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Diagnosis is based on demonstrating elevated serum free T4 levels, inappropriately normal or high TSH secretion, and MRI evidence of a pituitary adenoma. Elevated free glycoprotein hormone α subunits are seen in many patients.

It is important to exclude other causes of inappropriate TSH secre tion, such as resistance to thyroid hormone, an autosomal dominant disorder caused by mutations in the thyroid hormone β receptor (Chap. 394). The presence of a pituitary mass and elevated β subunit levels are suggestive of a TSH-secreting tumor. Dysalbuminemic hyperthyroxinemia syndromes, caused by mutations in serum thyroid hormone binding proteins, are also characterized by elevated thyroid hormone levels, but with normal rather than suppressed TSH levels. Moreover, free thyroid hormone levels are normal in these disorders, most of which are familial. PART 12 Endocrinology and Metabolism TREATMENT TSH-Secreting Adenomas The initial therapeutic approach is to remove or debulk the tumor mass surgically, usually using a transsphenoidal approach. Total resection is not often achieved as most of these adenomas are large and locally invasive. Normal circulating thyroid hormone levels are achieved in about two-thirds of patients after surgery. Thyroid ablation or antithyroid drugs (methimazole and propylthioura cil) can be used to reduce thyroid hormone levels. SRL treatment effectively normalizes TSH and α subunit hypersecretion, shrinks the tumor mass in 50% of patients, and improves visual fields in 75% of patients; euthyroidism is restored in most patients. Because SRLs markedly suppress TSH, biochemical hypothyroidism often requires concomitant thyroid hormone replacement, which may also further control tumor growth. ■ ■AGGRESSIVE ADENOMAS Despite the rarity of malignant transformation and metastatic lesions, a subset of pituitary adenomas undergoes aggressive local growth and central nervous system invasion with high Ki67 levels (>4%). Silent corticotrope and somatotrope tumors, as well as pro lactinomas occurring in middle-aged men, are particularly prone to aggressive growth and recurrence. Patients with these tumors usually require an integrated management approach including repeat surger ies and irradiation. Temozolomide has also been used with variable responses. ■ ■FURTHER READING Coopmans EC et al: Multivariable prediction model for biochemical response to first-generation somatostatin receptor ligands in acro megaly. J Clin Endocrinol Metab 105:2964, 2020. Elbelt U et al: Efficacy of temozolomide therapy in patients with aggressive pituitary adenomas and carcinomas: A German survey. J Clin Endocrinol Metab 105:e660, 2020. Fleseriu M et al: Acromegaly: Pathogenesis, diagnosis, and manage ment. Lancet Diabetes Endocrinol 10:804, 2022. Fleseriu M et al: An individualized approach to the management of Cushing disease. Nat Rev Endocrinol 19:581, 2023. Hamblin R et al: Natural history of non-

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Disorders of the Neurohypophysis The posterior pituitary consists of the distal axons of the hypothalamic magnocellular neurons that make up the neurohypophysis. The peri karya (cell bodies) of these axons are located in paired paraventricular and supraoptic nuclei of the hypothalamus. Some of these neurons produce arginine vasopressin (AVP), also known as antidiuretic hor mone (ADH); others produce oxytocin. AVP acts on the renal tubules to reduce water loss by concentrating the urine. Oxytocin stimulates postpartum milk letdown in response to suckling, and also elicits socioemotional responses. A deficiency of AVP secretion or action causes a syndrome characterized by the production of large amounts of dilute urine. Excessive or inappropriate AVP production impairs urinary water excretion and predisposes to hyponatremia. VASOPRESSIN ■ ■SYNTHESIS AND SECRETION AVP is a nonapeptide composed of a six-member disulfide ring and a tripeptide tail (Fig. 393-1). It is synthesized via a polypeptide precursor that includes AVP, neurophysin, and copeptin, all encoded by a single gene on chromosome 20. After preliminary processing and folding, the precursor is packaged in neurosecretory vesicles, where it is trans ported down the axon. It is further processed to AVP, neurophysin, and copeptin, and stored in neurosecretory vesicles in the posterior pituitary until it is released by exocytosis into peripheral blood. In healthy individuals, AVP secretion is regulated primarily by the “effective” osmotic pressure, which is determined largely by the plasma concentration of sodium and its anions. This regulation is mediated by specialized cells in the anteromedial hypothalamus, known as osmo receptors. The osmoreceptors receive blood from small perforating branches of the anterior communicating artery. They are extremely sensitive to small changes in the plasma concentration of sodium and its anions but normally are insensitive to other naturally occurring plasma solutes such as urea and glucose. This osmoregulatory system includes inhibitory as well as stimulatory components that function in concert to create an osmotic threshold, or set point, control system. Below this osmotic threshold, plasma AVP is suppressed to levels that permit the development of a maximum water diuresis. Above the threshold, plasma AVP rises steeply in direct proportion to plasma osmolarity, quickly reaching levels sufficient to produce maximum antidiuresis. The absolute levels of plasma osmolarity/sodium at which minimally and maximally effective levels of plasma AVP occur differ from person to person, apparently due to genetic influences on the set and sensitivity of the system. However, the average threshold, or set point, for AVP release corresponds to a plasma osmolarity and sodium of ~275 mosmol/L and 135 meq/L, respectively; levels only 2–4% higher normally result in maximum antidiuresis. AVP is also secreted in response to a decrease in blood pressure or by volume loss of >10–20%. These hemodynamic (baroregulated) influ ences are mediated by neuronal afferents that originate in transmural pressure receptors of the heart and large arteries and project via the vagus and glossopharyngeal nerves to the brainstem, which sends post synaptic projections to the hypothalamus. AVP secretion

also can be stimulated by nausea, acute hypoglycemia, glucocorticoid deficiency, smoking, and possibly angiotensin. Emetic stimuli are extremely potent in comparison to osmotic stimuli; they typically elicit immediate, 50- to 100-fold increases in plasma AVP even when the nausea is transient and not associated with vomiting or other symptoms. They act via the emetic center in the medulla and can be blocked completely by treat ment with antiemetics such as fluphenazine. There is no evidence that pain or other noxious stresses have any effect on AVP unless they elicit a vasovagal reaction and its associated nausea and hypotension.

DNA Vasopressin Neurophysin II Copeptin Oxytocin Neurophysin I FIGURE 393-1 Primary structure, production, and release of arginine vasopressin (AVP). AVP is a nonapeptide composed of a six-member disulfide ring and a tripeptide tail. It is synthesized via a polypeptide precursor that includes AVP, neurophysin, and copeptin, all encoded by a single gene on chromosome 20. The precursor hormone, pre-pro-vasopressin consists of three peptides: AVP, neurophysin 2, and copeptin. ■ ■ACTION The most important physiologic action of AVP is to reduce water excretion by promoting the concentration of urine. Other physiologic actions of AVP include stimulating ACTH and vasoconstriction. This antidiuretic effect is achieved primarily by increasing the hydroosmotic permeability of principal cells that line the distal tubule and medullary collecting ducts of the kidney (Fig. 393-2). In the absence of AVP, these cells are impermeable to water and reabsorb little, if any, of the relatively large volume of dilute filtrate that enters from the proximal nephron. In this condition, the rate of urine output can be as high as 0.2 mL/kg per min and the specific gravity and osmolarity as low as ~1.000 and 50 mOsmol/L, respectively. When AVP is secreted, it binds to V2 receptors on the basal surface of principal cells causing water channels composed of aquaporin-2 (AQ-2) to be inserted into the apical surface of the cell. These channels allow water to flow pas sively from the lumen through the cell down the osmotic gradient cre ated by the hypertonicity of the renal medulla. The magnitude of this antidiuretic effect varies in direct proportion to plasma AVP, the rate of solute excretion, and the level of hypertonicity in the renal medulla. The maximum antidiuresis achievable in healthy humans occurs at plasma AVP concentrations in the range of 1 to 3 pg/mL and results in a urine osmolarity as high as 1200 mOsmol/L. However, maximum concentrating capacity varies considerably depending on the level of hypertonicity in the renal medulla and that, in turn, is a function of the level and duration of AVP receptor 2 (AVPR2)–stimulated reabsorp tion of urea in the distal nephron. Hence, if basal AVP stimulation of AVPR2 is low (e.g., a high basal fluid intake in primary polydipsia), the rise in urine osmolarity that occurs immediately after an increase in AVP concentrations may be so blunted as to suggest a defect in antidi uretic function. This reduced concentrating capacity accounts for the shortcomings of the traditional indirect methods for the differential diagnosis of polyuric states (see below). At high concentrations, AVP also causes contraction of smooth muscle in blood vessels in the skin and gastrointestinal tract, induces glycogenolysis in the liver, and potentiates ACTH release by

Thirst Brainstem Osmoreceptor Disorders of the Neurohypophysis CHAPTER 393 Hypothalamus Baroreceptor Vagus nerve Posterior pituitary Luminal membrane AQ2 channel Migration to the luminal membrane mRNA for AQ2 channels Pre-formed AQ2 channels ATP cAMP Basolateral membrane V2 receptor AVP FIGURE 393-2 Antidiuretic effect of arginine vasopressin (AVP) in the regulation of urine volume. In a typical 70-kg adult, the kidney filters ~180 L/d of plasma. Of this, ~144 L (80%) is reabsorbed isosmotically in the proximal tubule and another 8 L (4–5%) is reabsorbed without solute in the descending limb of Henle’s loop. In the presence of AVP, solute-

free water is reabsorbed osmotically through the principal cells of the collecting ducts, resulting in the excretion of a much smaller volume of concentrated urine. This antidiuretic effect is mediated via a G protein–coupled V2 receptor that increases intracellular cyclic AMP, thereby inducing translocation of aquaporin 2 (AQP 2) water channels into the apical membrane. The resultant increase in permeability permits an influx of water that diffuses out of the cell through AQP 3 and AQP 4 water channels on the basal-lateral surface. The net rate of flux across the cell is determined by the number of AQP 2 water channels in the apical membrane and the strength of the osmotic gradient between tubular fluid and the renal medulla.

NORMAL AVP AND THIRST RESPONSE TO 5% SALINE INFUSION

Plasma AVP (pg/mL)

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LD

Plasma osmolality (mosm/kg) FIGURE 393-3 The relationship of plasma osmolality to arginine vasopressin (AVP) secretion and thirst. VAS, visual analogue scale. corticotropin-releasing factor. These effects are mediated by V1a or V1b receptors that are coupled to phospholipase C. They may also affect the sensitivity of the baroreceptor and influence sympathetic and parasym pathetic outflows to a variety of target organs, including the heart, the peripheral vasculature, and the kidneys. ■ ■METABOLISM AVP distributes rapidly into a space approximately equal to the extra cellular fluid volume. It is cleared irreversibly with a half-life (t1/2) of 10–30 min. Most AVP clearance is due to degradation in the liver and kidneys. During pregnancy, the metabolic clearance of AVP is increased three- to fourfold due to placental production of an N-terminal peptidase (vasopressinase). Importantly, the synthetic vasopressin analogue desmopressin (DDAVP) is more resistant to N-terminal pep tidases, resulting in a longer half-life. THIRST Because AVP cannot reduce water loss below a certain minimum level obligated by urinary solute load and evaporation from skin and lungs, a mechanism for ensuring adequate water intake is essential for preventing dehydration. This vital function is performed by the thirst mechanism. Like AVP, thirst and fluid intake are regulated primarily by an osmostat that is localized in the anteromedial hypothalamus and detects very small changes in the plasma concentration of sodium and its anions. The thirst osmostat appears to be “set” about 3% higher than the AVP osmostat (Fig. 393-3). This relationship ensures that thirst, polydipsia, and dilution of body fluids do not occur until plasma osmolarity/sodium exceeds the defensive capacity of the antidiuretic mechanism. Defects in thirst result in hypodipsia/adipsia. The gas trointestinal tract also has a mechanism that detects fluid intake and inhibits thirst and AVP secretion before water is absorbed sufficiently to lower plasma osmolarity/sodium. However, the resultant inhibition of thirst and AVP is transient unless plasma osmolarity/sodium is reduced, and the role of this system in clinical disorders of water bal ance has not been determined. OXYTOCIN Oxytocin (OXT) is also a nonapeptide that differs from AVP at posi tions 3 and 8 (Fig. 393-1). However, it has relatively little antidiuretic effect and seems to act mainly on mammary ducts to facilitate milk letdown during nursing. It also may help initiate or facilitate labor by stimulating contraction of uterine smooth muscle, but it is not clear if this action is physiologic or necessary for normal delivery. In addition to its release from axonal terminals, OXT is dendritically released into

Thirst (cm/VAS)

Plasma osmolality (mosm/kg)

the central extracellular space and directly projected to other brain regions, where it acts as a neurotransmitter. The central oxytocinergic system is key in regulating socioemotional functioning, including attachment and pair bonding, fear extinction, emotion recognition, and empathy. DEFICIENCIES OF AVP SECRETION AND ACTION ■ ■DIABETES INSIPIDUS (AVP DEFICIENCY AND AVP RESISTANCE) Clinical Characteristics Deficiencies in AVP secretion or action result in the excretion of abnormally large volumes of dilute urine. The 24-h urine volume exceeds 40–50 mL/kg body weight and conse quently leads to polydipsia. Signs and symptoms of dehydration (and biochemical hypernatremia) are uncommon unless thirst and/or water intake are also impaired. Etiology AVP deficiency and AVP resistance should be differenti ated from increased AVP metabolism in pregnancy and from primary polydipsia. Primary deficiency of AVP secretion was formerly called neurogenic, pituitary, cranial, or central diabetes insipidus but is now referred to as AVP deficiency. It can be caused by a variety of acquired, congenital, or genetic disorders but is often idiopathic (Table 393-1). The most common genetic form is transmitted in an autosomal domi nant mode and is caused by diverse mutations in the coding region of one allele of the AVP–neurophysin II (or AVP-NPII) gene. Renal insensitivity to the antidiuretic action of AVP leads to AVP resistance, which was formerly known as nephrogenic diabetes insipidus. It can be caused by a drug such as lithium, a disorder such as hypokalemia and hypercalcemia, or by a genetic mutation. In pregnancy, increased metabolism of AVP may occur due to AVP degradation by an N-terminal aminopeptidase (vasopressinase) pro duced in the placenta. This is referred to as gestational AVP deficiency because the signs and symptoms manifest during pregnancy and usu ally remit several weeks after delivery. These forms of AVP deficiency and AVP resistance should be dif ferentiated from excessive intake of fluids, which is commonly referred to as primary polydipsia. This disorder is common in patients with neu rodevelopmental or psychotic disorders, particularly chronic schizo phrenia. Outside the psychiatric setting, it is increasingly seen in the general population owing to the popularity of lifestyle programs and the belief that drinking large amounts of water is healthy and improves cognition (Table 393-1).

TABLE 393-1 Etiology of Polyuria–Polydipsia Syndromes BASIC DEFECT ACQUIRED CAUSES HEREDITARY CAUSES AVP Deficiency Deficiency in AVP synthesis or secretion • Trauma (surgery, deceleration injury) • Neoplasia (craniopharyngioma, meningioma, germinoma, metastases) • Vascular (cerebral or hypothalamic hemorrhage, infarction or ligation of anterior communicating artery aneurysm) • Granulomatous (histiocytosis, sarcoidosis) • Infectious (meningitis, encephalitis, tuberculosis) • Inflammatory or autoimmune (lymphocytic infundibuloneurohypophysitis, IgG4 neurohypophysitis) • Drug or toxin exposure • Osmoreceptor dysfunction (adipsic DI) • Others (hydrocephalus, ventricular or suprasellar cyst, trauma, and degenerative diseases) • Idiopathic AVP Resistance Reduced renal sensitivity to antidiuretic effect of physiologic AVP levels • Drug exposure (lithium, demeclocycline, cisplatin, etc.) • Hypercalcemia or hypokalemia • Infiltrating lesions (sarcoidosis, amyloidosis, multiple myeloma, etc.) • Vascular disorders (sickle cell anemia) • Mechanical (polycystic kidney disease and urethral obstruction) Primary Polydipsia Excessive fluid intake at a diminished set point • Dipsogenica (idiopathic or similar lesions as with central DI) • Psychosis intermittent hyponatremia–polydipsia (PIP) syndrome • Compulsive water drinking • Health enthusiasts Gestational AVP Deficiency Increased enzymatic metabolism of circulating AVP

hormone Pregnancy NA aDownward resetting of the thirst threshold. Abbreviations: AVP, arginine vasopressin; AVPR, AVP receptor; DI, diabetes insipidus; NA, not applicable; PCSK1, proprotein convertase subtilisin/kexin type 1; WFS1, Wolfram syndrome 1. Source: Reproduced with permission from M Christ-Crain et al: Diabetes insipidus. Nat Rev Dis Primers 5:54, 2019. Pathophysiology In AVP deficiency and resistance, the defect in urine concentration increases the rate of water excretion and causes a small (1–2%) decrease in body water and a commensurate increase in plasma osmolarity/sodium, which stimulates thirst and a compensa tory increase in water intake. The severity of the defect in antidiuretic function varies significantly from patient to patient. In some patients, AVP deficiency is nearly complete and cannot be overcome by even an intense stimulus such as nausea or severe dehydration. In others, AVP deficiency is incomplete, and a modest stimulus such as a few hours of fluid deprivation, smoking, or a vasovagal reaction is sufficient to concentrate the urine. However, even in patients with a partial defect, the maximum level of urine osmolarity produced by these stimuli is usually less than normal partly because the prior deficiency in basal AVP stimulation temporarily diminishes renal concentrating capacity. Nevertheless, the underlying cause of the AVP deficiency/resistance can be determined by analyzing the relationship of urine osmolar ity to plasma AVP/copeptin and of plasma AVP/copeptin to plasma osmolarity/sodium. The pathophysiology of primary polydipsia is the reverse of that in AVP deficiency or resistance. The increase in fluid intake reduces plasma osmolarity/sodium and leads to a physiologic decrease in AVP secretion. The resultant urinary dilution produces a compensa tory increase in urinary free-water excretion that usually offsets the increase in intake and stabilizes plasma osmolarity/sodium at a level below basal. Thus, hyponatremia is uncommon unless the polydipsia is very severe or the compensatory water diuresis is impaired (by another contributory factor that causes AVP release). In diagnostic tests, fluid deprivation or hypertonic saline infusion produces a normal rise in plasma AVP, but the resultant increase in urine concentration is usually subnormal because the capacity of the kidney to concentrate the urine

• Autosomal dominant: AVP mutations • Autosomal recessive, type a and b: AVP mutations • Autosomal recessive, type c: WFS1 mutations • Autosomal recessive, type d: PCSK1 Disorders of the Neurohypophysis CHAPTER 393 mutations • X-linked recessive: gene unknown • X-linked: AVPR2 mutations • Autosomal recessive or dominant: AQP2 mutations NA is temporarily diminished by the prior lack of AVP stimulation. Thus, the maximum level of urine osmolarity achieved is often indistinguish able from that produced by fluid deprivation and/or administration of ADH in partial pituitary or partial nephrogenic diabetes insipidus. However, unlike AVP deficiency or resistance, the relationships of the rise in plasma AVP to the rise in plasma and urine osmolarity are both normal in primary polydipsia. Differential Diagnosis If symptoms of polyuria, nocturia, and/or persistent thirst are present in the absence of glucosuria, the possibility of AVP deficiency or AVP resistance should be evaluated by collecting a 24-h urine on unrestricted fluid intake. If the volume is >40–50 mL/kg per day and/or >3 L/d, further investigations are indicated. If sodium levels are below the normal reference range (<135 mmol/L), this sug gests primary polydipsia since these patients can drink themselves into hyponatremia. If sodium levels are above the normal reference range, the diagnosis of AVP deficiency or resistance is likely, and a test with desmopressin (2 μg) followed by a repeat measurement of urine osmo larity will determine if hypotonic polyuria is due to a AVP deficiency or AVP resistance. This is subcutaneous and should be done in hospital to allow reassessment of urinary osmolality. However, in most patients, sodium levels will be in the normal range, making further tests for dif ferential diagnosis necessary (Fig. 393-4). The indirect water deprivation test was the gold standard for dif ferential diagnosis for

many years. This test is based on indirect assessment of AVP activity by measurement of the urine concentra tion capacity during a prolonged period of dehydration and again after a subsequent injection of an exogenous synthetic AVP analogue, desmopressin. However, the published criteria for interpretation were based on post hoc data from a small number of patients with an overall

Suspected hypotonic polyuria Confirm the presence of polyuria (>40–50 mL/kg/24 h) GU evaluation Urine osmolality <800 mosm/kg Measure serum sodium, plasma osmolality Low serum sodium (<135 mmol/L) PART 12 Endocrinology and Metabolism Primary polydipsia Normal serum sodium (136–146 mmol/L) Baseline copeptin level Water deprivation test Urine osmolality <300 mosm/kg Copeptin

> 21.4 pmol/L Copeptin <21.4 pmol/L Urine osmolality 300–800 mosm/kg Urine osmolality 800 mosm/kg Mild primary polydipsia Desmopressin test Desmopressin test Stimulated copeptin 4.9 pmol/L (at plasma sodium 150 mmol/L) <50% increase 50% increase 9% increase <9% increase Primary polydipsia Complete or partial central DI Nephrogenic DI Complete central DI Partial central DI Primary polydipsia FIGURE 393-4 Algorithm for differential diagnosis of polyuria polydipsia syndrome. If symptoms of polyuria, nocturia, and/or persistent thirst are present in the absence of glucosuria, the possibility of arginine vasopressin (AVP) deficiency or AVP resistance should be evaluated by collecting a 24-h urine on unrestricted fluid intake. If the volume is >50 mL/kg per day with a concomitant urinary osmolality <800 mOsm/kg, serum sodium and plasma osmolality should be measured. If sodium levels are below the normal reference range, it suggests primary polydipsia since these patients can drink themselves into hyponatremia. If sodium levels are above the normal reference range, the diagnosis of AVP deficiency or resistance can be made, and a test with desmopressin (2 µg) followed by a repeat measurement of urine osmolarity will determine if hypotonic polyuria is due to a AVP deficiency or AVP resistance. However, in most patients, sodium levels will be in the normal range, making further tests for differential diagnosis necessary. If copeptin measurement is available, a copeptin-based diagnostic algorithm is used. High baseline copeptin level of >21.4 pmol/L without prior water deprivation identifies AVP resistance. For the more difficult differential diagnosis of AVP deficiency and primary polydipsia, a copeptin level of >4.9 pmol/L at a high sodium level (≥150 mmol/L) after hypertonic saline infusion has an overall diagnostic accuracy of 97% to diagnose AVP deficiency. DI, diabetes insipidus; GU, genitourinary. diagnostic accuracy of 70% and only 41% for patients with primary polydipsia. To overcome these limitations, direct measurement of AVP was proposed, but despite initial promising results, this method is not in routine clinical use, mainly because of technical limitations of the AVP assay. Copeptin is the C-terminal segment of the AVP prohormone and is an AVP surrogate that is very stable ex vivo (Fig. 393-1). Studies have shown that a high baseline copeptin level of >21.4 pmol/L, without prior water deprivation, unequivocally identifies AVP resistance. For the more difficult differential diagnosis of AVP deficiency and

> primary polydipsia, a copeptin level of >4.9 pmol/L at a high sodium level (≥150 mmol/L) after hypertonic saline infusion has an overall diagnostic accuracy of 96.5%. Importantly, this test requires close monitoring of sodium levels. Copeptin levels after arginine infusion have also shown promising results in differentiating AVP deficiency from primary poly dipsia, but with a lower diagnostic accuracy. Currently, copeptin assays are commercially available in Europe, Australia, India, and Mexico, and tests are pending in several other countries. Once AVP deficiency has been diagnosed, the underlying pathology must be identified by magnetic resonance imaging (MRI) of the sella and suprasellar regions. Also, assessment of the posterior pituitary and the pituitary stalk can be helpful in the differential diagnosis of AVP deficiency. The pituitary bright spot on MRI (a radiologic marker of neurosecretory vesicles containing AVP) is an area of hyperintensity

Urinary volume <50 mL/kg/24 h High serum sodium (>147 mmol/L) Central or nephrogenic DI Complete or partial nephrogenic DI Hypertonic saline test Stimulated copeptin <4.9 pmol/L (at plasma sodium

> 150 mmol/L) seen in most healthy individuals, but may be lacking in patients with AVP deficiency. However, the absence of the pituitary bright spot is not sufficient to establish a diagnosis of AVP deficiency since it can be present in early stages of AVP deficiency or can be absent in elderly patients. Treatment The signs and symptoms of uncomplicated AVP defi ciency can be eliminated by treatment with DDAVP, a synthetic ana logue of AVP. DDAVP acts selectively at V2 receptors to increase urine concentration and decrease urine flow in a dose-dependent manner. It is also more resistant to degradation than is AVP and has a three- to fourfold longer duration of action. The dose of DDAVP impacts on the duration of action (i.e., the higher the dose, the greater the duration of action). DDAVP can be given by IV or SC injection, nasal inhalation, or orally by means of a tablet or melt. The doses required to treat AVP deficiency vary depending on the patient and the route of administra tion. Among adults, doses usually range from 1–2 µg qd or bid by injec tion, 10–20 µg bid or tid by nasal spray, or 100–400 µg bid or tid orally. The onset of antidiuresis is rapid, ranging from as little as 15 min after injection to 60 min after oral administration. Hyponatremia is the most common complication of desmopressin therapy, with mild depres sion of plasma sodium concentration (131–134 mmol/L) reported in about a quarter of patients with intact thirst. In 15% of patients,

hyponatremia is more severe, with plasma sodium concentration of <130 mmol/L. Desmopressin escape, which involves intermittently delaying DDAVP for a number of hours to allow a transient aquaresis, reduces the risk of hyponatremia. Treatment of primary polydipsia focuses on the reduction of exces sive fluid intake, optimally in a graded fashion to allow patients to slowly reduce

fluids. Treatments to reduce mouth dryness (e.g., ice chips, hard candy to stimulate salivary flow) are also useful to reduce thirst. Pharmacologic therapies have been tried without consistent success. A recent study suggests that glucagon-like peptide 1 (GLP-1) analogues reduce fluid intake, urine output, and thirst perception. AVP resistance is difficult to treat. Patients typically do not respond to desmopressin treatment; however, some patients may respond to high doses if their resistance is only partial. Treatment with conventional doses of a thiazide diuretic and/or amiloride in conjunction with a lowsodium diet and coadministration of nonsteroidal anti-inflammatory drugs (NSAIDs) usually reduces the polyuria and polydipsia, but this combination is nephrotoxic, and careful monitoring of renal function is important. Drug-induced AVP resistance should be treated by dis continuation of the causative agent—most commonly lithium—where possible. Persistent lithium-induced AVP resistance can be treated by hydrochlorothiazide and amiloride. It important to be aware that plasma volume contraction produced by thiazide diuretics can decrease lithium excretion and predispose to lithium toxicity. ■ ■HYPODIPSIC/ADIPSIC HYPERNATREMIA An increase in plasma osmolarity/sodium above the normal range (hypertonic hypernatremia) can be due to a decrease in total body water or an increase in total body sodium. The former results from a failure to drink enough water to replace normal or increased urinary and insensible loss due either to water deprivation or a lack of thirst (hypodipsia/adipsia). Clinical Characteristics Hypodipsic/adipsic hypernatremia is a rare syndrome characterized by chronic or recurrent hypertonic dehydration that most frequently coexists with AVP deficiency (adipsic diabetes insipidus or adipsic AVP deficiency). The hypernatremia var ies widely in severity and is often associated with signs of hypovolemia such as tachycardia, postural hypotension, azotemia, hyperuricemia, and hypokalemia due to secondary hyperaldosteronism. Muscle weak ness, pain, rhabdomyolysis, hyperglycemia, hyperlipidemia, thrombo embolic disease, acute renal failure, and obtundation can also occur. Etiology Hypodipsia/adipsia is usually due to abnormalities of osmoreceptors in the anterior hypothalamus that regulate thirst. The defect can result from various congenital malformations of midline brain structures or may be acquired due to diseases such tumors (pri mary or secondary, and their associated surgery) or aneurysms of the anterior communicating artery, head trauma, granulomatous diseases such as sarcoidosis and histiocytosis, AIDS, and cytomegalovirus encephalitis. Adipsic hypernatremia without demonstrable hypotha lamic lesions has also been associated with autoantibodies directed against the subfornical organ. Pathophysiology A deficiency in osmotically induced thirst results in a failure to drink enough water to replenish obligatory renal and extrarenal losses with resultant significant hypernatremia. Rarely, the regulation of AVP secretion is completely normal, suggesting that the lack of thirst is due to a defect in postosmoreceptor neural path ways to higher cognitive centers. Differential Diagnosis Hypodipsic/adipsic hypernatremia with or without coexisting AVP deficiency usually can be distinguished from other causes of inadequate fluid intake (e.g., coma, paralysis, restraints, absence of fresh water) by the clinical history and setting as well as measurements of serum and urine osmolality. Previous episodes and/ or denial of thirst and failure to drink spontaneously when the patient is conscious, unrestrained, and hypernatremic are virtually diagnostic. Treatment Hypodipsic hypernatremia can be corrected by admin istering water orally if the patient is alert and cooperative or by infusing

TABLE 393-2 Approach to the Management of Water Balance for Patients with Adipsic Arginine Vasopressin (AVP) Deficiency

1. Replace AVP with sufficient vasopressin (DDAVP).
2. Monitor fluid input/output initially as an inpatient to achieve eunatremia.

3. Weigh and record patient’s eunatremic weight.
4. Recommend 1.5–2 L of fluid intake per day assuming urinary losses are less.
5. Weigh daily.
6. If below eunatremic weight, then replace with equivalent volume of fluid to restore eunatremic weight.
7. Recommend increased fluid intake in times of increased perspiration or Disorders of the Neurohypophysis CHAPTER 393 ambient temperatures.
8. Regular plasma sodium measurements. hypotonic fluids (0.45% saline or 5% dextrose) if the patient is not. The amount of free water in liters required to correct the free water deficit should be estimated from body weight in kg and the serum sodium concentration in mmol/L. This amount plus an allowance for continuing insensible and urinary losses should be given over a 24- to 48-h period with close monitoring of serum sodium to ensure that it does not correct too rapidly. Plasma urea/creatinine should be moni tored closely for signs of acute renal failure caused by rhabdomyolysis, hypovolemia, and hypotension. Once the patient has been rehydrated, an MRI of the brain and tests of anterior pituitary function should be performed to look for the cause and collateral defects in other hypothalamic functions. A long-term management plan to prevent or minimize recurrence of the fluid and electrolyte imbalance also should be developed. This should include a practical method to regulate fluid intake in accordance with variations in water balance as indicated by changes in body weight or serum sodium determined by home moni toring analyzers, if available. Another potential treatment approach is summarized in Table 393-2. ■ ■INAPPROPRIATE ANTIDIURESIS (SEE IN MORE DETAIL CHAP. 56) Clinical Characteristics Syndrome of inappropriate antidiuresis (SIAD) is produced when plasma levels of AVP are elevated at times when the physiologic secretion of AVP from the posterior pituitary would normally be osmotically suppressed. The clinical abnormality is a decrease in the osmotic pressure of body fluids, such that the hall mark of SIAD is hypoosmolality. If hyponatremia is severe or develops acutely, it can cause a variety of neurologic symptoms and signs, such as headache, confusion, anorexia, nausea, vomiting, coma, and con vulsions. If the hyponatremia develops gradually or exists for more than a few days, it may be apparently asymptomatic, but even mild hyponatremia is associated with an increased rate of falls and fractures, neurocognitive and neuromuscular symptoms, and increased morbid ity and mortality. Etiology SIAD has many different etiologies, which are summa rized in Chap. 56. Pathophysiology In SIAD, the failure to mount a water diuresis when intake exceeds urinary and insensible loss results in a slight expansion of total body water followed by a modest increase in urinary sodium excretion. As a result, expansion of extracellular volume is minimal, and clinically detectable edema does not develop. However, intracellular volume increases in proportion to the severity and rapid ity of the change in plasma sodium. In the brain, this cellular swelling causes an increase in pressure that triggers a variety of symptoms. After several days, the swelling and symptoms may subside due to inactiva tion of some intracellular solutes and resultant decrease in cellular volume. Differential Diagnosis Evaluation of urine and serum osmo lality and sodium is the most useful investigation in establishing whether the diagnostic criteria for SIAD are met, alongside clinical assessment of volume status. Measurement of serum osmolality is important to exclude non-hypotonic causes of hyponatremia, such

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