Diabetes Insipidus

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Abstract

Diabetes insipidus is a syndrome of dysregulated free water balance resulting from vasopressin deficiency or insensitivity of the kidney to vasopressin action. In the absence of vasopressin-mediated urinary concentration, there is increased excretion (polyuria) of dilute urine. The loss of free water leads to increased thirst and water intake (polydipsia). If the thirst is not quenched, the progressive free water deficit leads to a hyperosmolar state characterized by plasma hypernatremia. Diabetes insipidus may be categorized as central (or neurogenic), when due to vasopressin deficiency, or nephrogenic, when the result of diminished renal responsiveness to the antidiuretic action of vasopressin. Central diabetes insipidus can be treated with vasopressin or vasopressin analogues such as desmopressin. Treatment of nephrogenic diabetes insipidus typically depends upon reversal of the underlying cause, but pharmacological treatment may be partly successful.

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Introduction

Diabetes insipidus is a syndrome of dysregulated free water balance resulting from vasopressin deficiency or insensitivity of the kidney to vasopressin action. In the absence of vasopressin-mediated urinary concentration, there is increased excretion (polyuria) of dilute urine. The loss of free water leads to increased thirst and water intake (polydipsia). If the thirst is not quenched, the progressive free water deficit leads to a hyperosmolar state characterized by plasma hypernatremia. Diabetes insipidus may be categorized as central (or neurogenic), when due to vasopressin deficiency, or nephrogenic, when the result of diminished renal responsiveness to the antidiuretic action of vasopressin. Central diabetes insipidus can be treated with vasopressin or vasopressin analogues such as desmopressin. Treatment of nephrogenic diabetes insipidus typically depends upon reversal of the underlying cause, but pharmacological treatment may be partly successful.

Normal Physiology of Water Balance

Vasopressin is the mammalian antidiuretic hormone and regulator of free water balance and plasma osmolality. Vasopressin regulates plasma sodium concentration but does not control total body sodium content and thus has little effect on total body volume. Vasopressin is synthesized in neurons of the hypothalamus and then undergoes axonal transport through the pituitary stalk to the nerve endings that form the posterior pituitary gland. Regulated vasopressin secretion from the posterior pituitary occurs in response to physiological stimuli, such as hyperosmolality and volume depletion [1]. In the kidney, circulating vasopressin can bind to V2 vasopressin receptors located on the basolateral surface of epithelial cells in the distal tubule and collecting duct of the nephron. V2 vasopressin receptor activation drives synthesis and translocation of water channels (aquaporin 2) to the luminal surface of the epithelial cells. These channels facilitate reabsorption of water from luminal fluid into the tubular cell [2]. Other water channels (aquaporin 3 and aquaporin 4) that are constitutively present in the basolateral membrane transport water from within the tubular cell to the circulation [3]. The overall effect of the tubular reabsorption of water is to concentrate the urine and conserve total body water.

Plasma osmolality normally is regulated within a narrow range of approximately 280–295 mosm/kg [1, 4]. After water deprivation, increased plasma osmolality stimulates release of vasopressin from the posterior pituitary. Vasopressin-mediated urine concentration increases urine osmolality to greater than plasma osmolality, and with maximal urinary concentration, urinary osmolality can be as high as 1,000 mosm/kg. If the action of circulating vasopressin is not sufficient to maintain appropriate free water balance, a further increase in plasma osmolality stimulates thirst, which is the behavioral drive for the intake of additional free water. With sufficient free water intake, plasma osmolality is maintained in the normal range [5]. However, if thirst is impaired or water is not available, continued dehydration will result in the development of hyperosmolarity.

Clinical Presentation

The clinical hallmarks of diabetes insipidus are polyuria of inappropriately dilute urine and hyperosmolarity. Polyuria can be defined as a urine output of greater than 2 l/m^2 per day or approximately 40 ml/kg/day [6] and may be due

to either a solute diuresis or water diuresis [7]. A solute diuresis can result from an excess excretion of either inorganic or organic solute. For example, after the intravenous administration of large volumes of saline, glomerular filtration of the excess sodium will produce a solute diuresis as the excess sodium is excreted in the urine. Most diuretics produce a diuresis by increasing distal delivery of isotonic tubular filtrate to increase the volume of urine output. Excess delivery of other inorganic solutes, such as ammonia or bicarbonate, also can induce a solute diuresis. Glucose will produce polyuria if plasma levels are sufficiently high (typically >180 mg/dl) so that the rate of glomerular filtration overwhelms the tubular reabsorption of glucose. Other organic solutes, such as mannitol, can be filtered but do not undergo tubular reabsorption and will produce a solute diuresis [7]. Therefore, a solute diuresis will result in copious production of urine, but the presence of solute typically produces in non-dilute urine with urine osmolality greater than or equal to plasma osmolality.

A water diuresis is characterized by production of large volume of dilute urine with an osmolality less than plasma osmolality and typically less than 200 mosm/kg. A water diuresis can occur in response to a large water load such as the intentional intake of excess free water (polydipsia) [7]. Primary polydipsia may be related to a pathophysiological disorder of thirst secondary to disruption of thirst regulation in the hypothalamus (dipsogenic polydipsia) [8]. More typically, primary polydipsia is a volitional act with water drunk in a volume in excess of the needs of the body to maintain a normo-osmolar state. Primary polydipsia may occur from habit or in response to social cues but when severe is usually related to a psychiatric disturbance (psychogenic polydipsia). Patients with non-dipsogenic polydipsia do not have increased thirst per se, but patients with psychogenic polydipsia have compulsive drinking that remits with resolution of psychiatric symptoms [5]. In contrast to primary polydipsia, patients with diabetes insipidus excrete dilute, hypo-osmolar urine due to impaired urinary concentrating ability, and the resulting increased thirst and secondary polydipsia are an appropriate physiological response to the loss of free water.

Hypernatremia is the most commonly measured manifestation of a hyperosmolar state. Sodium, with an equimolar amount of anions, accounts for most of the measurable and effective osmotic load of plasma. A free water deficit that results in a hyperosmolar state will produce hypernatremia and therefore the plasma sodium level frequently serves as a clinical surrogate for osmolality. Hypernatremia can result from sodium excess or free water deficit [9]. Most circumstances of excess sodium intake occur in situations where the individual has little control of intake. Examples of clinical situations with sodium excess include excess administration of hypertonic intravenous fluids and excessive oral ingestion of hypertonic fluids such as seawater or hypertonic infant formula [10]. Hypernatremia more commonly is the result of a free water deficit. Water deprivation with persistent insensible losses leads to a free water deficit that will cause a progressive increase in plasma osmolality. The normal response to hyperosmolality is increased secretion of vasopressin that acts on the kidney to concentrate the urine and facilitate free water conservation. After loss of both salt and water, impaired access to water or a relatively greater loss of water can lead to hypernatremia even if total body sodium is also depleted. Thus, a diuresis can produce both hypernatremia and a decrease in blood volume. Diabetes insipidus is characterized by a defect in renal free water conservation. Patients with diabetes insipidus develop increased thirst and polydipsia to prevent development of hyperosmolality, but if free water intake is impaired, hyperosmolality and hypernatremia will develop.

Diabetes insipidus may occur acutely or may present as a more chronic condition. Nontraumatic central diabetes insipidus and most cases of nephrogenic diabetes insipidus present as chronic conditions. Hypothalamic or pituitary damage can lead to the acute onset of diabetes insipidus. The classic triphasic response has been described after injury to the pituitary or neurohypophysis [11]. This is of particular note when managing

the postoperative care of patients after surgery of the pituitary or hypothalamus. Within the first 12–48 h after acute trauma, vasopressin secretion may be severely impaired and result in diabetes insipidus. If the damage is severe enough to produce axonal degeneration of vasopressin-secreting neurons, there will be unregulated release of vasopressin to the peripheral circulation. This can result in inappropriate anti-diuresis (SIADH) and may lead to development of hyponatremia between 5 and 12 days after pituitary damage. If the trauma is so severe as to cause death of vasopressinergic neurons, then prolonged diabetes insipidus may ensue. Only some phases of this response may be clinically evident after acute damage to the pituitary or pituitary stalk, with no more than 10% of patients exhibiting all three phases [11].

The effect of diabetes insipidus on growth and development of children depends upon the age at which the disease becomes clinically apparent. With untreated diabetes insipidus, increased fluid intake will alter caloric intake. Children who drink water in preference to food or who have anorexia related to hypernatremia may show growth delay due to chronic derangement of water balance and caloric malnutrition [12]. However, intake of large quantities of sweetened beverages in response to the increased thirst of diabetes insipidus can markedly increase caloric intake and lead to obesity. Nursing infants can receive both caloric and free water intake from breast milk or formula. Chronic water deprivation in infants can lead to failure to thrive, irritability, constipation, and even fever [13]. However, increased formula intake in response to increased thirst will provide calories in excess of needs and may result in the development of obesity in infants with diabetes insipidus [14].

Causes of Diabetes Insipidus

Diabetes insipidus results from an inadequate level of vasopressin or an impaired renal response to circulating vasopressin. Inadequate levels of vasopressin are nearly always associated with impaired pituitary secretion of vasopressin and can result from three main mechanisms: congenital deficiency of vasopressin, physical destruction of vasopressin-secreting neurons, or the presence of an infiltrative or inflammatory process that inhibits vasopressin synthesis, transport, or secretion (Table 9.1). The underlying cause may not be apparent in nearly half of the cases of central diabetes inspidus [15].

Table 9.1 Causes of central diabetes insipidus (reprinted with permission)

Congenital:
Developmental defects: septo-optic dysplasia, other mid-line defects
Inherited genetic defects: familial diabetes insipidus, wolfram (DIDMOAD) syndrome
Pituitary injury
Head trauma
Supra-sellar tumors: craniopharyngioma, germinoma
Pituitary macroademona
Surgery
Vascular: cerebral aneurysm, intracranial hemorrhage, sickle cell disease
Infiltrative and inflammatory disorders:
Granulomatous diseases: histiocytosis, sarcoidosis, Wegener's granulomatosis, syphilis
Neoplasm: CNS lymphoma, leukemia, metastatic carcinoma (breast)
Infections: bacterial meningitis, tubercular meningitis, viral encephalitis
Autoimmune hypophysitis

Vasopressin deficiency may occur with a wide variety of congenital disorders, such as septo-optic dysplasia, that disrupt the normal development of the pituitary gland and other midline structures [16]. Diabetes insipidus is part of Wolfram's (DIDMOAD) syndrome that is characterized by central Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and sensorineural Deafness resulting from mutation of the wolframin gene [17].

Familial diabetes insipidus is inherited as an autosomal dominant syndrome of vasopressin deficiency [18]. Infants are normal at birth, but between ages 2 and 10 years they develop vasopressin deficiency and diabetes insipidus. The few reported autopsies in individuals with this disorder have suggested that there may be degeneration of vasopressin-secreting neurons [19], but this has

not been confirmed. Mutations have been identified at more than 30 sites within the vasopressin pre-prohormone [20, 21]. Most of these mutations are located in regions of the vasopressin precursor that do not encode the vasopressin peptide. Vasopressin deficiency resulting from one identified point mutation within the vasopressin peptide sequence is inherited as an autosomal recessive disorder. This mutation produces leucine-vasopressin that has a limited ability to activate the vasopressin receptor in the kidney [22].

Destruction of the pituitary gland, pituitary stalk, or hypothalamus can cause diabetes insipidus [13, 15, 23, 24]. Head trauma can cause transection of the pituitary stalk to produce diabetes insipidus. However, the more common causes of pituitary destruction are tumors of the pituitary, hypothalamus, or surrounding structures. Suprasellar tumors such as craniopharyngioma and germinoma may present with diabetes insipidus. Surgical resection of pituitary or hypothalamic masses can cause temporary or permanent impairment of vasopressin secretion if there is damage to the pituitary gland or stalk. Radiation of the hypothalamus or pituitary can disrupt anterior pituitary function but rarely has been reported to cause vasopressin deficiency.

A wide variety of infiltrative and infectious disorders have been associated with the development of central diabetes insipidus [13, 15, 23–26]. Infiltration of the pituitary stalk can disrupt transport of vasopressin to the posterior pituitary. Germinomas, sarcoidosis, and histiocytosis X are the most commonly reported causes of diabetes insipidus due to infiltration of the pituitary gland or stalk. Acute bacterial meningitis and chronic meningeal processes such as tuberculosis and CNS lymphoma also can lead to central diabetes insipidus. "Idiopathic" central diabetes insipidus may represent a stalk lesion that is too small to visualize on MRI. Although more common in adults, lymphocytic hypophysitis with involvement of the stalk of posterior pituitary has been reported in children [27, 28]. One report has suggested a relationship between a prior viral infection and the onset of idiopathic diabetes insipidus [15].

Diabetes insipidus occasionally may present during pregnancy, particularly in individuals with a preexisting partial defect of vasopressin secretion. Circulating peptidases, synthesized in the placenta, can participate in the degradation of vasopressin [15]. If the pituitary is unable to respond with an appropriate increase in vasopressin production and synthesis, the patient may develop diabetes insipidus. This syndrome should resolve after delivery, but occurrence of diabetes insipidus during pregnancy may be evidence of an underlying partial diabetes insipidus and indicate a need for further evaluation of water balance regulation and vasopressin action in the postpartum period [29].

When the renal response to vasopressin is impaired, an individual develops nephrogenic diabetes insipidus. Inherited defects associated with nephrogenic diabetes insipidus have been identified in the V2 vasopressin receptor and in aquaporin 2, the water channel regulated by vasopressin [30]. Most mutations associated with abnormal V2 receptor function are inherited as X-linked recessive disorders and impair the receptor response to vasopressin [31] by decreasing vasopressin binding or downstream signaling [32]. Recently, gain of function mutations at the same codon within the V2 receptor gene have been shown to cause chronic nephrogenic syndrome of inappropriate antidiuretic hormone action in two patients [33]. Mutations of aquaporin 2 that are associated with nephrogenic diabetes insipidus are autosomal recessive. Most functional studies of these mutations have shown them to impair intracellular transport and subsequent vasopressin-mediated translocation of the aquaporin into the apical membrane of the renal tubular cell [34, 35]. However, some of these mutations may impair the water channel function of the aquaporin [36] or prevent formation of aquaporin tetramers in the cell membrane [37].

Acquired nephrogenic diabetes insipidus typically is not as severe as inherited forms and usually is related to underlying renal tubular or interstitial damage. Medullary or interstitial damage may affect water balance, not by inhibiting vasopressin action, but by disruption of the medullary gradient, which can prevent urinary concentration greater than plasma osmolality. Thus, interstitial kidney disease can produce a relative

Table 9.2 Reported causes of nephrogenic diabetes insipidus (reprinted with permission)

Congenital:
Inherited genetic disorders: mutations in V2 receptor or aquaporin 2
Renal malformations: congenital hydronephrosis, polycystic kidney
Acquired disorders:
Electrolyte disorders: hypokalemia, hypercalcemia
Renal diseases: obstructive uropathy, chronic pyelonephritis, polycystic kidney disease
Systemic diseases: sickle cell disease, amyloidosis, multiple myeloma, sarcoidosis
Drugs:
Lithium salts
Methoxyflurane
Alcohol
Demeclocycline and other tetracyclines
Anti-infectious agents: foscarnet, amphotericin, methicillin, gentamicin
Anti-neoplastic agents: cyclophosphamide, isophosphamide, vinblastine, platinum
Other: phenytoin, acetohexamide, glyburide, tolazamide, colchicine, barbiturates

vasopressin resistance [38]. A wide variety of agents and processes have been associated with development of nephrogenic diabetes insipidus (Table 9.2). The precise mechanism by which most of these agents inhibit vasopressin action and exert their effect is not known. Some drugs, such as demeclocycline, appear to impair post-receptor signaling of the V2 receptor. Nearly half of all cases of drug-induced nephrogenic diabetes insipidus are related to the long-term use of lithium salts [39], which may inhibit post-receptor activation and thereby decrease transcription of aquaporin mRNA, aquaporin synthesis, and translocation of aquaporin into the apical membrane of tubular cells. In individuals receiving chronic lithium therapy, the reported prevalence of lithium-induced diabetes insipidus varies between 20 and 70% and may depend upon the dose and duration of therapy. The differentiation of acute and chronic lithium injury remains unclear. Short-term exposure to lithium may impair urine concentrating ability in more than one-half of individuals. With discontinuation of lithium, renal function returns to normal. However, with prolonged exposure to lithium, irreversible changes occur with permanent renal tubule insensitivity to vasopressin and resulting impairment of urine concentration and free water preservation [40].

Diagnosis

The hallmarks of diabetes insipidus, polyuria and hyperosmolality, can present with varying degrees of severity, and each can be caused by a wide variety of other conditions. Thus, the diagnosis of diabetes insipidus requires sufficient evaluation to characterize the polyuria and hyperosmolarity and to rule out other conditions that could present with similar findings. It is important to confirm the diagnosis of diabetes insipidus before pursuing an extensive evaluation to determine the etiology or initiating therapy in an individual patient.

The diagnosis of diabetes insipidus depends upon confirmation of disrupted free water balance by characterizing the polyuria and the potential hyperosmolar state. Other causes of polyuria, such as primary polydipsia or an osmotic diuresis, must be ruled out by clinical evaluation and laboratory analysis. For example, the hyperglycemia of diabetes mellitus can produce polyuria and eventually result in hypernatremia. An individual with polydipsia and plasma sodium level that is low or low normal (and not near the upper range of normal) more likely has primary polydipsia and does not have diabetes insipidus. Conversely, in an individual with diabetes insipidus, polydipsia is driven by the free water deficit and resulting hyperosmolality, and it is unlikely that plasma sodium levels will be low.

The manner of diagnosing diabetes insipidus depends upon the presentation and clinical setting. A patient that slowly develops diabetes insipidus as an outpatient may be able to maintain sufficient oral intake of free water to maintain a normal plasma osmolality. This individual may present with complaints of excessive thirst and frequent urination. One clinical clue that these symptoms are not due to primary polydipsia may be bedwetting or frequent nocturia with high levels of urine output occurring during

periods of decreased water intake. Patients with well-compensated DI are at risk for decompensation if they develop an acute medical illness or are otherwise limited in free water intake. In the same way, an individual developing acute DI after pituitary surgery or head trauma may not be able to respond to the need for increased free water intake and quickly will develop a hyperosmolar state.

The diagnosis of diabetes insipidus can be confirmed by observing the response to water deprivation (Table 9.3). The normal response to a free water deficit and mild increase in plasma osmolality is increased vasopressin secretion, which acts on the renal tubules to conserve free water and maintain plasma osmolality in the normal range. In an individual with diabetes insipidus, impaired free water conservation permits persistent excretion of an inappropriate volume of dilute urine. In the absence of increased water intake, this leads to a free water deficit and the development of hypernatremia.

The possibility of diabetes insipidus may be raised if a patient has a marked polyuria after head trauma or a surgical procedure in which the pituitary could be damaged. If access to ad-lib water intake is limited, excretion of inappropriately dilute urine (urine osmolality less than plasma osmolality) will lead to continued free water loss and development of hypernatremia. Careful assessment of documented fluid balance (I+O's) in the operating room and postoperative period and measurement of plasma and urine concentration will help in determining if persistent polyuria is driven by prior fluid overload or due to the development of diabetes insipidus. Development of hypernatremia with inappropriately dilute urine should be confirmed with laboratory measurement of plasma and urine osmolality. In the absence of hypernatremia, postoperative polyuria is more likely to represent a diuresis in response to intravenous fluid administered during or after surgery. Appropriate management of individuals with postoperative diuresis and possible diabetes insipidus should include serial measurement of plasma sodium and urine-specific gravity every few hours until the diuresis resolves.

Table 9.3 Diagnostic testing for diabetes insipidus (summary) (reprinted with permission)

I. Basal testing:
A. Diabetes insipidus unlikely:
serum osmolality <270 mosm/kg, urine osmolality >600 mosm/kg, or urine output <1 l/m^2
B. Diabetes insipidus likely:
serum osmolality >300 (or serum sodium >150 meq/l) with urine osmolality <300 mosm/kg
II. Water deprivation study:
A. Water deprivation:
1) Precede by overnight fast (if tolerated and if indicated by clinical circumstances)
2) Continue complete water deprivation until:
loss of >5% of basal body weight or
plasma osmolality >300 mosm/kg or
urine osmolality >600 mosm/kg
3) Also discontinue if signs of hemodynamic compromise (blood pressure, heart rate)
B. Vasopressin administration:
1) Parenteral administration of vasopressin analogue
Vasopressin (Pitressin) 1 μ/m^2
Desmopressin (DDAVP) 0.1 μg/kg (maximum 4 μg)
2) Differential response to vasopressin
Central diabetes insipidus:
decrease in hourly urine output
urine osmolality increases by 50%
Nephrogenic diabetes insipidus:
no decrease in urine output
no increase in urine osmolality
III. Saline infusion:
1) Consider prior water load to suppress vasopressin secretion
2) 3% saline at 0.1 ml/kg/h for up to 3 h or until plasma osmolality >300 mosm/kg
3) Urine output decreases and urine osmolality increases when plasma osmolality reaches vasopressin secretory threshold
4) Analyze relationship between plasma osmolality, urine osmolality, and plasma/urine vasopressin levels using appropriate nomograms [4, 5, 41, 43]

In an individual with a likely cause for diabetes insipidus and acute development of dilute polyuria and hypernatremia, a clinical diagnosis of diabetes insipidus may be made. If this patient has hypernatremia in the presence of dilute urine, then a formal water deprivation may not be required for the diagnosis of diabetes insipidus.

In subjects with a clinical diagnosis of acute central diabetes insipidus, a therapeutic trial of desmopressin may be an appropriate diagnostic maneuver. However, pitfalls to this approach include the presence of a concurrent cause of polyuria and hypernatremia. For example, an osmotic diuresis following administration of mannitol during a neurosurgical procedure may produce polyuria and possibly mild hypernatremia if water access if impaired. Other medical problems may obscure the diagnosis of diabetes insipidus. For example, in patients with severe hypothalamic or pituitary destruction, centrally mediated cortisol or thyroid hormone deficiency may impair free water clearance [11].

In individuals where the diagnosis of diabetes insipidus is not well documented, a formal diagnostic test must be performed. One of the most common tests to confirm the diagnosis of diabetes insipidus is the water deprivation test [6, 13, 25, 41]. The water deprivation test should be performed in a clinical setting that provides adequate monitoring of the patient. This is particularly important when studying young children. The water deprivation test is rarely appropriate for the evaluation of infants. As illustrated in Table 9.3, the goal of the water deprivation test is to deprive the individual of sufficient free water so that vasopressin, if present, will be released and act on the kidney to promote urinary concentration. In the absence of vasopressin, free water deprivation will permit continued excretion of dilute urine, leading to a free water deficit and development of hyperosmolality. Subjects can be prepared for the formal water deprivation test by an overnight fast of food and water. It is important to ensure that the duration of overnight avoidance of food and fluid does not exceed the maximum duration the child can normally go without fluid intake. This decreases the osmotic load to the kidneys and begins the process of water deprivation. However, depending upon the clinical circumstances and age, some patients may require close observation during the entire period of deprivation. Up to 14 h of water deprivation may be required to complete an informative study in a patient with mild symptoms [13].

Once the diagnosis of diabetes insipidus is confirmed, the response to administration of vasopressin (or a vasopressin analogue such as desmopressin) demonstrates whether the diabetes insipidus is due to vasopressin deficiency or an impaired renal response to vasopressin [6, 13, 25, 41]. After vasopressin administration, patients with complete central diabetes insipidus typically have a greater than 50% increase in urinary osmolality. However, a urine osmolality greater than 600 mosm/kg is also an appropriate response and may be seen in cases of partial diabetes insipidus. Individuals with primary polydipsia should retain the ability to concentrate urine to greater than 600 mosm/kg and may demonstrate little additional response after desmopressin administration. Typically, when vasopressin or desmopressin is administered to patients with nephrogenic diabetes insipidus, the urine osmolality will not increase greater than 400 mosm/kg and usually remains less than plasma osmolality [25].

In some cases, the results of the formal water deprivation test may be inconclusive [5, 41]. With a partial central deficiency of vasopressin, there may be some measurable response to water deprivation, but urinary concentration may not be normal. In cases of long-standing central diabetes insipidus, the response to exogenous vasopressin administration may be impaired due to washout of the renal medullary gradient. Patients without diabetes insipidus, including those with primary polydipsia, should maximally concentrate urine with adequate water deprivation and thus may not have a significant additional response to exogenous vasopressin. Therefore, endpoints need to be set for concluding a water deprivation study [6, 13, 25, 41]. There are three: (1) persistent inappropriately low urinary osmolality despite a 3% loss of body weight, (2) hyperosmolarity and hypernatremia with an inappropriately low urinary osmolality, and (3) appropriate urinary concentration (greater than 600 mosm/kg). Urine osmolality may appear to plateau at a submaximal concentration (<600 mosm/kg) without development of plasma hyperosmolarity. However, if the patient shows no signs of volume deficiency, then the water deprivation should be continued to determine if further concentration of urine to greater than 600 mosm/kg can be achieved. A common error that leads to an inconclusive test is

ending the test after the patient has lost a certain percentage of body weight without regard for the clinical circumstances. In patients who are fluid replete or overloaded before the test (as in patients with primary polydipsia), the serum osmolality may not have risen enough to reach the threshold for vasopressin secretion at the end of the test. It is thus useful to also use increase in heart rate and other clinical criteria to assess the fluid status to decide when to end the test. In some cases, it may be appropriate to use a therapeutic trial of desmopressin for a week. If the patient responds to therapy this may confirm the diagnosis of central diabetes insipidus. If further testing is desired, the week of therapy should facilitate recovery of the concentrating gradient in the kidney, which may normalize the response to a test dose of desmopressin.

Other diagnostic tests may be needed to confirm the diagnosis of diabetes insipidus. Typically, urine or plasma vasopressin levels are not readily available but usually are not required for the diagnosis of diabetes insipidus. However, in selected clinical circumstances a vasopressin level may be helpful [5, 41, 42]. A plasma vasopressin level obtained after water deprivation will distinguish between central and nephrogenic diabetes insipidus [42], particularly in cases where there is only a partial defect in vasopressin secretion or action [5, 41]. To be most informative, plasma vasopressin must be evaluated as a function of plasma osmolality [41]. Vasopressin levels can be increased by hypotension, smoking, and nausea, and these stimuli should be avoided during testing for diabetes insipidus [15, 41]. Concurrent plasma osmolality and vasopressin levels obtained during a saline infusion also may help identify a partial defect in vasopressin secretion or may be useful when trying to study a patient that has a high likelihood of both central and nephrogenic diabetes insipidus.

The saline infusion test [5, 15, 43] may be useful in patients in whom water deprivation cannot be performed because of hemodynamic instability or in whom it would be difficult to obtain cooperation with water deprivation [43]. For example, infants cannot tolerate an extended fast. A solution of 3% sodium chloride infused over 2–3 h at a dose of 0.1 cm^3/kg/h will provide a hyperosmolar stimulus to vasopressin secretion [5, 43]. When the threshold for vasopressin secretion is reached, plasma and urinary vasopressin levels will increase, and urinary osmolality will increase abruptly in response to increased vasopressin action on the kidney. Some authors suggest a water load (20 ml/kg of 5% dextrose intravenous over 2 h) prior to the saline infusion to ensure that vasopressin levels are suppressed at the beginning of the saline infusion test [43]. Comparison of plasma vasopressin levels with corresponding plasma osmolality measurements can be used to determine if there is an appropriate relationship in the regulation of vasopressin secretion [5, 25, 43]. This test also is useful in identifying patients with normal vasopressin secretory ability, but an altered osmotic threshold for the release of vasopressin [25].

Interpretation of the saline infusion test may be complicated by a number of issues. Vasopressin is highly labile and can degrade if the blood sample is not collected, processed, and stored correctly. Blood samples should be kept on ice and carefully processed immediately after the blood is obtained, and the plasma kept frozen until assayed [44]. Vasopressin levels rarely are assayed in hospital labs and, thus, the samples must be sent to a reference laboratory, which will increase turnaround time for receiving test results. Clinical laboratories typically do not measure plasma osmolality with high precision, and this may further complicate the interpretation of the saline infusion test [5].

Once the diagnosis of diabetes insipidus is made, then efforts can be made to further identify the underlying cause if it is not clear from the clinical presentation. Patients with central diabetes insipidus should undergo imaging of the pituitary and hypothalamus. Unless a large intracranial mass is suspected, computed tomography (CT) is of little use in determining the cause of diabetes insipidus. Magnetic resonance imaging (MRI) allows a more detailed study of the neurohypophysis, including the pituitary and the pituitary stalk [45]. Anterior pituitary microadenomas do not cause diabetes insipidus. The normal posterior pituitary typically has a characteristic bright

spot on MRI, and absence of this characteristic may suggest loss of vasopressin-secreting neurons or deficient vasopressin production. However, a bright spot may not be seen in up to one-fifth of normal individuals [45]. The posterior pituitary bright spot is diminished or absent in both forms of diabetes insipidus, presumably because of decreased vasopressin synthesis in central disease and increased vasopressin release in nephrogenic disease [46–48].

Careful attention to the pituitary stalk may reveal a lesion disrupting vasopressin transport and secretion. Further evaluation of such a lesion will depend upon the clinical history of the patient. The previous diagnosis of a process, such as sarcoidosis that can cause pituitary stalk infiltration, may indicate that watchful observation, while treating the underlying process, is appropriate. Other tests may be needed to identify a systemic illness that may explain the infiltrative process. In rare circumstances, biopsy of the stalk lesion may be needed to rule out a diagnosis such as central nervous system lymphoma. However, this step should be undertaken with due consideration and guidance from experienced endocrinological and neurosurgical consultants, as the biopsy is likely to cause permanent damage to the pituitary stalk. If no lesion can be seen, then other causes, such as an inherited disorder or hypophysitis, should be considered. If no cause for diabetes insipidus can be identified, then the patient should be followed and reassessed regularly. For example, germinomas may disrupt pituitary function and cause diabetes insipidus many years before they are apparent on MRI of the pituitary [24, 26]. Follow-up should include periodic imaging for evidence of a growing mass and repeat assessment of anterior pituitary function, as stalk lesions also may disrupt anterior pituitary function [15, 25].

Patients with nephrogenic diabetes insipidus should be evaluated to exclude an electrolyte disorder, such as hypercalcemia or hypokalemia, that may contribute to renal insensitivity to vasopressin. Even in the absence of mechanical urinary outlet obstruction, diagnostic imaging may reveal hydronephrosis as a result of the high flow of urine in the ureters. This seems to be more common in children and may represent functional urinary obstruction as result of the high urinary flow rate compared to the relative size of the urinary outflow system [49]. Treatment of the diabetes insipidus should help reverse the hydronephrosis.

With a family history of diabetes insipidus, genetic studies may be appropriate to confirm the cause of diabetes insipidus in an individual patient. Genetic studies also should be performed in an individual in whom there is no other apparent mechanism to cause diabetes insipidus. Identification of a genetic cause will eliminate the need for more invasive diagnostic evaluation and may be important if symptoms of diabetes insipidus appear in other family members.

Treatment of Diabetes Insipidus

Adequate free water intake is the first line of therapy for all cases of diabetes insipidus. Patients with an intact thirst mechanism will appropriately regulate plasma osmolality if allowed free access to water. If the patient is unable to drink by mouth, then intravenous administration of free water in the form of hypotonic fluids should be used to prevent development of a hyperosmolar state. If the patient has severe hypernatremia, intravenous administration of hypotonic fluid should be used to replenish the free water deficit.

Vasopressin and analogues such as desmopressin are the specific therapy for central diabetes insipidus [50] (Table 9.4). Because vasopressin must be administered parenterally and has a relatively short half-life, it is not an ideal drug for long-term treatment of diabetes insipidus. However, these same characteristics occasionally make it useful for short-term treatment of acute-onset diabetes insipidus and for use in diagnostic testing.

The synthetic vasopressin analogue desmopressin (dDAVP) is now the standard therapy for central diabetes insipidus [51, 52]. Desmopressin has two molecular alterations compared to native vasopressin: de-amidation of the amino terminal cysteine and replacement of arginine-8 with D-arginine. These

Table 9.4 Vasopressin therapy for the treatment of central diabetes insipidus

Drug	Route	Conc	Adult dose	Duration
Synthetic vasopressin (Pitressin)	IM/SQ	20 U/ml	2–10 U	2–8 h
Desmopressin acetate				
(DDAVP)	IV/SQ	4 mcg/ml	1–4 mcg/day (divided doses)	6–12 h
			0.02–0.1 mcg/kg/dose in young children	
(Desmopressin)	Rhinal tube	100 mcg/ml	5–40 mcg/day	12–24 h
(DDAVP)	Nasal spray	100 mcg/ml	10–40 mcg/day (10 mcg/spray)	12–24 h
(DDAVP)	Oral	100 mcg/tab	100–800 mcg/day (50–300 mcg bid/tid)	8–12 h

two alterations result in a compound with a prolonged half-life of antidiuretic activity and elimination of the pressor activity found in native vasopressin. Desmopressin can be administered parenterally but also can be given by the nasal or oral route. Because of diminished delivery through the nasal or gastric mucosa and proteolysis by mucosal and gastric enzymes, these non-parenteral routes require higher doses of desmopressin than required with intravenous or subcutaneous administration (Table 9.4).

Nasal administration of desmopressin can be accomplished using a rhinal tube or nasal spray. To use the rhinal tube, the patient draws the dose of desmopressin into the flexible plastic rhinal tube, places one end of the tube into the nose, and uses the mouth to blow through the tube to puff the medicine into the nose. Use of the rhinal tube requires that the patient has the dexterity and understanding to follow this technique, although parents can assist children with tube placement and providing the puff of air. Nasal administration of desmopressin can also be performed with a spray pump that administers a premeasured dose of 10 mcg desmopressin per spray. However, utility of this form of nasal desmopressin can be limited in some situations. The fixed dose of the spray precludes small adjustments of dose, and children may require doses smaller than 10 mcg. Some authors suggest diluting the desmopressin 1:10 in saline to facilitate administration of small doses by rhinal tube [23]. Nasal absorption of desmopressin can be affected by upper respiratory congestion. It is however useful as an alternative to oral desmopressin in patients with diabetes insipidus who have nausea and vomiting due to illnesses such as gastroenteritis or in those patients who are unable to take fluids/food orally before anesthesia for a minor procedure.

Most patients with chronic central diabetes insipidus are treated with an oral formulation of desmopressin. As most of an orally administered desmopressin dose is degraded before it can be absorbed, the oral dose is 10- to 20-fold greater than an equivalent nasal dose. Because of variation among individuals in the duration of action of desmopressin, the appropriate dose and frequency must be determined for each individual patient. Although some patients may require only one dose per day, most find management of polyuria and polydipsia easier with oral administration of desmopressin two to three times a day. When initiating desmopressin therapy, it may be useful to start with one bedtime dose and then titrate the size and frequency of dosage based on the patient's response to therapy.

Administration of vasopressin or desmopressin requires careful attention to free water intake to prevent the development of hyponatremia. Oral intake of fluids may be driven by stimuli other than thirst, such as social cues and habitual drinking ingrained during a period of untreated diabetes insipidus. Providing a daily period of "breakthrough" with mild polyuria as the effect of the exogenous vasopressin decreases may be a convenient way to ensure that there is no excessive anti-diuresis with an accumulation of excess free water and progressive development of hyponatremia [50].

In patients treated with desmopressin, oral intake of fluids must be driven by and regulated by thirst. Management of diabetes insipidus in patients with an impaired thirst mechanism requires special attention to fluid balance.

Daily measurement of intake and output as well as body weight may be needed to maintain fluid balance. Frequent monitoring of plasma sodium levels should be used to provide early identification of problems with water balance. However, management of diabetes insipidus in these individuals requires vigilance by the patient, family, and physician.

Perioperative management of diabetes insipidus requires careful attention to fluid balance as assessed by intake and output, daily weight, and laboratory tests such as serum sodium and urine osmolality [11, 50]. Careful measurement of urine volume and concentration may be facilitated by continuing the use of an indwelling urinary catheter for the first 1–2 days after surgery. In patients with preexisting diabetes insipidus, continuing desmopressin therapy will help in the maintenance of water balance. Care must be coordinated with other members of the healthcare team to ensure that fluid balance is carefully managed to prevent hyponatremia due to excess intravenous fluid administration.

Many approaches have been suggested for the management of acute postoperative diabetes insipidus. The first line of treatment remains adequate free water administration to prevent hyponatremia. Some clinicians prefer to use only fluids, while others initiate desmopressin therapy to help fluid balance and to improve patient comfort by decreasing thirst and decreasing the need to void. After trans-sphenoidal pituitary surgery, parenteral administration is used because of the difficulty of nasal administration of desmopressin. Parenterally administered desmopressin also is used as it has a shorter duration of action and decreases the chance of hyponatremia developing in response to excess fluid intake. An intravenous infusion of vasopressin at a low dose (0.08–0.10 mU/kg) can be used in the immediate perioperative period or during other procedures, such as administration of chemotherapy, which have potential disruption of free water balance [53].

Once a postoperative patient is taking oral fluids, fluid balance may be regulated by thirst. Depending upon the likely extent of pituitary and hypothalamic damage, the clinician must be sure that thirst is intact and that the patient is not responding to other cues, such as mouth dryness. Acute pituitary damage is likely to be accompanied by some or all of the classic triphasic response [11]. Patients are at risk for development of severe hyponatremia if desmopressin is continued into the period of SIADH or if a patient drinks to excess during therapy. Therefore, the decision as to whether to use desmopressin in the immediate postoperative period may depend upon the clinician's assessment as to the severity of polyuria, the likelihood that the patient will have permanent diabetes insipidus, the presence or the absence of an intact thirst drive, other medical conditions that may be affected by hypernatremia (or hyponatremia), and patient comfort and convenience. Although symptoms may resolve, there should still be close monitoring of urine output volume, urinary osmolality (or specific gravity, which can be performed at the bedside), and plasma sodium levels to ensure that there is adequate, but not excessive, therapy. When patients are receiving intermittent desmopressin therapy, the onset of polyuria of dilute urine indicates the need for the next dose of desmopressin. Each subsequent dose of desmopressin should not be delayed until the patient again develops hypernatremia. However, patients should not be treated on an arbitrary fixed schedule, as the periodic breakthrough prevents the development of hyponatremia that may result with accumulation of excess free water [50].

Infants are a special challenge in the management of diabetes insipidus as fluid intake is linked to caloric intake and usually is regulated by parents or other caregivers. Their obligatory high oral fluid requirement combined with vasopressin treatment can cause free water accumulation and hyponatremia. For this reason, infants with central diabetes insipidus are often managed with fluid therapy alone. The use of breast milk or low-solute formula (e.g., Similac 60/40) can reduce the urine volume by 20–30% because of the lower renal solute load. Some infants may benefit from the addition of the diuretic chlorothiazide that can increase urine osmolality and decrease urine output. It is available as an oral

suspension and can be given to infants with central and nephrogenic diabetes insipidus at a dose of 5 mg/kg two or three times a day. These two therapeutic interventions significantly reduce the amount of free water supplementation needed in infants with both forms of diabetes insipidus to about 20–30 ml for every 120–160 ml of formula [54]. In some circumstances, infants with central diabetes insipidus can be treated successfully with once-daily subcutaneous injections of desmopressin (initial dose 0.002–0.1 μg/kg once daily, dose can be increased and given twice daily if necessary) until they have transitioned to solid food. Desmopressin therapy in infants through the subcutaneous route has been associated with far fewer episodes of hyponatremia and hypernatremia than the intranasal and the oral routes [55]. However, in general, many infants with central diabetes insipidus can be treated successfully with a combination of low-solute formula (or breast milk) and sufficient free water to maintain a normo-osmolar state. This can be accomplished by careful attention to intake and output and calculation of the volume of formula needed to meet the infant's caloric needs. If an infant is breastfeeding, it may be easier to have the mother use a breast pump so that the volume of milk can be measured accurately. Additional free water then is given to maintain water balance and normal plasma osmolality.

Treatment of nephrogenic diabetes insipidus can be a challenging endeavor. Discontinuation or a decreased dose of the precipitating drug may permit remission of the diabetes insipidus. However, this must be done in consultation with appropriate specialists that can help in management of the underlying disease and in identification of other agents that may be used without the development of diabetes insipidus. For example, use of other neuropsychiatric agents, such as valproic acid or carbamazepine, may permit a dose reduction or discontinuation of lithium. However, some clinical circumstances require continuation of the causative agent and subsequent management of the resulting diabetes insipidus.

Decreasing the solute load to the kidney, with a low-salt and low-protein diet, will decrease the total urine volume and limit the degree of polyuria. Some patients with partial nephrogenic diabetes insipidus may respond to high doses of desmopressin [5]. A variety of agents, including nonsteroidal anti-inflammatory agents and diuretics, have been reported to improve the symptoms of diabetes insipidus. Indomethacin can decrease polyuria and polydipsia, while other agents such as ibuprofen appear to be much less effective [56]. Diuretics, such as hydrochlorothiazide and amiloride (Midamor), probably ameliorate diabetes insipidus by producing a mild chronic volume depletion that leads to increased volume reabsorption in the proximal tubule of the kidney. With decreased distal delivery of filtrate, there is an overall decrease in urine volume. Combined therapy with hydrochlorothiazide and amiloride has been reported to be successful [57]. Amiloride may decrease entry of lithium into tubular cells and thereby decrease the effect of lithium on vasopressin action, and sometimes amiloride therapy will provide complete resolution of lithium-induced nephrogenic diabetes insipidus [40]. Amiloride may not be available in many community pharmacies but should be available from a hospital pharmacy. Individuals with nephrogenic diabetes insipidus can be managed with a combination of hydrochlorothiazide, a nonsteroidal agent such as indomethacin, and high-dose desmopressin, but most patients have only partial remission of symptoms and require increased free water replacement to maintain normo-osmolality.

The use of diuretics for the treatment of diabetes insipidus is not risk-free. The persistent decrease in extracellular volume caused by diuretic therapy puts the patient at risk of hypovolemia and severe dehydration, particularly during an episode of febrile illness or water deprivation. Thiazide diuretics may cause hypokalemia, which can further impair renal responsiveness to vasopressin. Subjects with concurrent lithium-induced diabetes insipidus and hyperparathyroidism are particularly susceptible to water deprivation, as dehydration can precipitate hypercalcemia, and the hypercalcemia can further exacerbate the diabetes insipidus. In patients treated with diuretics for lithium-induced

diabetes insipidus, the resulting volume depletion and the effects on tubular function can decrease lithium clearance and may lead to increased plasma lithium levels.

Management of possible drug-induced nephrogenic diabetes insipidus should begin prior to the development of symptoms such as polyuria and polydipsia. When teenagers and young adults start lithium therapy, they should be informed of the possible development of diabetes insipidus and instructed to monitor urine volume. Progressive development of polyuria may be one indication to reevaluate the need for chronic lithium therapy and consideration of substituting other therapies for lithium.

With attention to water balance and appropriate therapy, diabetes insipidus can be well controlled and have minimal impact on quality of life. Treatment of diabetes insipidus decreases sleep disruption and facilitates full participation in school and daily activities. Treatment of diabetes insipidus has been reported to improve school performance and behavior and to allow normal growth [7, 12]. With appropriate treatment, diabetes insipidus does not cause mental retardation [58]. Patients and families should understand that even short periods of noncompliance with therapy could lead to serious medical complications. However, intercurrent illness or stress can disrupt management of diabetes insipidus even in a well-controlled patient. Patients and caregivers should be instructed to closely follow water intake and urine output and to obtain daily weights during febrile or gastrointestinal illness. Evaluation of any change in mental status should include measurement of serum sodium to rule out hypernatremia due to exacerbation of the diabetes insipidus or hyponatremia secondary to water intoxication. If a patient or family is unable to communicate the history of diabetes insipidus, severe derangement in water balance could occur before the diagnosis of diabetes insipidus is recognized by emergency personnel or health providers unfamiliar with the patient. Thus, patients should be encouraged to wear a medical alert bracelet or other form of identification that provides a clear indication that they have diabetes insipidus.

References

1. Vokes T, Robertson GL. Physiology of vasopressin secretion. In: Czernichow P, Robinson AG, editors. Diabetes insipidus in man, Frontiers of hormone research, vol. 13. Basel: Karger; 1984. p. 127–55.
2. Knepper MA, Verbalis JG, Nielsen S. Role of aquaporins in water balance disorders. Curr Opin Nephrol Hypertens. 1997;6:367–71.
3. Nielsen S, Frokiaer J, Marples D, Kwon TH, Agre P, Knepper MA. Aquaporins in the kidney: from molecules to medicine. Physiol Rev. 2002;82:205–44.
4. Schrier RW, Berl T, Anderson RJ. Osmotic and nonosmotic control of vasopressin release. Am J Physiol. 1979;236:F321–32.
5. Robertson GL. Differential diagnosis of polyuria. Annu Rev Med. 1988;39:425–42.
6. Baylis PH, Cheetham T. Diabetes insipidus. Arch Dis Child. 1998;79:84–9.
7. Oster JR, Singer I, Thatte L, Grant-Taylor I, Diego JM. The polyuria of solute diuresis. Arch Intern Med. 1997;157:721–9.
8. Hammond DN, Moll GW, Robertson GL, Chelmicka-Schorr E. Hypodipsic hypernatremia with normal osmoregulation of vasopressin. N Engl J Med. 1986;315:433–6.
9. Adrogue HJ, Madias NE. Hypernatremia. N Engl J Med. 2000;342:1493–9.
10. Colle E, Ayoub E, Raile R. Hypertonic dehydration (hypernatremia): the role of feedings high in solutes. Pediatrics. 1958;22:5–12.
11. Verbalis JG, Robinson AG, Moses AM. Post-operative and post-traumatic diabetes insipidus. In: Czernichow P, Robinson AG, editors. Diabetes insipidus in man, Frontiers of hormone research, vol. 13. Basel: Karger; 1984. p. 247–65.
12. Kauli R, Galatzer A, Laron Z. Treatment of diabetes insipidus in children and adolescents. In: Czernichow P, Robinson AG, editors. Diabetes insipidus in man, Frontiers of hormone research, vol. 13. Basel: Karger; 1985. p. 304–13.
13. Czernichow P, Pomerade R, Brauner R, Rappaport R. Neurogenic diabetes insipidus in children. In: Czernichow P, Robinson AG, editors. Diabetes insipidus in man, Frontiers of hormone research, vol. 13. Baser: Karger; 1985. p. 190–209.
14. Rogers DG. Morbid obesity in a young child. Clin Pediatr. 2000;39:169–71.
15. Maghnie M, Cosi G, Genovese E, et al. Central diabetes insipidus in children and young adults. N Engl J Med. 2000;343:998–1007.
16. Lees MM, Hodgkins P, Reardon W, et al. Frontonasal dysplasia with optic disc anomalies and other midline craniofacial defects: a report of six cases. Clin Dysmorphol. 1998;7:157–62.
17. Strom TM, Hortnagel K, Hofmann S, et al. Diabetes insipidus, diabetes mellitus, optic atrophy and deafness (DIDMOAD) caused by mutations in a novel

gene (wolframin) coding for a predicted transmembrane protein. Hum Mol Genet. 1998;7:2021–8.
18. Pedersen EB, Lamm LU, Albertsen K, et al. Familial cranial diabetes insipidus: a report of five families. Genetic, diagnostic and therapeutic aspects. Q J Med. 1985;57:883–96.
19. Bergeron C, Kovacs K, Ezrin C, Mizzen C. Hereditary diabetes insipidus: an immunohistochemical study of the hypothalamus and pituitary gland. Acta Neuropathol. 1991;81:345–8.
20. Rittig S, Robertson GL, Siggaard C, et al. Identification of 13 new mutations in the vasopressin-neurophysin II gene in 17 kindreds with familial autosomal dominant neurohypophyseal diabetes insipidus. Am J Hum Genet. 1996;58:107–17.
21. Grant FD, Ahmadi A, Hosley CM, Majzoub JA. Two novel mutations of the vasopressin gene associated with familial diabetes insipidus and identification of an asymptomatic carrier infant. J Clin Endocrinol Metab. 1998;83:3958–64.
22. Willcutts MD, Felner E, White PC. Autosomal recessive familial neurohypophyseal diabetes insipidus with continued secretion of mutant weakly active vasopressin. Hum Mol Genet. 1999;8:1303–7.
23. Greger NG, Kirkland RT, Clayton GW, Kirkland JL. Central diabetes insipidus. 22 years' experience. Am J Dis Child. 1986;140:551–4.
24. Charmandari E, Brook CG. 20 years of experience in idiopathic central diabetes insipidus. Lancet. 1999; 353:2212–3.
25. Moses AM. Clinical and laboratory observations in the adult with diabetes insipidus and related syndromes. In: Czernichow P, Robinson AG, editors. Diabetes insipidus in man, Frontiers of hormone research, vol. 13. Basel: Karger; 1985. p. 156–75.
26. Mootha SL, Barkovich AJ, Grumbach MM, et al. Idiopathic hypothalamic diabetes insipidus, pituitary stalk thickening, and the occult intracranial germinoma in children and adolescents. J Clin Endocrinol Metab. 1997;82(5):1362–7.
27. Heinze HJ, Bercu BB. Acquired hypophysitis in adolescence. J Pediatr Endocrinol Metab. 1997;10:315–21.
28. Honegger J, Fahlbusch R, Bornemann A, et al. Lymphocytic and granulomatous hypophysitis: experience with nine cases. Neurosurgery. 1997;40:713–22.
29. Iwasaki Y, Oiso Y, Kondo K, et al. Aggravation of subclinical diabetes insipidus during pregnancy. N Engl J Med. 1991;324:522–6.
30. Fujiwara TM, Morgan K, Bichet DG. Molecular biology of diabetes insipidus. Annu Rev Med. 1995;46: 331–43.
31. Schoneberg T, Schulz A, Biebermann H, et al. V2 vasopressin receptor dysfunction in nephrogenic diabetes insipidus caused by different molecular mechanisms. Hum Mutat. 1998;12:196–205.
32. Wildin RS, Cogdell DE, Valadez V. AVPR2 variants and V2 vasopressin receptor function in nephrogenic diabetes insipidus. Kidney Int. 1998;54:1909–22.
33. Feldman BJ, Rosenthal SM, Vargas GA, et al. Nephrogenic syndrome of inappropriate antidiuresis. N Engl J Med. 2005;352:1884–90.
34. Kamsteeg EJ, Deen PM, van Os CH. Defective processing and trafficking of water channels in nephrogenic diabetes insipidus. Exp Nephrol. 2000;8: 326–31.
35. Tamarappoo BK, Yang B, Verkman AS. Misfolding of mutant aquaporin-2 water channels in nephrogenic diabetes insipidus. J Biol Chem. 1999;274:34825–31.
36. Goji K, Kuwahara M, Gu Y, Matsuo M, Marumo F, Sasaki S. Novel mutations in aquaporin-2 gene in female siblings with nephrogenic diabetes insipidus: evidence of disrupted water channel function. J Clin Endocrinol Metab. 1998;83:3205–9.
37. Kamsteeg EJ, Wormhoudt TA, Rijss JP, van Os CH, Deen PM. An impaired routing of wild-type aquaporin-2 after tetramerization with an aquaporin-2 mutant explains dominant nephrogenic diabetes insipidus. EMBO J. 1999;18:2394–400.
38. Leung AK, Robson WL, Halperin ML. Polyuria in childhood. Clin Pediatr. 1991;30:634–40.
39. Bendz H, Aurell M. Drug-induced diabetes insipidus: incidence, prevention and management. Drug Saf. 1999;21:449–56.
40. Timmer RT, Sands JM. Lithium intoxication. J Am Soc Nephrol. 1999;10:666–74.
41. Robertson GL. Diagnosis of diabetes insipidus. In: Czernichow P, Robinson AG, editors. Diabetes insipidus in man, Frontiers of hormone research, vol. 13. Basel: Karger; 1985. p. 176–89.
42. Dunger DB, Seckl JR, Grant DB, Yeoman L, Lightman SL. A short water deprivation test incorporating urinary arginine vasopressin estimations for the investigation of posterior pituitary function in children. Acta Endocrinol (Copenh). 1988;117:13–8.
43. Mohn A, Acerini CL, Cheetham TD, Lightman SL, Dunger DB. Hypertonic saline test for the investigation of posterior pituitary function. Arch Dis Child. 1998;79:431–4.
44. Kluge M, Riedl S, Erhart-Hofmann B, Hartmann J, Waldhauser F. Improved extraction procedure and RIA for determination of arginine8-vasopressin in plasma: role of premeasurement sample treatment and reference values in children. Clin Chem. 1999;45:98–103.
45. Elster AD. Imaging of the sella: anatomy and pathology. Semin Ultrasound CT MR. 1993;14:182–94.
46. Halimi P, Sigal R, Doyon D, Delivet S, Bouchard P, Pigeau I. Post-traumatic diabetes insipidus: MR demonstration of pituitary stalk rupture. J Comput Assist Tomogr. 1988;12(1):135–7.
47. Maghnie M, Villa A, Arico M, et al. Correlation between magnetic resonance imaging of posterior pituitary and neurohypophyseal function in children with diabetes insipidus. J Clin Endocrinol Metab. 1992;74:795–800.
48. Moses AM, Clayton B, Hochhauser L. Use of T1-weighted MR imaging to differentiate between primary polydipsia and central diabetes insipidus. AJNR Am J Neuroradiol. 1992;13:1273–7.
49. Uribarri J, Kaskas M. Hereditary nephrogenic diabetes insipidus and bilateral nonobstructive hydronephrosis. Nephron. 1993;65:346–9.

50. Robinson AG, Verbalis JG. Treatment of central diabetes mellitus. In: Czernichow P, Robinson AG, editors. Diabetes insipidus in man, Frontiers of hormone research, vol. 13. Basel: Karger; 1985. p. 292–303.
51. Richardson DW, Robinson AG. Desmopressin. Ann Intern Med. 1985;103:228–39.
52. Cobb WE, Spare S, Reichlin S. Neurogenic diabetes insipidus: management with dDAVP (1-desamino-8-D arginine vasopressin). Ann Intern Med. 1978; 88:183–8.
53. Bryant WP, O'Marcaigh AS, Ledger GA, Zimmerman D. Aqueous vasopressin infusion during chemotherapy in patients with diabetes insipidus. Cancer. 1994; 74:2589–92.
54. Rivkees SA, Dunbar N, Wilson TA. The management of central diabetes insipidus in infancy: desmopressin, low renal solute load formula, thiazide diuretics. J Pediatr Endocrinol Metab. 2007;20:459–69.
55. Blanco EJ, Lane AH, Aijaz N, Blumberg D, Wilson TA. Use of subcutaneous DDAVP in infants with central diabetes insipidus. J Pediatr Endocrinol Metab. 2006;19:919–25.
56. Libber S, Harrison H, Spector D. Treatment of nephrogenic diabetes insipidus with prostaglandin synthesis inhibitors. J Pediatr. 1986;108:305–11.
57. Kirchlechner V, Koller DY, Seidl R, Waldhauser F. Treatment of nephrogenic diabetes insipidus with hydrochlorothiazide and amiloride. Arch Dis Child. 1999;80:548–52.
58. Hoekstra JA, van Lieburg AF, Monnens LA, Hulstijn-Dirkmaat GM, Knoers VV. Cognitive and psychosocial functioning of patients with congenital nephrogenic diabetes insipidus. Am J Med Genet. 1996;61:81–8.