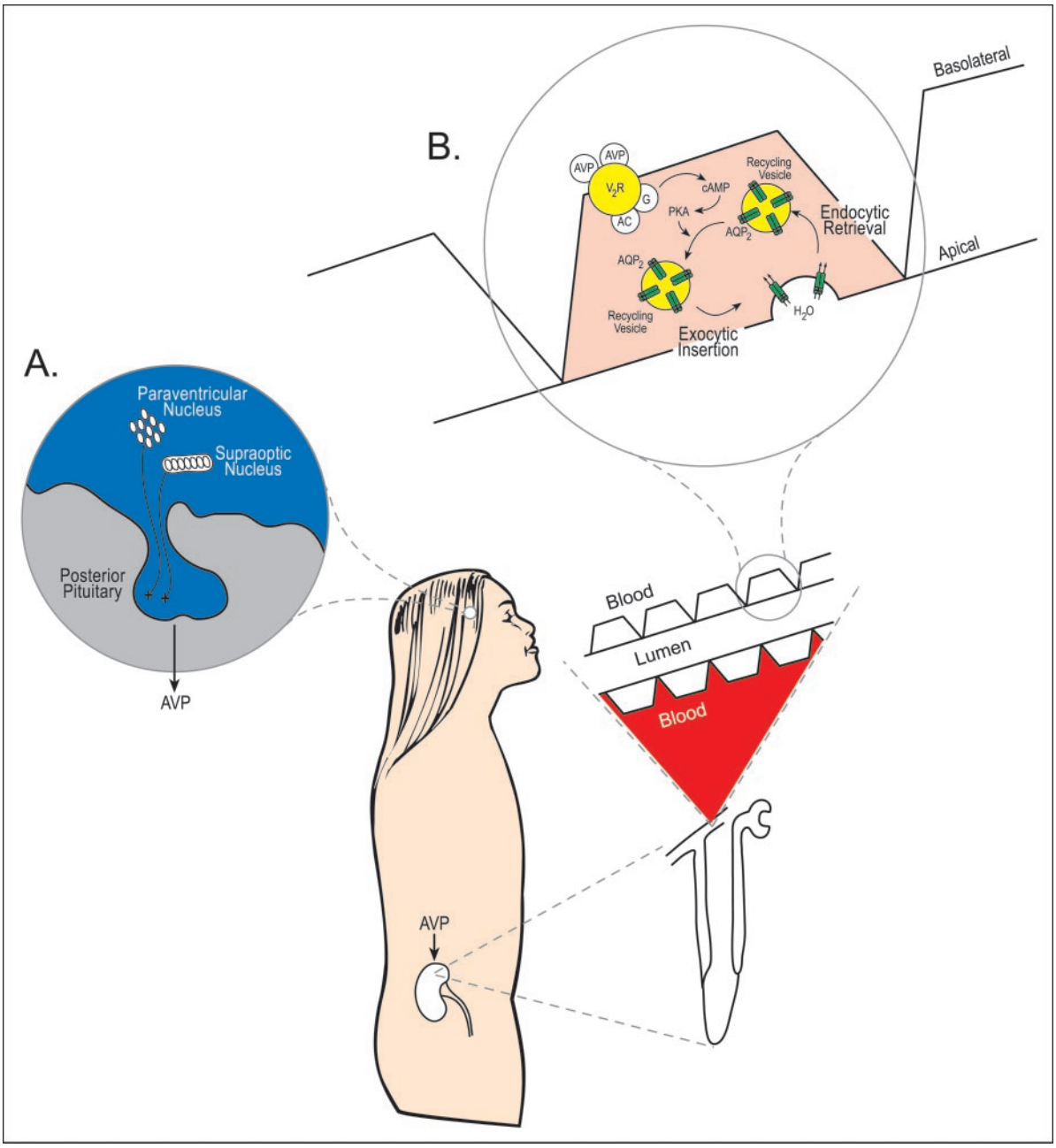

FIGURE 1. A. Central secretion of arginine vasopressin (AVP). AVP is secreted by the posterior pituitary in relation to paraventricular nuclear and supraoptic nuclei. AVP exerts its action at target sites in the kidney. B. Water channel recycling. At the basolateral membrane of the renal cortical collecting duct cell, AVP is bound to vasopressin V_2 receptor (V_2R). G protein links V_2R to adenylate cyclase (AC), increasing the concentration of cyclic adenosine monophosphate (cAMP). The cAMP-dependent protein kinase A (PKA) acts on recycling vesicles that carry the tetrameric water channel proteins. The water channels are fused, by exocytic insertion, to the apical basement membrane to increase water permeability. When AVP becomes unavailable, the water channels are retrieved (endocytic retrieval). Water permeability is lowered. Modified from Dean PMT, Knoers NVAM. Physiology and pathophysiology of aquaporin 2 water channel. Curr Opin Neph Hypertens. *1998;7:37–42 and Bichet DG. Nephrogenic and central diabetes insipidus. In: Schrier RW, Gottschalk CW, eds.* Disease of the Kidney. *6th ed. Boston, Mass: Little Brown and Co; 1997.*

results from a vasopressin-receptor or AQP_2 water channel defect, with the misfolding of the mutated membrane protein and its retention in the endoplasmic reticulum. The genetic defect is transmitted by an X-linked recessive or autosomal recessive trait. The genetic defect in the $AVPR_2$ is transmitted by an X-linked recessive trait. The AQP_2 gene defect is transmitted by an autosomal recessive trait.

The acquired form of nephrogenic diabetes insipidus may result from adverse drug reactions, electrolyte disorders, urinary tract obstruction, or other conditions (Table 3). The polyuria associated with these conditions and medications is not as severe as that seen in central diabetes insipidus or nephrogenic diabetes

TABLE 1. Pathogenesis of Central Diabetes Insipidus

ETIOLOGY	CHILDREN	ADULTS
Primary brain tumor: craniopharyngioma, glioma, neoplasm, leukemia, lymphoma, meningioma, germinoma	50%	30%
Idiopathic (isolated or familial)	29%	25%
Head trauma	2%	17%
Neurosurgery	—	9%
Metastatic carcinoma	—	8%
Intracranial hemorrhage and hypoxia, postpartum pituitary necrosis (Sheehan syndrome), aneurysm, thrombosis, sickle cell crisis	—	6%
Infection: tuberculosis, meningitis, encephalitis, intracranial abscess, syphilis	2%	—
Histiocytosis X	16%	—
Granulomatosis, sarcoidosis, alcohol, phenytoin, clonidine	—	5%

insipidus. Drugs such as lithium, amphotericin, and cisplatin are implicated regularly in this condition. Common electrolyte disorders, such as hypokalemia, hypercalcemia, and hypercalciuria, also can cause acquired nephrogenic diabetes insipidus. Associated systemic diseases include sickle cell disease and trait, amyloidosis, sarcoidosis, Sjögren syndrome, Fanconi syndrome, and renal tubular acidosis. Obstructive uropathy, diffuse renal injury, or any cause of renal failure can precipitate the development of acquired nephrogenic diabetes insipidus. Finally, variance neoplasms, such as sarcoma, are associated with this condition.

In compulsive water drinking, also referred to as primary polydipsia, an individual may ingest up to 15 L of water daily and produce an equal volume of urine output. This huge water ingestion leads to physiologic suppression of vasopressin secretion and results in a hypoosmolar urine. Polyuria is decreased at night as polydipsia ceases with sleep. Thus, moderate nocturia distinguishes compulsive water drinking from the other forms of diabetes insipidus (Table 4).

Clinical Aspects

The diagnosis of diabetes insipidus in infants and children requires a high index of suspicion because the presenting clinical features of poor feeding, failure to thrive, and irritability are nonspecific. Symptoms usually occur a few weeks after birth. The mother initially notices nothing unusual because human milk delivers a low renal solute load. Later in life, as food is introduced to the diet, the increased solute load causes more water excretion.

Neonates who have diabetes insipidus suck vigorously during feeding but vomit immediately afterwards. Nocturia often is reported in children who have diabetes insipidus, and the parents describe the diapers as dripping in urine. These patients usually are irritable as a result of hypernatremia, dehydration, and fever. Because the fever frequently is intermittent and high, affected infants who have diabetes often are evaluated initially for fever of unknown origin. In addition, they may present with constipation or pebble-like hardened stools. Parents usually report relief of these symptoms when water is given.

Because of excessive fluid consumption, the appetite is blunted, and growth retardation is a common feature of children who have diabetes insipidus. Frequent hypernatremic dehydrations and seizures led to reports of mental retardation as a common feature of diabetes insipidus in the past. With earlier recognition and better management today, seizures are less common, and mental retardation no longer is considered a hallmark of the disease. These children often suffer from hyperactivity and short-term memory disorders, which are believed to be due to frequent urination, con-

TABLE 2. Modes of Inheritance of Diabetes Insipidus (DI)

TYPE	INHERITANCE	MOLECULAR GENETICS	AGE OF PRESENTATION
Central DI	Autosomal dominant	Prepro-AVP_2 gene mutations	>1 y
Central DI	Autosomal recessive	Mitochondrial deletions 4p16	<1 y
Nephrogenic DI	X-linked recessive	$AVPR_2$ gene mutations	<1 wk
Nephrogenic DI	Autosomal recessive or dominant	AQP_2 gene mutations	<1 wk

$AVPR_2$ = arginine vasopressin receptor$_2$; AQP_2 = aquaporin$_2$.

TABLE 3. Acquired Nephrogenic Diabetes Insipidus

Drug-induced:
—Aminoglycoside
—Amphotericin B
—Cisplatin
—Colchicine
—Demeclocycline
—Diphenylhydration
—Foscarnet
—Furosemide
—Gentamicin
—Isophosphamide
—Lithium
—Methicillin
—Methoxyflurane
—Nicotine
—Rifampin
—Vasopressinoic acid
—Vinblastine
Electolyte disorders:
—Hypokalemia
—Hypercalcemia
—Hypercalciuria
Systemic disorders:
—Amyloidosis
—Diffuse renal injury or any cause of renal failure
—Fanconi syndrome
—Obstructive uropathy
—Renal tubular acidosis
—Sarcoidosis
—Sickle cell disease and trait
—Sjögren syndrome
Neoplasm:
—Sarcoma

TABLE 4. Presentations of Central Diabetes Insipidus (CDI), Nephrogenic Diabetes Insipidus (NDI), and Compulsive Water Drinker (CWD)

	CDI	NDI	CWD
Onset of polyuria	Sudden	Variable	Variable
Volume of urine	Large	Large	Variable
Nocturia	Frequent	Frequent	Moderate
Preference for ice water	Great	Variable	Variable

Modified from T Berl, RW Schrier. Disorder of serum sodium concentration. In:* McGaw Fluid and Electrolytes Monogram Series. *Irving, Calif: McGaw Laboratories; 1979.

stant search for fluids, and continual disruptions of normal activities and focus.

A typical physical examination may reveal an irritable infant who has a dripping diaper. There usually are findings suggesting dehydration, such as a notable decrease in tearing, a depressed anterior fontanelle, sunken eyes, and mottled and doughy skin turgor. In infants and older children, the pulse usually is weak, and hypotension is manifested. Mobile fecaliths often present as abdominal masses.

Table 4 summarizes the presentations of central diabetes insipidus, nephrogenic diabetes insipidus, and the compulsive water drinker. With central diabetes insipidus, the onset of polyuria is sudden, the volume of urine is large, nocturia is frequent, and there is a marked preference for ice water. Diabetes insipidus due to trauma or neurosurgical injury is characterized by polyuria that often is triphasic: an initial, intense polyuria lasting for hours to several days, followed by an antidiuretic phase of equal duration, and finally return of transient or permanent polyuria. Polyuria, nocturia, and preference for ice water are more variable in nephrogenic diabetes insipidus and the compulsive water drinker.

Diagnosis

HISTORY

Diabetes insipidus must be considered in any dehydrated infant who has a history of polyuria and laboratory findings of hypernatremia and urinary concentration defect. A family history of diabetes insipidus may focus the diagnosis on specific disorders. Polyuria following head trauma or injury or the presence of neurologic deficits or precocious puberty point to neurogenic diabetes insipidus. A weak urinary stream and a dilated collecting system should alert the physician to the diagnosis of obstructive uropathy.

PRESENTATION

Infants who have nephrogenic diabetes insipidus often present with fever due to dehydration, which may result in convulsions. Infants and children who have nephrogenic diabetes insipidus frequently present with hypernatremia, hyperchloremia, and prerenal azotemia as well as acidosis, which is dependent on the severity of dehydration and hypovolemia. These abnormalities, together with hyperosmolality, are reversed with rehydration. Serum uric acid generally is elevated because of the dehydration, and urinary sodium and chloride levels often are below normal. The urine continues to be dilute, despite hypernatremia in excess of 180 mmol/L (180 mEq/L). Because of the large urine volume that passes through the lower urinary tract system, older children who have a long history of nephrogenic diabetes insipidus often have functional hydronephrosis and an enlarged bladder.

LABORATORY TESTS

A 24-hour urine collection is needed to quantitate the polyuria and to estimate the rate of excretion of osmoles. The urinary specific gravity of the first morning voiding provides a simple estimation of the renal concentration capacity. However, the urinary specific gravity is affected by the presence of glucosuria, proteinuria, or radiocontrast material. Serum calcium, glucose, creatinine, potassium, and urea levels provide additional clues to the correct diagnosis. Low serum osmolality coupled with hypo-osmolar urine suggest the diagnosis of a compulsive water drinker. A high serum osmolality in the presence of normal serum glucose and urea concentrations points to a deficiency or insensitivity to vasopressin.

A diagnostic approach to a child who has polyuria and hypernatremic dehydration is shown in Fig. 2. The

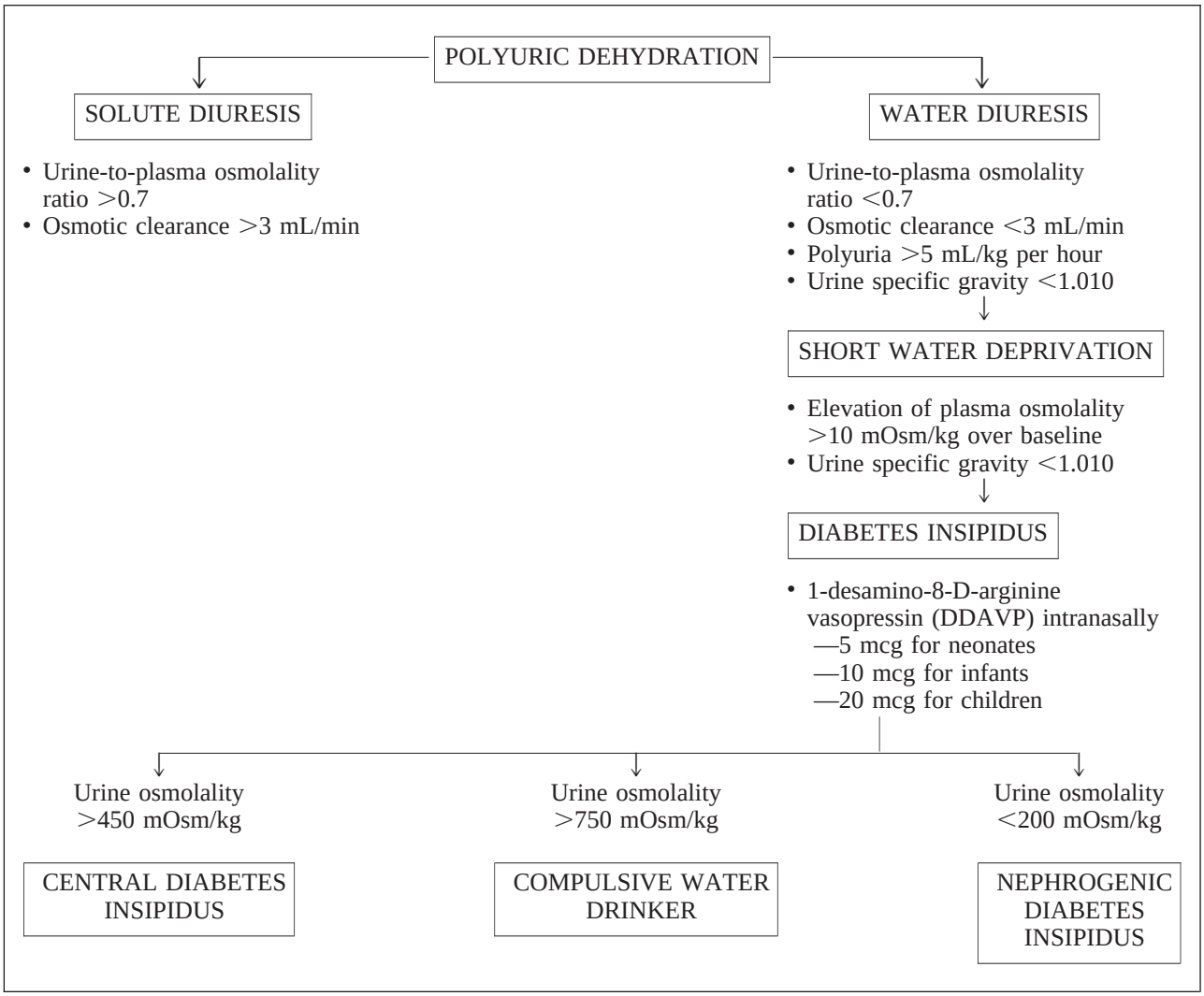

FIGURE 2. Differential diagnostic evaluation for polyuric dehydration, including the use of short water deprivation and 1-desamino-8-D-arginine vasopressin (DDAVP).

water deprivation test (Table 5) should be performed during daytime hours because of the better availability of medical and nursing personnel. An elevation of plasma osmolality in excess of 10 mOsm/kg over baseline, with the urine specific gravity remaining less than 1.010 after a short water deprivation test, establishes the diagnosis of diabetes insipidus. The next diagnostic step uses 1-desamino-8-D-arginine vasopressin (DDAVP) intranasally at 5 mcg for neonates, 10 mcg for infants, and 20 mcg for children to differentiate the type of diabetes insipidus. If the urine osmolality is increased by more than 450 mOsm/kg, central diabetes insipidus is established. If the urine osmolality remains less than 200 mOsm/kg, nephrogenic diabetes insipidus is the likely diagnosis. Urine osmolality increasing in excess of 750 mOsm/kg suggests a compulsive water drinker. If rhinitis or sinusitis preclude intranasal administration, DDAVP can be administered intravenously at 1/10 the intranasal dose.

Table 6 shows the serum and urine osmolality associated with the different types of diabetes insipidus in the basal state and after water deprivation or antidiuretic hormone administration.

Fig. 3 shows how the plasma arginine vasopressin correlates with plasma osmolality and allows the distinction of central diabetes insipidus from normal and from nephrogenic diabetes insipidus.

MAGNETIC RESONANCE IMAGING (MRI)

Both the anterior and posterior pituitary glands and stalk can be visualized by use of MRI. The posterior pituitary lobe appears as a round, high-intensity signal ("bright spot") in the sella turcica; the presence of such a signal is inconsistent with a diagnosis of central diabetes insipidus.

In addition, MRI has been used to delineate the cause of central diabetes insipidus. Sagittal MRI enhanced with gadolinium may demonstrate a large suprasellar mass. Loss of the bright T1-weighted signal within the sella may indicate a pituitary cyst, pituitary hypoplasia, or an atopic lobe of the posterior pituitary, which can be the cause of complete or partial vasopressin deficiency. In combination with a displaced bright signal of the posterior gland, such a finding indicates an ectopic gland.

TABLE 5. Water Deprivation Test

Method
• Collect baseline urine and blood (osmolality and electrolytes).
• Deprive of water after breakfast until significant dehydration occurs.
• Weigh every 2 hr; limit dehydration to 3% to 5% loss of body weight.
• Monitor urine specific gravity hourly; if 1.014 or greater, terminate test and obtain appropriate blood and urine specimens for osmolality.
• Limit water deprivation to 7 hr (4 hr for infants).
• Collect urine and blood for osmolality and electrolytes.
• If polyuria persists, administer intranasal DDAVP.* • Replace urine output with fluid.
• After 4 hr (2 hr in infants), obtain urine and blood osmolality.
Results
• Normal response to dehydration or DDAVP: —Urine osmolality >450 mOsm/kg. —Urine/serum osmolality ≥1.5. —Urine/serum osmolality increases from baseline 1.0 or more.
• Expect normal response in central and psychogenic diabetes insipidus.
• Above criteria not met in nephrogenic diabetes insipidus.

DDAVP = 1-desamino-8-D-arginine vasopressin, 10 mcg for infants and 20 mcg for children.
Modified from Linshaw MA. Congenital nephrogenic diabetes insipidus. In: Jacobson HR, Sticker GE, Klahr S, eds.* Principles and Practice of Nephrology. *Philadelphia, Penn: BC Decker Inc; 1991:426–430.

Differential Diagnosis

The differential diagnosis of polydipsia or polyuria should include diabetes mellitus. This is easily differentiated from diabetes insipidus by the hyperglycemia, ketonuria, glucosuria, and high anion gap acidosis associated with diabetic ketoacidosis. Chronic renal failure also must be included in the differential diagnosis. Although the polyuria of chronic renal failure is less severe than that seen in diabetes insipidus, it is more difficult to reverse azotemia with hydration.

Diabetes insipidus always should be differentiated from small-volume urinary frequency. In this condition, the polyuria is not accompanied by polydipsia. Increased urinary frequency may be due to cystitis, masturbation, sexual abuse, urethral irritation, and urethritis.

Polyuria may follow solute (glucose, saline, mannitol, urea) diuresis. A urine-to-plasma osmolality ratio greater than 0.7 and clearance of osmolality of more than 3 mL/min points to solute-induced diuresis, instead of water diuresis, which occurs in diabetes insipidus. The hypernatremia of primary hyperaldosteronism is mild and accompanied by hypertension, hypervolemia, and suppression of plasma renin activity.

Management

The treatment of choice for central diabetes insipidus is intranasal DDAVP at doses of 5 to 20 mcg daily. Rhinitis and sinusitis may reduce intranasal absorption of this drug. Antibodies to this synthetic analog of vasopressin have not been encountered. The dose of oral preparations is 20-fold greater than the intranasal dose. Aqueous vasopressin or desmopressin (4 mcg/mL ampule) can be used intravenously for acute hypophysectomy diabetes insipidus and often is used in brain-dead organ donors.

Central diabetes insipidus has responded to chlorpropamide with a 25% to 75% reduction in polyuria. The antidiuretic mechanism of this hypoglycemic agent is not entirely clear. Clofibrate also has been shown to reduce polyuria in central diabetes insipidus and may be used alone or in conjunction with DDAVP or chlorpropamide. Finally, thiazide diuretics (hydrochlorothiazide 2 to 3 mg/kg per day) decrease the frequency of urination by 50% or more when accompanied by salt restriction and are effective in both central and nephrogenic diabetes insipidus.

Oral repletion of water often is sufficient to reverse acute dehydration in diabetes insipidus. However, if parenteral rehydration is required, 3% rather than 5% dextrose is preferred. Glucose infusion exceeding the rate of glucose utilization may worsen the patient's pre-existing state of hyperosmolality. In addition, the ensuing glucosuria may result in an osmotic diuresis, which aggravates the hyperosmolality and dehydration further.

There are no effective pharmacologic agents to treat a compulsive water drinker. Small, short-acting doses of DDAVP administered at bedtime may reduce nocturia, although this therapeutic approach is controversal. Headaches and hypertension may result from water retention caused by the DDAVP. This approach should be used cautiously.

A low-osmolar, low-sodium diet should be initiated to manage congenital nephrogenic diabetes insipidus. Human milk is preferred in infancy because protein constitutes 6% of caloric intake. Sodium intake should be reduced to 0.7 mEq/kg per day. In a child who has nephrogenic diabetes insipidus, protein intake should constitute 8% of caloric intake, and sodium intake should be less than 0.7 mEq/kg per day. This low-solute diet should be coupled with thiazide diuretics (hydrochlorothiazide 2 to 3 mg/kg per day in three divided doses or chlorothiazide 30 mg/kg per day). The diuretics increase sodium loss by inhibiting its reabsorption in the cortical diluting tubule. The ensuing extracellular fluid contraction augments proximal tubular reabsorption of water. These maneuvers usually result in a 50% reduction in polyuria. Side effects of thiazide diuretics include hypokalemia and (rarely) neutropenia. The tendency toward hypokalemia can be countered with potassium supplementation or the use of potassium-sparing diuretics,

TABLE 6. Interpretation of Serum and Urine Osmolality

SUBJECTS	BASAL STATE					PLATEAU AFTER H_2O DEPRIVATION		AFTER ADH
	DAILY URINE VOLUME (L)	SERUM SODIUM (MEQ/L)	SERUM OSMOLALITY (MOSM/KG)	URINE SG	URINE OSMOLALITY	PLASMA VASOPRESSIN (MOSM/KG)	PLASMA VASOPRESSIN	URINE OSMOLALITY (MOSM/KG)	CHANGE IN URINE OSMOLALITY
Normal	0.5 to 1.0*	135 to 145	280	>1.010	50 to 1,400	Normal	Increased	>800	<5%
CDI	4 to 10	>145	>300	<1.010	<200	Low	Low	<200	>50%
NDI (cortex)	4 to 10	170	>300	<1.005	50 to 200	Normal or increased	High	150	<50%
NDI (medullary)	4 to 10	170	>300	<1.005	<300	Normal or increased	High	300	<50%
CWD	2.5 to 20	140	<280	<1.020	<200	Decreased	Increased	600	<5%

CDI = central diabetes insipidus; NDI = nephrogenic diabetes insipidus; CWD = compulsive water drinkers; SG = specific gravity; ADH = antidiuretic hormone.
**Daily urine volume: normal newborn, 0.05 to 0.3 L; infant, 0.4 to 0.5 L; child, 0.5 to 1 L; adolescent, 0.7 to 1.4 L; adult male, 0.8 to 1.8 L; adult female, 0.6 to 1.6 L.*

FIGURE 3. Correlation of plasma arginine vasopressin (AVP) with plasma osmolality in normal subjects, in patients who have central (pituitary) diabetes insipidus, and in those who have nephrogenic diabetes insipidus. Reprinted with permission from Robertson GL, Mahr EA, Athar S, Sinha T. Development of clinical application of a new method for radioimmune assay of arginine vasopressin in human plasma. J Clin Invest. *1973;82:2340–2352. By copyright permission of The American Society for Clinical Investigation. As modified by Culpepper RM, Hebert SC, Andreoli TE. Nephrogenic diabetes insipidus. In: Stanbury JB, Wyngaarden JB, Fredrickson DS, Goldstein JL, Brown MS, eds.* The Metabolic Basis of Inherited Disease. *New York, NY: McGraw Hill Book Company; 1983: 1867–1888.*

such as amiloride 0.1 to 0.2 mg/kg per day to a maximum of 10 mg/m^2 per day. No long-term side effects have been reported with this combination of medications. In addition, indomethacin 0.25 to 3 mg/kg per day in two divided doses or aspirin 10 to 30 mg/kg per day in two divided doses has an additive effect on hydrochlorothiazide in reducing water excretion in some patients. Long-term side effects of indomethacin, such as deterioration of renal function, require careful monitoring. Accordingly, such nonsteroidal anti-inflammatory medication should be used only after other therapies have failed.

In hereditary diabetes insipidus, genetic counseling and follow-up are important. Finally, the body temperature, appetite, and linear growth should be monitored at all follow-up clinic visits.

Prognosis

Although mental retardation resulting from hypernatremic dehydration and encephalopathy has been associated with diabetes insipidus in the past, early recognition and treatment have eliminated this feature of the disease. However, short attention span, hyperactivity, and learning and psychomotor delays continue to be seen. Nonobstructive functional hydronephrosis and hydroureters may be encountered and should be followed by renal ultrasonography and urography. Chronic renal insufficiency may occur by the second decade of life in children who have nephrogenic diabetes insipidus due to glomerular thromboembolic complications of dehydration.

Transient diabetes insipidus may follow neurosurgery, although this usually resolves spontaneously. If vasopressin deficiency persists beyond a few weeks, however, permanent diabetes insipidus will ensue. On rare occasions, chronic central diabetes insipidus has remitted spontaneously despite persistent deficiency of vasopressin. The mechanism of this remission is not known.

As long as water is available to replace the large urine output, patients remain asymptomatic except for the inconvenience of the polydipsia and polyuria. However, when the need for water cannot be communicated, such as in infancy, or when patients are anesthetized or unconscious, the lack of water replacement precipitates a life-threatening risk of dehydration.

Recent Developments

Perinatal testing for carrier detection of X-linked nephrogenic diabetes insipidus with mutation analysis of the $AVPR_2$ gene now is available. Cord blood obtained immediately after delivery and before placental extraction has yielded favorable results for such early genetic diagnosis.

SUGGESTED READING

Alon U, Chan JCM. Hydrochlorothiazide-amiloride in the treatment of nephrogenic diabetes insipidus. *Am J Nephrol.* 1985;5:9–13

Leung AKC, Robson WLM, Halperin ML. Polyuria in childhood. *Clin Pediatr.* 1991;11:634–640

Mulders SM, Bichet DG, Rijss JPL, et al. An aquaporin-2 water channel mutant which causes autosomal dominant nephrogenic diabetes insipidus is retained in the Golgi complex. *J Clin Invest.* 1998;102:57–66

Yamamoto T, Sasaki S. Aquaporins in the kidney: emerging new aspects. *Kidney Int.* 1998;54:1041–1051

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PIR QUIZ

Quiz also available online at www.pedsinreview.org.

7. A 2-month-old infant presents with fever, vomiting, and irritability for 3 days. His mother states that he drinks large quantities of milk and water, and his diapers are frequently wet, dripping in urine. Examination reveals an irritable child who has dry mouth. Respirations are 40 breaths/min, heart rate is 150 beats/min, temperature is 38.5°C (101.3°F), and blood pressure is 78/50 mm Hg. The skin has a doughy feel with decreased turgor. Laboratory evaluation reveals: serum sodium, 165 mmol/L (165 mEq/L); potassium, 4 mmol/L (4 mEq/L); chloride, 130 mmol/L (130 mEq/L); bicarbonate, 20 mmol/L (20 mEq/L); and blood urea nitrogen, 20.35 mmol/L (57 mg/dL). The infant passes a large amount of urine during examination. Urine specific gravity is 1.004, and the urine is negative for blood, glucose, and protein. An abnormality at which of the following sites best explains this child's illness?
   A. Collecting tubule.
   B. Distal tubule.
   C. Glomerulus.
   D. Loop of Henle.
   E. Proximal tubule.

8. A 14-year-old girl presents with polydipsia and polyuria for the past 2 months. She states that she feels very thirsty and has to ingest 7 to 8 L of fluid every day. She also passes large amounts of urine 10 to 12 times a day. She appears well-hydrated and has normal vital signs. Results of her urinalysis are normal, and her urine specific gravity is 1.004. Serum electrolyte levels are within normal limits. Her basal state plasma vasopressin is low. After water deprivation for 7 hours, her urine volume decreases and has a specific gravity of 1.018. Which of the following is the *most* likely diagnosis?
   A. Central diabetes insipidus.
   B. Compulsive water drinking.
   C. Nephrogenic diabetes insipidus.
   D. Obstructive uropathy.
   E. Syndrome of inappropriate antidiuretic hormone secretion.

9. A 2-month-old male infant presents with vomiting and irritability of 3 days' duration. He appears moderately dehydrated, with dry mucous membranes and doughy skin. Laboratory examination reveals: serum sodium, 158 mmol/L (158 mEq/L); potassium, 4 mmol/L (4 mEq/L); chloride, 120 mmol/L (120 mEq/L); bicarbonate, 22 mmol/L (22 mEq/L); and blood urea nitrogen, 16.4 mmol/L (46 mg/dL). Findings on urinalysis are normal, and the urine specific gravity is 1.004. After appropriate rehydration, a 4-hour water deprivation test is performed. The infant continues to pass urine at a rate of 5 to 6 mL/kg per hour without appreciable response to vasopressin administration. Which of the following is the *most* appropriate long-term management?
   A. Intranasal desmopressin.
   B. Lithium.
   C. Low-osmolar diet.
   D. Mineralocorticoids.
   E. Water restriction.

10. Which of the following conditions is *most* likely associated with neurogenic diabetes insipidus?
   A. Absent corpus callosum.
   B. Ataxia telengiectasia.
   C. Cerebellar astrocytoma.
   D. Chiari malformation.
   E. Craniopharyngioma.

Diabetes Insipidus

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