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Disorders of Water and Salt Metabolism Associated with Pituitary Disease

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Disorders of water and sodium homeostasis are very common problems encountered in clinical medicine. Disorders of water metabolism are divided into hyperosmolar and hypoosmolar states, with hyperosmolar disorders characterized by a deficit of body water in relation to body solute, and hypoosmolar disorders characterized by an excess of body water in relation to total body solute. Because sodium is the main constituent of plasma osmolality, these disorders are typically characterized by hypernatremia and hyponatremia, respectively. Hyponatremia is far more common, occurring at prevalences as high as 6% to 22% of hospitalized patients [1], and has been associated with mortality rates from 0% to 50%, depending on the acuteness and severity of the hyponatremia. Hypernatremia has a prevalence of only 1% of hospitalized patients, but is associated with high mortality rates, from 42% to 60% [2].

In the setting of intrasellar and suprasellar lesions, excessive water loss from diabetes insipidus is more likely than inappropriate water retention from the syndrome of inappropriate antidiuretic hormone secretion (SIADH), although both can occur following surgical resection of these lesions. This article briefly reviews the physiology of hyperosmolar and hypoosmolar syndromes, then focuses on a discussion of the pathophysiology, evaluation, and treatment of specific pre- and postoperative disorders of water metabolism in patients with pituitary lesions.

Overview of normal water metabolism

Water metabolism is controlled primarily by arginine vasopressin (AVP), a nonapeptide that is synthesized in the neurohypophyseal magnocellular

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neurons of the supraoptic and paraventricular nuclei of the hypothalamus. The newly synthesized AVP prohormone is packaged into neurosecretory granules and then transported down the supraopticohypophyseal tract to the posterior pituitary, during which it is enzymatically cleaved into AVP, neurophysin, and a C-terminal glycopeptide. When release is stimulated, circulating AVP binds to AVP V2 receptors in the collecting duct of the kidney, activating a cyclic AMP-mediated signal transduction pathway that stimulates insertion of aquaporin-2 (AQP2) water channels into the apical membrane of the collecting duct epithelial cells. The AQP2 channels render the collecting duct permeable to water, which facilitates passive reabsorption of water along osmotic gradients. This reabsorption of water, or antidiuresis, is dependent on the presence of interstitial hyperosmolality in the inner medulla of the kidney established by the countercurrent multiplier mechanism [3].

Secretion of AVP is stimulated by osmotic and nonosmotic factors, with changes in plasma osmolality serving as the primary stimulus for AVP release. Osmoreceptors located in the anterior hypothalamus are exquisitely sensitive to even small increases in plasma osmolality. There is a discrete osmotic threshold for AVP secretion, which usually occurs when plasma osmolality reaches 282 milliosmole (mOsm)/kg H_2O to 285 mOsm/kg H_2O, above which a linear relationship between plasma osmolality and AVP levels occurs. In general, each 1 mOsm/kg H_2O increase in plasma osmolality causes an increase in plasma AVP levels from 0.4 picogram (pg)/mL to 0.8 pg/mL, with a corresponding renal concentrating response [4]. Thus, changes of 1% or less in plasma osmolality will trigger an increase in plasma AVP levels and urine osmolality.

Baroreceptors located in the carotid arteries and aortic arch also stimulate AVP release in response to decreases in blood volume and arterial pressure. The resulting urinary concentration and renal water conservation is an appropriate physiologic response to the volume depletion. However, AVP secretion is much less sensitive to small changes in blood pressure and volume than to changes in osmolality [5]. As a result, modest changes in blood volume and pressure are relatively weak stimuli for AVP release.

AVP secretion is also influenced by multiple other factors. Many of these can stimulate AVP release, including nausea, pain, medications, angiotensin II, histamine, dopamine, bradykinin, and acetylcholine. Many others can inhibit AVP release, including nitric oxide, atrial natriuretic peptide, and opioids [6,7]. Because AVP secretion is influenced by many different factors, any defects in the normal regulation of AVP secretion can lead to problems with either water conservation or water excretion.

Hyperosmolality and hypernatremia

Hyperosmolality indicates a deficiency of water relative to solute in the extracellular fluid. Because water moves freely between the extracellular

(ECF) and intracellular (ICF) fluid, this also indicates a deficiency of total body water relative to total body solute. In evaluating hypernatremia, it is helpful to classify it broadly by etiology: hypervolemic, inadequate water intake, and increased free water losses.

Hypervolemic hypernatremia

Hypervolemic hypernatremia is caused by an excess of body sodium with normal or expanded body water. Although uncommon, it can occur in the postoperative or hospital setting from the infusion of hypertonic fluids or from enteral feedings without adequate free water administration [8]. More rarely, cases of true sodium chloride (NaCl) intoxication have been reported [9].

Inadequate fluid intake

Hypernatremia from inadequate fluid intake is usually seen in the hospital or postoperative setting in patients who have an intact thirst mechanism, but are unable to obtain or ingest fluids. This usually occurs when the patient has a depressed sensorium because of illness or medications, or during recovery from anesthesia in the postoperative setting. Less commonly, inadequate fluid intake can be caused by defects in the thirst mechanism resulting from surgical damage to the anterior hypothalamus, causing hypodipsia [10].

Increased water losses

Hypernatremia from increased water losses occurs commonly, with hyperglycemia and resultant glucosuria being the most common etiology. Other forms of solute diuresis, gastrointestinal water losses, intrinsic renal disease, hypercalcemia, and hypokalemia can all cause increased free water losses. When not a result of any of these causes, excessive free water loss is usually caused by a deficiency of AVP secretion or impaired AVP effects in the kidney [11].

Diabetes insipidus

Diabetes insipidus (DI) is the most well-known manifestation of a deficiency in AVP secretion or abnormal renal response to AVP. Central DI is caused by a variety of acquired or congenital anatomic lesions that disrupt the hypothalamic-posterior pituitary axis, and include some types of tumors, trauma, hemorrhage, thrombosis, infarction, granulomatous disease, and pituitary surgery. It is unusual for pituitary adenomas to present with DI. This is because synthesis of AVP occurs in the supraoptic and paraventricular nuclei of the hypothalamus, rather than in the posterior pituitary. Even large intrasellar masses usually grow slowly over long periods of

time, and this allows an adaptation of neurohypophyseal function to occur. In such cases, the site of AVP release shifts from the posterior pituitary to the median eminence, which sometimes can be detected by an upward migration of the posterior bright spot by MRI [12].

Incidence

DI complicates the postoperative course in as many as 30% of patients undergoing pituitary surgery, although the disease is transient and relatively benign in the majority of cases [13]. Chronic postoperative DI has been reported in from 0.5% to 15% in neurosurgic reviews. It is relatively uncommon because experimental studies have shown that more than 90% of the magnocellular AVP neurons in the supraoptic and paraventricular nuclei must degenerate bilaterally before permanent DI occurs [14].

Diagnosis

The diagnosis of DI should be considered when a neurosurgical patient excretes large volumes of dilute urine in the postoperative period, typically more than 2.5 mL/kg body weight to 3.0 mL/kg body weight per hour. When such postoperative polyuria is noted, it is important to consider several other potential clinical scenarios before a diagnosis of DI is concluded. First, patients who undergo surgery in the suprasellar region very frequently receive stress doses of glucocorticoids to prevent secondary adrenal insufficiency. In cases where steroid-induced insulin resistance produces hyperglycemia, the resulting osmotic diuresis from glucosuria can be confused with DI. Therefore, urine and blood glucose should be measured and any elevated glucose levels brought under control to eliminate an osmotic diuresis as a cause of the polyuria. Second, excess fluids are sometimes administered intravenously during the perioperative period, which are then excreted appropriately postoperatively. If this large postoperative diuresis is matched with continued intravenous fluid infusions, an incorrect diagnosis of DI may be made based on the resulting hypotonic polyuria. Therefore, if the serum [Na^+] is not elevated concomitantly with the polyuria, the rate of parenterally administered fluid should be slowed with careful monitoring of the serum [Na^+] and urine output until a diagnosis of DI can be confirmed by continued hypotonic polyuria in the presence of hypernatremia or hyperosmolality [15].

The diagnosis of DI in the postoperative setting is made based on both clinical and biochemical data. Patients characteristically complain of an abrupt onset of polyuria and polydipsia, which typically is manifest in the first 24 to 48 hours following neurosurgery. This precipitous onset reflects the fact that patients are able to maintain urinary concentration fairly well until the number of AVP-producing neurons in the hypothalamus decreases to 10% to 15% of normal, after which plasma AVP levels decrease to the range where urine output increases dramatically [14]. Patients with DI

often describe a craving for ice-cold water, which better quenches osmotically-stimulated thirst [16]. Urine studies should reveal a hypotonic (ie, dilute) urine, with specific gravity less than 1.005 or urine osmolality greater than 200 mOsm/kg H_2O. Urine output is often voluminous, ranging from 4 to18 liters per day [17]. Serum hyperosmolality and hypernatremia also strongly support the diagnosis of DI. However, most patients with DI generally have intact thirst mechanisms; therefore, as long as they are allowed free access to oral fluids, they usually do not present with either hyperosmolality or hypernatremia. Consequently, it is often necessary to limit fluid intake until either hyperosmolality or hypernatremia develop in order to confirm a diagnosis of DI. Diagnostic criteria for a diagnosis of DI are summarized in Box 1.

MRI has been explored as a diagnostic tool for DI, as a bright spot in the sella can be visualized on T1-weighted images when stored vasopressin and oxytocin are present in neurosecretory granules of the posterior pituitary. Absence of this bright spot is characteristic of DI, [18] although a persistence of the bright spot has been reported in patients with clinical evidence of DI [19]. This does not exclude a diagnosis of DI, and can be explained by the presence of the bright spot early in the disease process, when partial DI is more likely to be present, with subsequent disappearance as the severity of DI progresses. Alternatively, the presence of oxytocin in the pituitary may be responsible for some cases of DI despite a normal bright spot. Additionally, while many small studies have reported the presence of a bright spot in all normal subjects, larger studies have noted the absence of the bright spot in some clinically normal patients, particularly with increasing age [20]. Thus, neither the absence nor the presence of a posterior pituitary bright spot is diagnostic of DI or its absence.

Box 1. Diagnosis of postoperative diabetes insipidus

Rule out osmotic diuresis or fluid overload
Clinical signs and symptoms
- Polyuria, high volumes (4 L/day–18 L/day), with abrupt onset, typically within 24–48 hours postoperatively
- Polydipsia, with craving for cold fluids
- With/without hypovolemia, depending on whether the patient has an intact thirst mechanism

Laboratory data
- Dilute urine (specific gravity less than1.005, urine osmolality less than 200 mOsm/kg H_2O)
- Normal to increased serum osmolality
- Serum [Na^+] greater or equal to 145 milliequivalent/L with continued diuresis of hypotonic urine

Postoperative clinical course

The postoperative course of DI can be transient, permanent, or triphasic, as described in classic studies of pituitary stalk transection [21]. Transient DI almost always begins within 24 to 48 hours of surgery and usually abates within several days. Both transient DI and the first phase of the triphasic pattern are thought to be caused by temporary dysfunction of AVP-producing neurons, secondary to severing of the neuronal connections between the magnocellular cell bodies and the nerve terminals in the posterior pituitary, or axonal shock from perturbations in the vascular supply to the pituitary stalk and posterior pituitary. Transient DI usually resolves as the vasopressinergic neurons regain full function. Less commonly, persistent DI may follow as preformed stores of AVP are depleted and no additional AVP is synthesized. Previous studies showed that the major determinant of permanent DI, following pituitary stalk sectioning, was related to the level of the lesion: the closer the lesion to the magnocellular cell bodies in the hypothalamus, the more likely that the hypothalamic cell bodies will degenerate, resulting in permanent DI. In a series of 24 patients receiving a low pituitary stalk section at the level of the diaphragm sella, only 62% developed permanent DI [22], compared to an incidence of 80% to 100% with higher stalk injury [23].

In the triphasic pattern, the first phase of DI typically lasts 5 to 7 days, and then transitions into a second antidiuretic phase of SIADH (Fig. 1A). The second phase of the triphasic response is caused by the uncontrolled release of AVP from degenerating posterior pituitary tissue, or from the remaining magnocellular neurons whose axons have been severed [14,21]. In this phase, the urine quickly becomes concentrated in response to the elevated plasma AVP levels and urine output markedly decreases. Continued administration of excess water during this period can quickly lead to hyponatremia and hypoosmolality. The duration of the second phase is highly variable, and can last from 2 to 14 days [14]. After the AVP stores are depleted from the degenerating posterior pituitary, the third phase of chronic DI then typically ensues, although not always [24]. In this phase, there are insufficient remaining AVP neurons capable of synthesizing additional AVP, thereby resulting in permanent DI.

Treatment

Treatment of postoperative DI is summarized in Box 2, and should be individualized to each patient. Optimally, patients should be monitored in an expectant fashion for the development of polyuria or hypoosmolality. Fluid intake and output should be carefully recorded, and patients questioned regarding symptoms of thirst. Once a diagnosis of DI has been verified as described above, antidiuretic hormone therapy should be initiated. Because of the alternative reasons for a postoperative diuresis discussed in the previous section, it is important not to begin antidiuretic therapy until the presence of

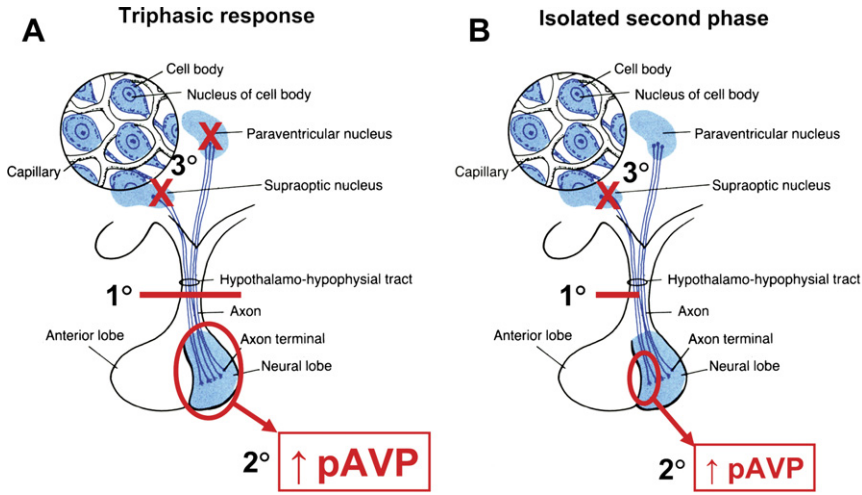

Fig. 1. Mechanisms underlying the pathophysiology of the triphasic pattern of diabetes insipidus and the isolated second phase. (*A*) In the triphasic response, the first phase of DI is initiated following a partial or complete pituitary stalk section, which severs the connections between the AVP neuronal cell bodies in the hypothalamus and the nerve terminals in the posterior pituitary gland, thus preventing stimulated AVP secretion (1°). This is followed in several days by the second phase of SIADH, which is caused by uncontrolled release of AVP into the bloodstream from the degenerating nerve terminals in the posterior pituitary (2°). After all of the AVP stored in the posterior pituitary gland has been released, the third phase of DI returns if greater than 80% to 90% of the AVP neuronal cell bodies in the hypothalamus have undergone retrograde degeneration (3°). (*B*) In the isolated second phase, the pituitary stalk is injured, but not completely cut. Although maximum AVP secretory response will be diminished as a result of the stalk injury, DI will not result if the injury leaves intact at least 10% to 20% of the nerve fibers connecting the AVP neuronal cell bodies in the hypothalamus to the nerve terminals in the posterior pituitary gland (1°). However, this is still followed in several days by the second phase of SIADH, which is caused by uncontrolled release of AVP from the degenerating nerve terminals of the posterior pituitary gland that have been injured or severed (2°). Because a smaller portion of the posterior pituitary is denervated, the magnitude of AVP released as the pituitary degenerates will be smaller and of shorter duration than with a complete triphasic response. After all of the AVP stored in the damaged part of the posterior pituitary gland has been released, the second phase ceases, but clinical DI will not occur if less than 80% to 90% of the AVP neuronal cell bodies in the hypothalamus undergo retrograde degeneration (3°).

DI is confirmed by continued hypotonic polyuria despite hyperosmolality. However, the criteria for subsequent redosing need not be as stringent, and can be based simply on the redevelopment of polyuria [14].

Desmopressin (1-deamino-8-D-arginine-vasopressin) is the drug of choice for acute and chronic treatment of central DI [25]. Postoperatively, desmopressin may be given in a dose of 1 to 2 micrograms subcutaneously, intramuscularly, or intravenously. Parenteral routes are preferable, because this obviates any concern about absorption, causes no significant pressor effects, and has the same total duration of action as the other routes. Treatment generally results in a prompt reduction in urine output and the

Box 2. Treatment of postoperative diabetes insipidus

Expectant monitoring
Accurate recording of fluid intake and output
Urine osmolality or specific gravity every 4 to 6 hours, until resolution or stabilization
Serum [Na^+] every 4 to 6 hours, until resolution or stabilization

Antidiuretic hormone therapy
Desmopressin, initial dose of 1 μg to 2 μg intravenously or subcutaneously
Redose when urine output 200 mL to 250 mL per hour for greater than or equal to 2 hours, with urine specific gravity less than 1.005 or urine osmolality less than 200 mOsm/kg H_2O

Maintenance of fluid balance
Allow patient to drink according to thirst
Supplement hypotonic intravenous fluids (D_5W to $D_5$1/2NSS) if patient is unable to maintain a normal plasma osmolality and serum [Na^+] through drinking

Monitor for resolution of transient DI or triphasic response
Positive daily fluid balance greater than 2 L suggests possibility of inappropriate antidiuresis
Antidiuretic hormone therapy should be held and fluids restricted to maintain serum [Na^+] within normal ranges

Manage anterior pituitary insufficiency
Cover with stress dose corticosteroids (hydrocortisone 100 mg intravenously every 8 hours, tapered to 15 mg to 30 mg by mouth daily) until anterior pituitary function can be fully evaluated

duration of antidiuresis is approximately 6 to 12 hours. It is important to follow urine osmolality and volume, and serum [Na^+] at frequent intervals to ensure improvement in hypernatremia and to determine when redosing should occur. In order to avoid fluid retention and hyponatremia, each dose of desmopressin should be given after the recurrence of polyuria, but before the patient actually becomes hyperosmolar. In general, excretion of 200 mL to 250 mL per hour of urine with an osmolality less than 200 mOsm/kg H_2O or specific gravity less than 1.005 affirms the need for retreatment with desmopressin [16]. Dosing desmopressin on an as needed basis, rather than on a fixed schedule, also has the benefit of allowing the detection of return of endogenous AVP secretion, or the start of the second phase of a triphasic response, by a lack of return of polyuria after the effects of the previous desmopressin dose have dissipated. However, even this strategy

will not always prevent the occurrence of hyponatremia during the second phase of SIADH. Consequently, it is important to follow the serum [Na^+] at frequent intervals in all postoperative patients.

The side effects of desmopressin are uncommon, mild, and generally dose-related. Patients occasionally experience headache, nausea, nasal congestion, flushing and abdominal cramping. Desmopressin has virtually no pressor effects because it selectively binds to the AVP V2 receptors, but not the AVP V1a receptors on vascular smooth muscle cells, thus rendering it safe in patients with coronary or hypertensive cardiovascular disease [25].

Fluid replacement is also important to manage in the setting of postoperative DI. If the patient is awake and has an intact thirst mechanism, the patient's own symptom of thirst is the best guide to water replacement. Increases in plasma osmolality of 2% to 3% triggers the sensation of thirst, which prevents significant hyperosmolality from occurring [26]. If the patient is unable to respond to thirst because of hypothalamic damage to thirst centers or because of decreased consciousness, fluid balance can be maintained by intravenous fluids. The established water deficit may be estimated using the following formula [27]:

$$\text{Water deficit} = 0.6 \times \text{premorbid weight} \times \left[1 - 140/\left(\text{serum}\left[Na^+\right], \text{mmol/L}\right)\right]$$

where [Na^+] is the serum sodium concentration in mmol/L and body weight is in kilograms. However, because this formula does not take into account ongoing water losses, it is at best an estimate of fluid requirements; therefore, serum electrolytes should be measured frequently (eg, every 6 to 8 hours) to ensure that appropriate fluid replacement is occurring.

Patients with chronic DI can be treated with intranasal or oral desmopressin. The nasal spray delivers metered single doses of 0.1 mL (10 micrograms). The reliability of intranasal desmopressin can be diminished in patients with mucosal atrophy, nasal congestion, scarring, or nasal discharge; thus, in general it is advisable to wait until several days postoperatively before using intranasal desmopressin, especially in patients who have nasal packing in place. The duration of action of intranasal desmopressin generally ranges from 6 to12 hours, though occasional patients may exhibit longer responses. Consequently, most patients require twice daily dosing. Treatment should be designed to minimize polyuria and polydipsia, while avoiding hyponatremia from over-treatment. It is often useful to permit intermittent polyuric episodes every 1 to 2 weeks by delaying a dose of desmopressin, thereby verifying continued presence of DI and allowing any retained excess water to be excreted so that normal water balance is maintained.

Oral desmopressin has also been shown to be effective for treatment of central DI. Patients with chronic rhinitis or mucosal scarring may find it

to be a more viable option than the intranasal spay. Oral tablets are available in 0.1 mg to 0.2 mg dosing options, with most patients requiring a 20 times higher dose than with the intranasal spray because more than 99% of the orally administered dose of desmopressin is destroyed by gastrointestinal peptidases. Most patients with central DI require on average 200 μg to 600 μg of oral desmopressin times per day to control polyuria [12]. Oral tablets should be taken on an empty stomach to maximize absorption.

Anterior pituitary function

Finally, as a practical consideration, any patient with postoperative DI, and particularly those manifesting a triphasic response, should be assumed to have anterior pituitary insufficiency and covered with corticosteroid replacement. In the postoperative setting, hydrocortisone 50 mg to 100 mg intravenously every 8 hours is generally utilized and then rapidly tapered to daily maintenance doses (15 mg–30 mg per day) until anterior pituitary function can be definitively evaluated.

Hypoosmolality and hyponatremia

Hyponatremia is the most common electrolyte disorder in hospitalized adult patients. The reported incidence of hyponatremia varies depending on the age of hospitalized patients studied, and the definition of hyponatremia used. When hyponatremia is defined as a serum [Na^+] less than 135 mmol/L, incidences of 6% to 22% have been reported [1]. However, when hyponatremia is defined by more stringent criteria of serum [Na^+] less than 130 mmol/L, incidences fall to 1% to 4%. This cutoff likely represents the clinically significant incidence of hyponatremia in the hospital setting, as adverse clinical events are rarely seen unless the serum sodium is less than 130 mmol/L [28,29]. Clinically, hyponatremia is generally categorized based on serum tonicity as isotonic, hypotonic, or hypertonic.

Isotonic hyponatremia

Hyponatremia with a normal plasma osmolality is usually synonymous with pseudohyponatremia, and can be produced by marked elevation of plasma lipids and proteins. In this situation, the concentration of sodium per liter of plasma is decreased because the nonaqueous portion of the plasma that is occupied by lipid or protein is increased, but the concentration of sodium per liter of plasma water is normal.

Hypertonic hyponatremia

Hyponatremia with an elevated plasma osmolality occurs when there are osmotically active solutes in the plasma, such as glucose, mannitol, sorbitol,

or radiocontrast agents. These osmotically active particles induce the movement of water from the ICF to the ECF, decreasing the serum [Na^+], even though serum osmolality remains elevated.

Hypotonic hyponatremia

Hyponatremia with corresponding hypotonicity is the most frequent type of hyponatremia encountered in clinical practice, and the most clinically relevant category. It is generally subdivided according to the clinical assessment of the ECF volume status [30].

Hypovolemic hyponatremia

Hypovolemic hyponatremia occurs when there are simultaneous losses of body water and sodium, resulting in ECF volume depletion. The decrease in blood volume and pressure results in secondary stimulated AVP secretion, and ultimately decreased free water excretion by the kidney. Retention of water from ingested or infused fluids can then lead to the development of hyponatremia. Primary solute depletion, from either renal losses (eg, diuretics, mineralocorticoid deficiency, and various nephropathies) or extrarenal losses (eg, vomiting, diarrhea, hemorrhage, and excessive sweating), all can lead to hypovolemic hyponatremia if predominantly water or hypotonic fluids are ingested or infused in response to the body fluid losses [11]. A low urine sodium concentration (U_{Na}) suggests a nonrenal cause of solute depletion, whereas a high U_{Na} suggests renal causes of solute depletion. Diuretic use is the most common cause of hypovolemic hypoosmolality, with thiazides more commonly associated with severe hyponatremia than loop diuretics [31].

Hypervolemic hyponatremia

In hypervolemic hyponatremia, there is an excess of total body water and total body sodium, resulting in clinically evident hypervolemia manifested by edema or ascites. Hyponatremia occurs because the increase in total body water is usually in excess of the increase in total body sodium as a result of potent AVP secretion in response to a decreased effective arterial blood volume (EABV) [32]. Hypoosmolality in these patients suggests a relatively decreased intravascular volume, leading to water retention as a result of elevated plasma AVP levels and decreased distal delivery of glomerular filtrate [32]. Cirrhosis, congestive heart failure, and nephrotic syndrome all share this common pathophysiology. These patients usually have a low U_{Na} because of secondary hyperaldosteronism; however, the U_{Na} can be difficult to interpret if the patient is on concomitant diuretic therapy.

Euvolemic hyponatremia

Euvolemic hyponatremia can be caused by virtually any disorder causing hypoosmolality. The pathogenesis of euvolemic hyponatremia is typically excessive water retention, caused by either impaired water excretion from advanced renal failure, or more likely from increased secretion of AVP. Occasionally, hyponatremia can occur from over-ingestion of water, where the gastrointestinal tract absorbs water faster than the kidney's ability to excrete it. Because clinical assessments of volume status are often not very sensitive, the presence of normal or low serum urea nitrogen and uric acid concentrations can be helpful correlates of normal ECF volume. SIADH, glucocorticoid deficiency, and hypothyroidism are the most common etiologies of euvolemic hyponatremia.

Postneurosurgical hyponatremia

Hyponatremia has been reported as either an early or late complication of pituitary surgery, and can occur as an isolated entity or as the second phase of the triphasic response to postoperative DI. Hyponatremia after any neurosurgical procedure can be life threatening [33]; however, the majority of cases are mild and relatively asymptomatic because the serum [Na^+] levels are generally not very low (eg, 130 mmol/L–134 mmol/L). The incidence of hyponatremia appears to be higher after resection of ACTH-secreting adenomas, occurring in as high as 61% of patients with Cushing's disease [33]. This may be because the rapid decrease in serum cortisol, after removal of an ACTH-producing adenoma, can produce relative glucocorticoid deficiency, predisposing patients to hyponatremia. Given that many cases of hyponatremia occur as a late complication of transsphenoidal surgery, it is recommended that serum [Na^+] be monitored daily during hospitalization in patients undergoing transsphenoidal surgery [34]. As most patients are discharged within a few days postoperatively, serum [Na^+] levels are assessed within a week after discharge, and patients should be cautioned to monitor for the abrupt onset of dilute polyuria.

Transient hyponatremia without preceding or subsequent DI has been reported following transphenoidal surgery for pituitary microadenomas. This generally occurred 5 to 10 days postoperatively in as many as 30% of patients when they were carefully followed in some series [34]. This scenario can be best understood within the framework of the pathophysiology of the triphasic response, except that in these cases only the second phase of inappropriate AVP secretion occurs because the degree of neural lobe or pituitary stalk damage is not sufficient to cause dysfunction or loss of greater than 85% to 90% of AVP neurons, either acutely or chronically (see Fig. 1B). Consequently, this syndrome has been named the "isolated second phase" of the triphasic response, because the first and third phases of DI are absent [35].

When euvolemic hyponatremia occurs after transsphenoidal pituitary surgery, hypothyroidism, and adrenal insufficiency must always be excluded. However, most patients receive stress doses of glucocorticoids intraoperatively and immediately postoperatively, and many days are required for thyroid hormone levels to fall sufficiently to cause hyponatremia after cessation of thyrotropin secretion. Consequently, both of these potential causes of hyponatremia are uncommon in the immediate postoperative setting. In these cases, a diagnosis of SIADH or cerebral salt wasting must be carefully considered. The distinction between these two disorders is important because of the differing nature of their treatments.

Syndrome of inappropriate antidiuretic hormone secretion

SIADH is characterized by hyponatremia in the setting of an inappropriately concentrated urine, increased urine sodium concentration, and evidence of normal or slightly increased intravascular volume. SIADH is primarily caused by inappropriate plasma AVP levels at plasma osmolalities where pituitary AVP secretion is normally inhibited, leading to renal water reabsorption and expansion of the ECF volume. Because the volume expansion is primarily because of water rather than sodium, it is usually not apparent clinically, and patients typically do not have edema or distended neck veins on physical exam. However, modest expansion of the intravascular volume can be measured by increases in the glomerular filtration rate and renal blood flow. These changes can lead to decreased sodium reabsorption from the proximal tubule, leading to an increased urinary sodium excretion that is characteristic of SIADH. Concentrations of uric acid and urea, which are reabsorbed along with sodium in the proximal tubule, are also decreased in the blood [36]. SIADH is a diagnosis of exclusion, and nonhypotonic hyponatremia from pseudohyponatremia or hyperglycemia, as well as other etiologies of euvolemic hyponatremia, such as hypocortisolism and hypothyroidism, must be ruled out before a diagnosis of SIADH can be made (Box 3) [37].

Cerebral salt wasting

In contrast to SIADH, cerebral salt wasting (CSW) is defined as the renal loss of sodium during intracranial disease, ultimately leading to hyponatremia and a decrease in ECF volume [36]. CSW was initially described in the 1950s by Peters and colleagues [38] in a report of three patients with neurologic disorders who presented with hyponatremia, renal salt wasting, and clinical evidence of volume depletion without any obvious disturbances in the hypothalamic-pituitary-adrenal axis. CSW is now being diagnosed with increasing frequency in neurologic and neurosurgical patients [39], although the true incidence of this disorder remains controversial.

Box 3. Criteria for diagnosis of syndrome of inappropriate antidiuretic hormone secretion

Decreased effective osmolality of the extracellular fluid (plasma Osm less than 275 mOsm/kg H_2O)
Inappropriate urinary concentration (urine Osm greater than 100 mOsm/kg H_2O with normal renal function)
Clinical euvolemia
Elevated urinary sodium excretion on a normal salt and water diet
Absence of other potential causes of euvolemic hypoosmolality
- Hypothyroidism
- Hypocortisolism
- Diuretic use

The mechanism by which cerebral disease or neurosurgical procedures leads to renal salt wasting is poorly understood. One theory is that it involves disruption of neural inputs to the kidney, causing decreased renal sodium absorption in the proximal nephron. This ultimately leads to a large delivery of sodium to the distal nephron, increased sodium excretion, and a decrease in EABV; the decrease in EABV in turn activates baroreceptor-stimulated AVP release [36]. Another proposed mechanism is that there is a central release of one or more natriuretic factors, such as atrial natriuretic peptide (ANP) or brain natriuretic peptide (BNP). Both of these factors increase urinary excretion of sodium because of a direct inhibitory effect on sodium transport in the inner medullary collecting duct [40]. Ten subjects with subarachnoid hemorrhage, who underwent clipping of an aneurysm, had significantly higher levels of BNP both before surgery and up to 8 days postoperatively, compared to controls, and the BNP concentrations were significantly correlated with both urinary sodium excretion and intracranial pressure [41].

Diagnosis

Distinguishing CSW from SIADH in clinical practice can be difficult, given that both are caused by similar neurologic processes, and their laboratory values in terms of plasma osmolality, urine osmolality and urine sodium can look identical (Table 1). Determination of ECF volume remains the single best method of distinguishing the between the two: ECF volume is normal or increased in SIADH and low in CSW. The presence of orthostatic changes in blood pressure and pulse, dry mucus membranes and flat neck veins, negative fluid balance, and weight loss all support a diagnosis of CSW. Laboratories that suggest hemoconcentration, as evidenced by an increased hematocrit, increased serum albumin, and increased serum

Table 1
Diagnosis of cerebral salt wasting versus syndrome of inappropriate antidiuretic hormone secretion

Symptom	CSW	SIADH
Extracellular fluid volume	Decreased	Normal to increased
Plasma albumin/protein concentration	Increased	Normal
Signs or symptoms of dehydration	Present	Absent
Weight	Decreased	Normal to increased
Central venous pressure	Decreased	Increased or normal
Hematocrit	Increased	Decreased or no change
Osmolality	Increased or normal	Decreased
Serum urea nitrogen to creatinine ratio	Increased	Normal
Serum potassium concentration	Increased or no change	Decreased or no change
Plasma uric acid	Normal	Decreased

bicarbonate concentration, also support a diagnosis of CSW. Uric acid levels are depressed in patients with SIADH, reflecting the slight increase in ECF volume seen in this disorder. One would expect that in CSW the uric acid levels would be high, reflecting the volume contracted state of this disorder. However, reported uric acid levels in CSW are unexpectedly low [42]. Consequently, uric acid levels are not helpful in distinguishing between these two entities. Although individual cases of CSW have been well documented, most studies lack sufficiently rigorous documentation of hypovolemia to justify this diagnosis. It is important to remember that elevations of urine sodium concentration are common in SIADH, and therefore this cannot be viewed as evidence of "salt wasting" by the kidneys in the absence of clinical evidence of volume contraction, which is often lacking. Urine sodium concentrations are particularly difficult to interpret once therapy with isotonic saline has begun, as this markedly elevates U_{Na}, even in normal subjects. Because most postoperative patients are euvolemic unless they have DI, it is likely that the majority of postneurosurgical hyponatremia is caused by SIADH, with relatively fewer cases attributable to CSW.

The possibility that both disorders might coexist should be considered. Ample precedent certainly exists for hyponatremia caused by Na^+ wasting with a secondary antidiuresis in Addison's disease, as well as diuretic-induced hyponatremia. Characteristic of these disorders, normalization of ECF volume with isotonic NaCl infusions restores plasma osmolality to normal ranges by virtue of shutting off the secondary AVP secretion. If hyponatremia in patients with CSW occurred via a similar mechanism, it should also respond to this therapy. However, several studies indicate that it does not. Nineteen patients with subarachnoid hemorrhage (SAH) were treated with large volumes of isotonic NaCl sufficient to maintain plasma volume at normal or slightly elevated levels; but despite removal of any volemic stimulus to AVP secretion, 32% still developed hyponatremia in association with nonsuppressed plasma AVP levels, an incidence equivalent to that found in previous studies of SAH [43]. These types of results support the existence of

disordered AVP secretion, as well as a coexisting stimulus to natriuresis in many such patients. It therefore seems most likely that SAH and other intracranial diseases associated with CSW represent a mixed disorder in which some patients have both exaggerated natriuresis and inappropriate AVP secretion. Which effect predominates in terms of the clinical presentation will depend on their relative intensities, as well as the effects of concomitant therapy. Consequently, many cases of postneurosurgical hyponatremia probably entail inappropriate secretion of both AVP and ANP/BNP; in such cases the natriuretic peptides would act to further exacerbate the secondary natriuresis already produced by AVP-induced water retention.

Treatment

In SIADH, fluid restriction is the mainstay of treating hyponatremia, with the goal of maintaining fluid intake at least 500 mL per day below the urine output. However, this degree of fluid restriction is often difficult to maintain, especially in a hospital setting where the obligate fluid requirements for various therapies and parenteral nutrition often exceed this level. In contrast, treatment of hyponatremia in CSW entails volume replacement and maintenance of a positive sodium balance. Intravascular volume can be maintained with intravenous isotonic saline, and once patients are capable of taking oral medications NaCl tablets can be used.

It is important to distinguish between these two disorders, because treatment that is appropriate for one disorder can potentially result in poor outcomes when inappropriately applied to the other [44]. As an example, the potential for fluid restriction to worsen an underlying neurologic condition in the setting of CSW was suggested in a retrospective study of patients with SAH, where 44 of 134 patients were found to have developed hyponatremia between 2 to 9 days following their hemorrhage; 21 of 44 patients treated with fluid restriction developed a cerebral infarction, including 15 of 17 patients who clinically met the criteria for SIADH. This suggests that the fluid restriction aggravated an already decreased plasma volume, thereby leading to cerebral ischemia as a result of vasospasm, as well as potentially decreasing cerebral blood flow by increasing blood viscosity and decreasing cardiac output [44].

Conversely, when intravenous isotonic NaCl is infused in patients with SIADH, this can potentially cause a further lowering of serum sodium concentrations, resulting in the development of symptomatic hyponatremia [45,46].

Reeder and Harbaugh [47] have advocated the use of urea and saline in patients with hyponatremia caused by intracranial disease, where it is unclear whether SIADH or CSW is the diagnosis, or where there is the possibility that both coexist. Urea induces a mild osmotic diuresis and depresses urinary sodium excretion, and supplemental NaCl restores sodium deficits. In their retrospective review of 48 neurosurgical patients treated with urea and saline, mean serum [Na^+] increased by 8 mmol/L without treatment

complications. Randomized controlled trials of this and other therapies will be necessary before definitive recommendations can be made.

Evidence-based guidelines for treatment of hyponatremia are lacking, but a recent consensus statement summarizes areas of general agreement concerning the treatment of various types of hyponatremia [48]. The neurologic sequelae associated with acute hyponatremia are caused when there is a rapid, osmotic influx of water along osmotic gradients into the central nervous system, leading to brain edema. The brain has an early adaptive mechanism to decrease edema by extruding inorganic solutes, and thus water. A later more effective adaptive mechanism occurs whereby the brain regulates its volume by extruding small organic molecules called osmolytes [49]. Once brain edema decreases via this adaptive process, neurologic symptoms generally abate, explaining why patients with chronic hyponatremia may be relatively asymptomatic, despite very low serum [Na^+] [50].

Several studies have shown that the rate of decrease of serum [Na^+] is more strongly correlated with morbidity and mortality than is the actual magnitude of the hyponatremia [51]. This is because of the fact that the volume adaptation process takes a finite period of time to complete: the more rapid the fall in serum [Na^+], the more brain edema will be accumulated before the brain is able to lose solute, and along with it part of the increased water content [4]. Acute hyponatremia, defined as lasting less than 48 hours in duration, can result in sufficient brain edema to cause seizures, tentorial herniation, respiratory arrest, irreversible brain damage and, in severe cases, death. Chronic hyponatremia, defined as lasting more than 48 hours, produces more subtle symptoms, including headache, lethargy, disorientation, and nausea, or may even be asymptomatic if complete brain volume regulation has occurred [52].

It is important for clinicians to understand how the brain volume adapts in response to hyponatremia in order to correct serum [Na^+] safely. In both animal and human studies, brain demyelination has clearly been shown to be associated with correction of existing hyponatremia, rather than simply with the presence of severe hyponatremia itself [53]. It is generally agreed that treatment of symptomatic hyponatremia is necessary, regardless of the etiology, but some debate remains as to how quickly the serum [Na^+] can be corrected without risk of precipitating pontine and extrapontine myelinolysis, also called the osmotic demyelination syndrome (ODS). Rapid correction of hyperacute hyponatremia (occurring in less than 24 hours), rarely if ever leads to ODS, and rates of serum [Na^+] increase can safely exceed 2 mmol/L per hour in such cases [54]. However, in patients with chronic hyponatremia, correction rates must be lower in order to prevent potential demyelination. It is generally accepted that a correction of 12 mmo/L in the first 24 hours, and 18 mmol/L in the first 48 hours, is generally safe [53], but there have been a few case reports of osmotic demyelination that appear to have occurred with corrections slower than 12 mmol/L per 24 hours [55,56]. Thus, in cases of known chronic hyponatremia or

hyponatremia of unknown duration, and particularly in patients with other known risk factors for pontine and extrapontine demyelination (eg, alcoholism, malnutrition, liver failure), a more prudent approach would be to aim for a rate of correction of no faster than 8 mmol/L per 24 hours [54].

New developments in water homeostasis

Vasopressin receptor antagonists

A new class of agents, AVP receptor antagonists, have been recently introduced as a method of correcting hyponatremia by blocking the binding of AVP to V2 receptors in the kidney. AVP receptor antagonists are highly effective in producing a safe and predictable increased excretion of free water that increases the serum [Na^+] in hyponatremic patients. Because these agents induce excretion of free water without accompanying natriuresis or kaliuresis, this effect has been termed ''aquaresis,'' to differentiate it from the increased water and solute excretion produced by traditional diuretic agents [57].

Several AVP receptor agonists are under clinical investigation for use in euvolemic hyponatremia: conivaptan (YM-087), lixivaptan (VPA-985), satavaptan (SR-121463), and tolvaptan (OPC-41061). All drugs in this class carry the suffix ''vaptan,'' so as a group they are often referred to as ''the vaptans.'' All four of the current vaptans increase urine volume and decrease urine osmolality, but have no effect on 24-hour sodium excretion [58]. Conivaptan has antagonist activity at both the V1a and V2 AVP receptors, whereas the other three vaptans are selective V2 receptor antagonists [59]. Conivaptan is currently Food and Drug Administration-approved for the treatment of euvolemic and hypervolemic hyponatremia in hospitalized patients. There are several recent reviews for more detailed summaries of clinical trials of various vaptans [58].

Conivaptan is currently the only available agent for treatment of hyponatremia. Phase 3 studies show that it reliably raises serum [Na^+], beginning as early as 1 to 2 hours after administration. In most patients, the serum [Na^+] normalizes over a 4-day continuous infusion, with the greatest increase in serum [Na^+] during the first 24 to 48 hours of treatment. It is interesting to note that no cases of osmotic demyelination have occurred during clinical trials of any of the vaptans [60]. In part, this is because the dosing employed in the clinical protocols infrequently caused increases in serum [Na^+] greater than12 mmol/L in any 24-hour period. However, it is also because the protocols were constructed to include monitoring of the serum [Na^+] frequently (at least every 6 hours) during active corrections of hyponatremia, and the drug was discontinued if set limits of correction rate were exceeded. Consequently, analogous guidelines should be employed with clinical use of these agents to avoid correcting the serum [Na^+] at a rate faster than 8 mmol/L to 12 mmol/L per 24 hours. Although all of the vaptans have a half-life of less

than 12 hours, which should allow dose titration to avoid over-correction, an occasional patient may continue to increase the serum [Na^+] for several hours after discontinuation of the drug, in which case free water should be given to the patient to prevent further correction and clamp the serum [Na^+] at a safe level.

The clearest indication for conivaptan use is in patients with symptomatic euvolemic hyponatremia and mild to moderate neurologic symptoms, such as impaired cognition, confusion, and disorientation. Conivaptan is known to reliably increase serum [Na^+] by several mmol/L within 5 hours at the 20-mg and 40-mg doses, and 6 mmol/L to 9 mmol/L within 24 hours after initiation of therapy [61]. The induced free water aquaresis should resolve such neurologic symptoms promptly by decreasing cerebral edema, with no risk of worsening the hyponatremia. Importantly, in severely symptomatic hyponatremic patients with seizures, obtundation, coma, and respiratory distress, hypertonic saline should still be used as first-line therapy. The vaptan clinical trials excluded patients with symptomatic hyponatremia for ethical reasons of not potentially randomizing critically ill patients to a placebo arm of a double-blinded protocol. Thus, it is not currently known whether sufficiently rapid correction can be achieved with conivaptan alone to prevent herniation and respiratory arrest in patients with severe hyponatremic encephalopathy. Therefore, these patients should receive the current standard of care, which is infusion of hypertonic (3%) NaCl or mannitol [53]. Theoretically, combined treatment with both hypertonic NaCl and conivaptan should be complementary [62], but clinical trials with such protocols will be necessary before their efficacy and safety can be determined.

In the postoperative setting following neurosurgery for sellar lesions, many patients have a transient form of SIADH, either as part of a triphasic response or an isolated second phase, and in such case a short, several-day course of a V2 receptor antagonist can help to resolve the hyponatremia quickly, without need for more chronic therapy. Vaptans theoretically should not be used in patients with CSW, because these patients are by definition hypovolemic and the resultant aquaresis would cause further intravascular volume depletion. However, as previously discussed, many patients who are labeled as having CSW are actually clinically euvolemic, and more likely have SIADH. Furthermore, patients with subarachnoid hemorrhage are generally aggressively volume expanded with hypervolemic-hypertensive therapy to prevent cerebral vasospasm; in this situation, the use of a vaptan can be helpful to prevent further hyponatremia, resulting from continuous administration of large volumes of isotonic saline, as also discussed earlier. The free water aquaresis should normalize the serum [Na^+], thus decreasing cerebral edema caused by hyponatremia and simultaneously allowing continued concurrent infusion of large volumes of isotonic saline to prevent vasospasm.

Some significant side effects with the use of conivaptan have become apparent, including drug interactions via interference with CYP3A4-mediated

hepatic metabolism and a high occurrence of infusion site reactions caused by the need to use polypropylene glycol to achieve solubility [61]. Despite the need for cautious use, as with any new class of therapeutic agents, it is abundantly clear that the availability of potent AVP receptor antagonists heralds the beginning of a new era in the treatment of hyponatremia.

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