



AMGAD N. MAKARYUS, MD

North Shore University Hospital, New York University
School of Medicine, Manhasset, NY

SAMY I. McFARLANE, MD, MPH

State University of New York-Downstate and Kings
County Hospital Center, Brooklyn, NY

Diabetes insipidus: Diagnosis and treatment of a complex disease

ABSTRACT

Diabetes insipidus, characterized by excretion of copious volumes of dilute urine, can be life-threatening if not properly diagnosed and managed. It can be caused by two fundamentally different defects: inadequate or impaired secretion of antidiuretic hormone (ADH) from the posterior pituitary gland (neurogenic or central diabetes insipidus) or impaired or insufficient renal response to ADH (nephrogenic diabetes insipidus). The distinction is essential for effective treatment.

KEY POINTS

Urine osmolality is easy to measure and helps in determining whether polyuria is due to diabetes insipidus or another condition.

The water deprivation test can help in distinguishing central diabetes insipidus from nephrogenic diabetes insipidus.

ADH preparations are used in treating central diabetes insipidus but do not help in nephrogenic diabetes insipidus.

Nephrogenic diabetes insipidus is treated by correcting hypokalemia and hypercalcemia and by discontinuing any drugs that may be causing it. Thiazide diuretics are also used.

PATIENTS WHO PRESENT with diabetes insipidus need immediate care because the body's delicate water and electrolyte balance is threatened. It is essential to perform a knowledgeable assessment based on characterizing features, intervene rapidly with the proper treatment, and continue to reevaluate the patient's condition.

Complicating matters, the proper treatment depends on the cause in the individual patient. Therefore, the physician must determine whether the defect is in the brain or in the kidney.

INABILITY TO CONSERVE WATER

Diabetes insipidus is caused by the inability to conserve water and maintain an optimum free water level. The kidneys pass large amounts of dilute urine regardless of the body's hydration state, leading to symptoms of extraordinary thirst, copious water intake (up to 20 liters per day), dry skin, and constipation.

Two very different mechanisms can cause diabetes insipidus (**FIGURE 1**):

- Inadequate release of antidiuretic hormone (ADH, also called vasopressin) from the hypothalamus (central diabetes insipidus) and
- Inadequate response of the kidney to ADH (nephrogenic diabetes insipidus).

The distinction is essential, since the treatment is different for the two causes, and is best achieved by a combination of hormonal and clinical observations.¹⁻³

TABLE 1

Causes of central diabetes insipidus

Injury to the central nervous system

Neoplastic/autoimmune disease
Hypothalamic or pituitary surgery or ischemia
Radiation to the brain
Infection: meningitis, encephalitis
Cerebral edema
Intracranial hemorrhage

Familial disease

Idiopathic*

*Some cases may be due to autoimmune or genetic disorders or psychogenic polydipsia

EVALUATING POLYURIA, DIAGNOSING DIABETES INSIPIDUS

Polyuria is defined as urine volume of more than 3 liters in 24 hours. The history is essential in differentiating diabetes insipidus from other causes of polyuria and in determining the cause of diabetes insipidus.

Urine osmolality is an easy differentiating test. A urine osmolality of 300 mOsm/kg or more plus a high serum glucose level points to the diagnosis of diabetes mellitus; high urine osmolality plus high serum urea points to renal disease. If the urine osmolality is less than 200 mOsm/kg in the presence of polyuria, then diabetes insipidus is present. A water deprivation test, although not required for the diagnosis of diabetes insipidus, is helpful in differentiating between central and nephrogenic diabetes insipidus.

The water deprivation test, which should be done only by experienced physicians, involves withholding all fluids until the patient is sufficiently dehydrated to provide a potent stimulus for ADH secretion. Deprivation lasts 4 to 18 hours, with hourly measurements of body weight and urine osmolality, until two or three consecutive samples vary by less than 30 mOsm/kg (or < 10%) or until the patient loses 5% of his or her body weight. At this point, the serum ADH level is measured, and then 5 units of ADH or 1 μ g of desmopressin (DDAVP, a synthetic analogue of ADH) is injected. Urine

osmolality is then measured 30 and 60 minutes later. Plasma osmolality is also measured at various points during the test.

In normal subjects and patients with psychogenic diabetes insipidus (ie, due to mental disturbances that lead to excess fluid intake, which suppresses ADH secretion), the urine osmolality is greater than the plasma osmolality following fluid restriction, and the urine osmolality increases only minimally (< 10%) after ADH injection.

In central diabetes insipidus, urine osmolality remains less than plasma osmolality after dehydration. After ADH injection, urine osmolality increases by more than 50%.

In nephrogenic diabetes insipidus, urine osmolality remains less than plasma osmolality; after giving ADH, urine osmolality increases by less than 50%.^{2,3}

CENTRAL DIABETES INSIPIDUS

Central diabetes insipidus results from any condition that impairs the synthesis, transport, and release of ADH. It occurs in both sexes equally and affects all ages, with the most frequent age of onset between 10 and 20 years.

The main evidence of ill health is polyuria and polydipsia (besides the symptoms from the underlying disease that damaged the neurohypophyseal system in the first place). Water deprivation for even a short time results in rapid dehydration and compulsive thirst. The thirst is so extreme that it even awakens the patient during the night.

The complete form of the disease is less common than a more moderate partial form with only moderately excessive diuresis. As long as the thirst center remains intact and the patient can seek water, the osmotic concentration of plasma usually remains around values only slightly exceeding 290 mOsm/kg (normal value 280–295 mOsm/kg).¹

Causes of central diabetes insipidus

The causes of central diabetes insipidus (TABLE 1) can be divided into three major categories.

Damage to the hypothalamo-neurohypophyseal region due to head trauma, surgery, or primary or metastatic tumors.^{1–3}

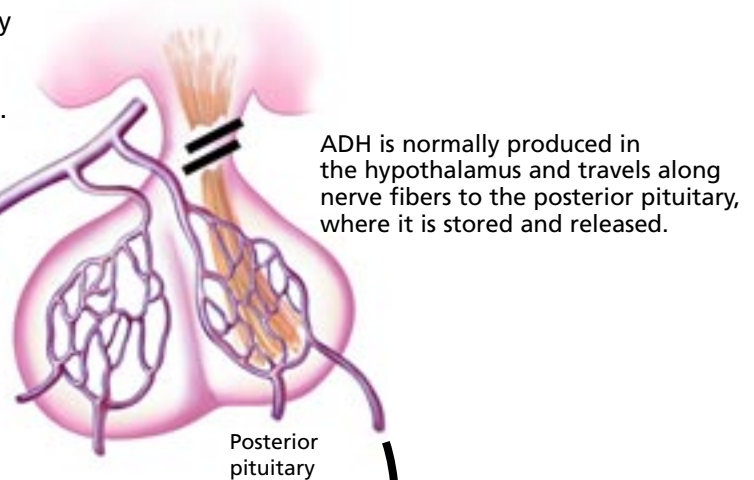
In central diabetes insipidus, thirst is so extreme it wakens the patient at night



Two different mechanisms of diabetes insipidus

Diabetes insipidus, characterized by excretion of copious volumes of dilute urine, can be caused by a variety of defects that fall into two broad categories: central and nephrogenic.

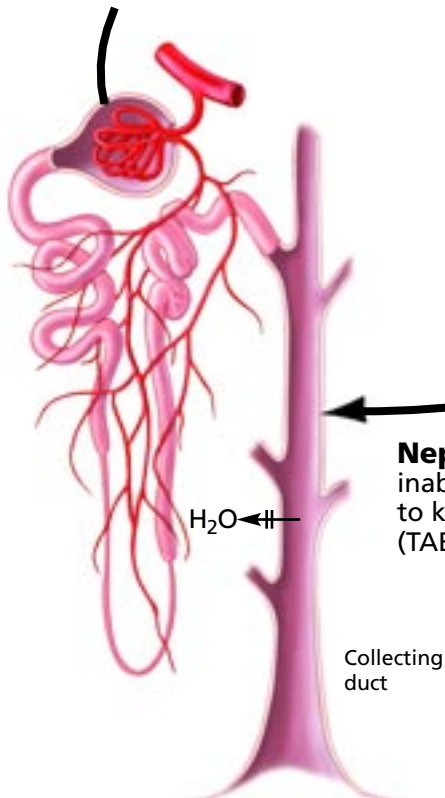
Central diabetes insipidus results from any condition (injury, genetic defect, or idiopathic cause) that impairs the synthesis, transport, or release of antidiuretic hormone (ADH; TABLE 1).



ADH is normally produced in the hypothalamus and travels along nerve fibers to the posterior pituitary, where it is stored and released.

Increased plasma osmolality normally stimulates release of ADH. If urine osmolality remains lower than plasma osmolality during fluid restriction, the patient may have central diabetes insipidus.

ADH normally promotes reabsorption of water in the collecting duct of nephrons. If urine osmolality does not increase after injection of exogenous ADH, the patient may have nephrogenic diabetes insipidus.



Nephrogenic diabetes insipidus results from inability of the kidneys to respond to ADH, owing to kidney disease, drug toxicity, or other causes (TABLE 2).

CCF
Medical Illustrator: Beth Halasz ©2006

FIGURE 1

Damage to the proximal part of this sensitive region kills more neurons of the hypothalamo-neurohypophyseal tract than do distal injuries. Proximal lesions account for 30% to 40% of all cases of posttraumatic and postoperative diabetes insipidus, whereas distal lesions (below the median eminence) account for 50% to 60%. With the low (distal) lesions, only a small proportion of magnocellular neurons degenerate, and intact cell bodies are able, over weeks to months, to regenerate new axonal terminals at the level of the portal vessels of the median eminence.⁴

Identification of the anatomical location in the brain of the area of neuronal damage is often helpful and necessary in the assessment of the functional significance of the lesion. This is performed with magnetic resonance imaging of the hypothalamus and pituitary.

Idiopathic cases may actually have an identifiable cause. In the few autopsy series performed in patients with this form of central diabetes insipidus, there were reports of atrophic neurohypophyses as well as supraoptic and paraventricular nuclei. Other reports have noted circulating antibodies against ADH-secreting hypothalamic neurons, suggesting an autoimmune variant of this disease.⁴

Genetic. Some of the idiopathic forms of central diabetes insipidus have recently been ascribed to a newly discovered mutation in the neurophysin II coding region of the ADH gene.^{5,6} Exons 1 and 3 are normal, but in exon 2, thymine is substituted for guanine at nucleotide 1884. This in turn induces a substitution of a glycine for a valine in the ADH molecule. Affected patients have both normal and mutant alleles, indicating that this mutation is heterozygous. Accumulation of abnormal ADH in the posterior pituitary cells leads to destruction of the entire cell and the clinical syndrome of diabetes insipidus.

Another form of familial central diabetes insipidus may be due to a substitution of valine for alanine in the gene for the signal peptide for ADH-neurophysin II/copeptide precursor.⁷

Hereditary forms account for only 1% to 2% of all cases of central diabetes insipidus, and autopsy findings in these cases have consistently shown neuronal degeneration and

gliosis of variable numbers of supraoptic and paraventricular nuclei, usually accompanied by a small posterior pituitary gland.⁴

Treatment of central diabetes insipidus

Water is essential: in sufficient quantity, it will correct any metabolic abnormality due to excessive dilute urine.

ADH replacement. The earliest available preparation of ADH was a crude acetone dried extract from bovine or porcine posterior pituitary, given by nasal insufflation. Problems with this preparation included variable duration of activity and local irritation of the nasal mucosa.

Subsequently, a more purified preparation of ADH was developed, known as Pitressin (vasopressin tannate in oil). This is given intramuscularly every 2 to 4 days and provides relief for 24 to 72 hours. Its side effects include abdominal cramping, hypertension, and angina.

The disadvantages of these preparations prompted the development of oral agents to aid in antidiuresis.

Desmopressin (1-deamino-8-*D*-arginine vasopressin, DDAVP) is the current drug of choice for long-term therapy of central diabetes insipidus.⁸ It can be given parenterally, orally, or intranasally. For all dosage forms, the starting dosage is 10 µg at night to relieve nocturia. A morning dose can be added if symptoms persist during the day. The duration of effect of this synthetic peptide is well reproducible in an individual. Therefore, desmopressin dosage and scheduling should be adjusted individually according to the degree of polyuria.

Chlorpropamide (Diabinese), an antidiabetes drug, decreases the clearance of solute-free water, but only if the neurohypophysis has some residual secretory capacity. Its antidiuretic effect is likely due to raising the sensitivity of the epithelium of the collecting duct to low concentrations of circulating ADH.

Carbamazepine (Tegretol), an anticonvulsant, reduces the sensitivity of the osmoregulatory system of ADH secretion and simultaneously raises the sensitivity of the collecting duct to the hydro-osmotic action of the hormone.

Clofibrate (Atromid-S), a lipid-lowering

Desmopressin is the current drug of choice for central diabetes insipidus



agent, stimulates residual ADH production in patients with partial central diabetes insipidus. Chlorpropamide, carbamazepine, and clofibrate all can be used in cases of partial central diabetes insipidus.^{9,10}

Thiazide diuretics paradoxically can be used for treating central diabetes insipidus. They exert their effect by decreasing sodium and chloride absorption in the distal tubule, therefore allowing more sodium absorption—and therefore water absorption—in the proximal tubule.^{9,10}

After starting one of the above agents, it is important to monitor the efficacy of the therapy. This is easily performed by follow-up of electrolyte values.

■ NEPHROGENIC DIABETES INSIPIDUS

In nephrogenic diabetes insipidus, the posterior pituitary is hyperstimulated because of increased plasma osmolality and produces a sufficient amount of ADH, but the kidneys cannot produce maximally concentrated urine in response to it.

Nephrogenic diabetes insipidus can be characterized by three main disturbances in kidney function:

- Disturbance of the generation or maintenance (or both) of the corticomedullary osmotic gradient, which is the driving force for the osmotic water flow from collecting ducts into the interstitial tissue
- Disturbance of osmotic equilibration between the tubular contents and the medullary interstitium due to a defect of the proximal component of the ADH-cyclic adenosine monophosphate system or the distal component or both
- Osmotic diuresis, which produces rapid flow of the tubular fluid and thus prevents its complete osmotic equilibration with the medullary interstitium.^{1,4}

The degree of disease varies among patients. In patients with the complete form, the urine osmolality remains consistently lower than the plasma osmolality, while in partial forms of the syndrome the urine osmolality can be considerably higher.⁴

The many causes of nephrogenic diabetes insipidus can be divided into two categories: acquired and familial (TABLE 2).

TABLE 2

Causes of nephrogenic diabetes insipidus

Acquired

- Renal disease
 - Chronic renal failure
 - Chronic renal medullary disease
 - Pyelonephritis
 - Obstructive uropathy
 - Polycystic kidney disease
 - Renal transplantation
- Electrolyte disturbances
 - Chronic hypokalemia
 - Chronic hypercalcemia

Drugs

- Amphotericin B
- Colchicine
- Demeclocycline
- Gentamicin
- Lithium
- Loop diuretics
- Methoxyflurane
- Pregnancy
- Multiple myeloma
- Sickle cell disease
- Protein starvation

Familial

- V2 receptor mutation (X-linked)
- Aquaporin-2 mutation (autosomal-recessive)

Acquired forms of nephrogenic diabetes insipidus

Acquired forms are more common than familial forms. The kidney is structurally or functionally altered, either permanently or transiently, by disease (the most common cause), drugs, or other conditions so that it is less sensitive to ADH.

Among the systemic circumstances leading to acquired nephrogenic diabetes insipidus are hypokalemia, hypercalcemia, various types of renal disease, and sickle cell anemia.

Hypokalemia. Potassium depletion due to insufficient dietary intake or due to losses (eg, in gastroenteritis) is usually associated with the development of polyuria, polydipsia, and a renal concentrating defect that is resistant to ADH.

Two mechanisms have been proposed to explain the diuresis seen in potassium depletion: an alteration of the generation and

Mutations that cause diabetes insipidus have been discovered

maintenance of the medullary osmotic gradient and resistance of the collecting ducts to the hydro-osmotic effect of ADH.

Chronic hypercalcemia may result in renal interstitial calcification and fibrosis with secondary anatomic disruption of the renal concentrating mechanism, which therefore produces large amounts of dilute urine.

Advanced chronic renal failure in most of its forms features a defect in the renal concentrating capacity, as does **sickle cell anemia**.²⁻⁴

Pregnancy is yet another cause: during pregnancy, vasopressinase produced by the placenta can destroy ADH too rapidly. This type of ADH deficiency often disappears 4 to 6 weeks after delivery, but often recurs with subsequent pregnancies.

Drug-induced diabetes insipidus

A variety of widely used drugs can cause acquired nephrogenic diabetes insipidus.

Lithium salts cause polydipsia and polyuria at the start of treatment in as many as 60% of patients, and these side effects persist in 20% to 25% even if plasma lithium levels are within the therapeutic range. In one reported case, a patient undergoing chronic lithium therapy presented with transient central diabetes insipidus on top of underlying chronic nephrogenic diabetes insipidus.¹¹ Lithium salts have been proposed as a treatment for the chronic syndrome of inappropriate secretion of ADH, but another agent, demeclocycline, has been proven to be more effective.⁴

Demeclocycline, an antibiotic of the tetracycline group, is commonly used by dermatologists to treat acne. In high doses (900–1,200 mg/day), demeclocycline induces polyuria and polydipsia. These side effects might not manifest themselves in the first days or weeks of use, and complete restoration of renal function usually requires several weeks after the drug is stopped.

Both lithium salts and demeclocycline are thought to affect renal function by disturbing some aspect of the proximal component of the ADH-cyclic adenosine monophosphate second-messenger system.⁴

Amphotericin B, a potent antifungal agent, is nephrotoxic. It disturbs the generation and maintenance of the medullary osmotic gradient in the kidney.

Gentamicin seems to impair the cellular response to ADH.

Colchicine inhibits the action of the second messenger by disrupting microtubule function.

Loop diuretics have been shown to worsen renal function in some cases.¹

Foscarnet, which is used to treat cytomegalovirus infection, has recently been shown to cause nephrogenic diabetes insipidus in certain patients.¹²

Familial nephrogenic diabetes insipidus

Familial nephrogenic diabetes insipidus is rare and can be caused by two different genetic defects.

V2 receptor mutations. Mutations in the gene encoding the ADH type 2 receptor (V2 receptor) cause an X-linked form of the disease. More than 60 different disease-causing mutations have been identified throughout the V2 receptor gene.¹³

Aquaporin-2 mutations. Mutations in the gene encoding the ADH-dependent water channel aquaporin-2 are responsible for an autosomal-recessive form, and in some cases an autosomal-dominant type of the disease. The conformational change in the aquaporin-2 channel leads to improper fluid exchange in the distal collecting system and polyuria.¹³ Autosomal-recessive nephrogenic diabetes insipidus appears in 10% of families. In these patients, a normal extrarenal response to ADH is observed, indicating unresponsiveness to ADH restricted to the kidney.

Earm et al¹⁴ examined the effect of hypercalcemia on the expression of aquaporin-2 in rat kidneys. They found that hypercalcemia decreased the expression of aquaporin-2 in the inner medulla and cortex of the kidneys, and they concluded that aquaporin-2 downregulation and reduced plasma membrane delivery of aquaporin-2 play important roles in the development of polyuria in association with hypercalcemia.

The way to distinguish between patients with a V2 receptor defect and those with an aquaporin-2 defect is with a trial of desmopressin therapy: those with an aquaporin-2 defect will have a response to desmopressin, but those with a V2 receptor defect will not.¹³

Thiazide diuretics can paradoxically improve diabetes insipidus



Treatment of nephrogenic diabetes insipidus

Treating nephrogenic diabetes insipidus involves a different regimen than for central diabetes insipidus. Nephrogenic diabetes insipidus does not respond to ADH; instead, it is treated by correcting hypokalemia and hypercalcemia and by discontinuing any drugs that may be causing it.

Thiazide diuretics are used along with modest salt restriction to reduce the delivery of filtrate to the diluting segments of the nephron. They exert their effect by decreasing sodium and chloride absorption in the distal tubule, thereby allowing more sodium absorption and therefore more water absorption in the proximal tubule.^{10,15}

REFERENCES

1. **Cagno JM.** Diabetes insipidus. *Crit Care Nurse* 1989; 9:86–93.
2. **Singer I, Oster JR, Fishman LM.** The management of diabetes insipidus in adults. *Arch Intern Med* 1997; 157:1293–1301.
3. **Adam P.** Evaluation and management of diabetes insipidus. *Am Fam Physician* 1997; 55:2146–2153.
4. **Kovacs L, Lichardus B.** Vasopressin, Disturbed Secretion and Its Effects. Prague: Kluwer Academic Publishers, 1989.
5. **Ueta Y, Taniguchi S, Yoshida A, et al.** A new type of familial central diabetes insipidus caused by a single base substitution in the neurophysin II coding region of the vasopressin gene. *J Clin Endocrinol Metab* 1996; 81:1787–1790.
6. **Rauch F, Lenzner C, Nurnberg P, Frommel C, Vetter U.** A novel mutation in the coding region for neurophysin-II is associated with autosomal dominant neurohypophyseal diabetes insipidus. *Clin Endocrinol (Oxf)* 1996; 44:45–51.
7. **Repaske DR, Medlej R, Gultekin EK, et al.** Heterogeneity in clinical manifestation of autosomal dominant neurohypophyseal diabetes insipidus caused by a mutation encoding Ala-1 → Val in the signal peptide of the arginine vasopressin/neurophysin II/copeptin precursor. *J Clin Endocrinol Metab* 1997; 82:51–56.
8. **Lam KS, Wat MS, Choi KL, Ip TP, Pang RW, Kumana CR.** Pharmacokinetics, pharmacodynamics, long-term efficacy, and safety of oral 1-deamino-8-D-arginine vasopressin in adult patients with central diabetes insipidus. *Br J Clin Pharmacol* 1996; 42:379–385.
9. **Gregerman RI.** Selected endocrine problems. In: Barker LR, Burton JR, Zieve PD, editors. *Principles of Ambulatory Medicine*, 3rd edition. Baltimore, MD: Williams and Wilkins Publishers, 1991:997–998.
10. **Seckl JR, Dunger DB.** Diabetes insipidus. Current treatment recommendations. *Drugs* 1992; 44:216–224.
11. **Posner L, Mokrzycki MH.** Transient central diabetes insipidus in the setting of underlying nephrogenic diabetes insipidus associated with lithium use. *Am J Nephrol* 1996; 16:339–343.
12. **Navarro JF, Quereda C, Quereda C, et al.** Nephrogenic diabetes insipidus and renal tubular acidosis secondary to foscarnet therapy. *Am J Kidney Dis* 1996; 27:431–434.
13. **Knoers NV, van Os CH.** Molecular and cellular defects in nephrogenic diabetes insipidus. *Curr Opin Nephrol Hypertens* 1996; 5:353–358.
14. **Earm JH, Christensen BM, Frokiaer J, et al.** Decreased aquaporin-2 expression and apical plasma membrane delivery in kidney collecting ducts of polyuric hypercalcemic rats. *J Am Soc Nephrol* 1998; 9:2181–2193.
15. **Kim GH, Lee JW, Oh YK, et al.** Antidiuretic effect of hydrochlorothiazide in lithium-induced nephrogenic diabetes insipidus is associated with upregulation of aquaporin-2, Na-Cl co-transporter, and epithelial sodium channel. *J Am Soc Nephrol* 2004; 15:2836–2843.

ADDRESS: *Samy I. McFarlane, MD, Department of Medicine, Box 50, State University of New York Health Science Center at Brooklyn, Kings County Hospital Center, 450 Clarkson Avenue, Brooklyn, NY 11203; e-mail Samy.McFarlane@downstate.edu.*

Dear Doctor:

We'd like to know...

As editors, we'd like you to look into every issue, every page of the *Cleveland Clinic Journal of Medicine*.

1 How many issues do you look into?

Here's our goal:

- All Most Half Few

2 How do you read the average issue?

Here's our goal:

- Cover-to-cover
 Most articles
 Selected articles

We put it in writing...please put it in writing for us.
We want to hear from you.

CLEVELAND CLINIC JOURNAL OF MEDICINE
The Cleveland Clinic Foundation
9500 Euclid Avenue, NA32
Cleveland, Ohio 44195

PHONE 216.444.2661

FAX 216.444.9385

E-MAIL ccjm@ccf.org

