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Hyponatremia: a problem-solving approach to clinical cases

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Abstract

Hyponatremia, defined as a serum sodium concentration of <135 mmol/L, often develops as a consequence of elevated levels of arginine vasopressin (AVP) hormone. AVP elevation can occur in a number of common clinical conditions, including syndrome of inappropriate secretion of AVP, volume depletion, postoperative states, heart failure, cirrhosis, neuroendocrine disorders and trauma. A history of concurrent illness and medication use, assessment of extracellular fluid volume as well as measurement of serum and urine osmolality and urine sodium concentration will help to establish the primary underlying causes. Presence or absence of significant neurologic signs and symptoms must guide treatment. Symptomatic hyponatremia must be treated promptly with 3% hypertonic saline to increase the serum sodium by 1-2 mmol/L per hour until symptoms abate, or a total magnitude of correction of 12 mmol/L in 24 hours or 18 mmol/L in 48 hours is achieved. Initial infusion rate (ml/kg per hour) can be estimated by body weight (kg) x desired rate of increase in sodium (mmol/L per hour). An overly rapid increase in sodium (>12 mmol/L per 24 hours) may result in serious neurologic injury. Fluid restriction and loop diuretic are frequently employed to treat volume overload. Vasopressin receptor antagonists provide prompt and effective water diuresis and increase in serum sodium concentration in both euvolemic and hypervolemic hyponatremia. In this review article, the author introduces a problem-solving approach to dissect the different clinical cases with hyponatremia and presents simple algorithms for the evaluation and management of hyponatremia that are useful at the bedside to improve quality, safety and cost-effectiveness of the patient's care.

Key words: *Cerebral salt-wasting, Hyponatremia, Hyponatremic encephalopathy, Neurogenic syndrome of inappropriate secretion of antidiuretic hormone, Reset osmostat*

Introduction

Hyponatremia is the most common of the electrolyte abnormalities in hospitalized patients and may have a significant impact on morbidity and mortality in a variety of disorders (1). A prompt diagnosis of the underlying causes, with appropriate management is very crucial. Hyponatremia is defined as serum sodium <135 mmol/L, and it usually implies a state of hypotonicity with a relative excess of total body water compared with total body sodium (2, 3).

Mortality and morbidity

The mortality of acute symptomatic hyponatremia has been reported to be as high as 55%. The risk of mortality increases with the severity of hyponatremia (27% when serum sodium is <120 mEq/L). Patients with acute hyponatremia (developing over 48 hours or less) are subject to more severe degrees of cerebral edema for a given serum sodium level. The primary cause of morbidity and death is brainstem herniation and mechanical compression of vital midbrain structures. Rapid identification and correction of serum sodium level is necessary in patients with severe acute hyponatremia to avert brainstem herniation and death. Patients with chronic hyponatremia (developing over more than 48 hours) experience milder degrees of cerebral edema for a given serum sodium level. Brainstem herniation has not been observed in patients with chronic hyponatremia.

Incidence and prevalence

In a recent prospective study of inpatients in a US hospital, the incidence of hospital-acquired hyponatremia (Na^+ <135 mEq/L) was reported to be between 20% and 25%. Hyponatremia has also been observed in approximately 30% of all patients treated in the intensive care unit, and 87% of all hospitalized patients with congestive heart failure had hyponatremia. On the surgical ward, approximately 4.4% of postoperative patients developed hyponatremia within 1 week of surgery (4).

Pathophysiology

Normally, osmolality in the blood regulates arginine vasopressin (AVP) hormone, which modulates urine flow. However, there is also a nonosmotic pathway that is dependent on the integrity of the arterial circulation, and with a decrease in cardiac output or hypovolemic stimuli, that nonosmotic pathway is stimulated, and it can override the osmotic pathway. When this happens, the plasma osmolality falls and hyponatremia occurs.

It is not the hyponatremia per se that increases the risk of cerebral edema, nor is it the measured or calculated osmolality. It is the tonicity (effective osmolality) that is really related to the risk of cerebral edema. Osmolality is a function of the total concentration of solutes (largely ions) in a solution, and this measure does not depend on whether the solutes can cross cell membranes. Effective osmolality (tonicity) refers to the osmotic gradient due to solutes that do not cross the cell membrane, and it is a measure of the ability of a solution to exert an osmotic pressure upon the membrane, and is numerically the concentration of the solutes that cannot cross the membrane. Only solutes that cannot cross the membrane (i.e., nonpenetrating solutes) separating the 2 compartments generate an effective osmotic pressure (tonicity). Urea crosses the cell membrane easily and does not contribute to osmotic pressure (a penetrating solute, or an ineffective solute, another example is ethanol), but will be measured as part of the plasma osmolality by the osmometer, while effective solutes (such as sodium, glucose and mannitol) are confined largely to the extracellular fluid (ECF) compartment and contribute to both measured osmolality and effective osmolality (tonicity).

Signs and symptoms

Symptoms range from mild anorexia, headache and muscle cramps, to significant alteration in mental status including confusion, obtundation, coma or status epilepticus. The number and severity of symptoms increase with the degree of hyponatremia and the rapidity with which it develops. When the serum sodium level falls gradually, over a period of several days or weeks, sodium levels as low as 110 mEq/L may be reached with minimal symptomatology. In contrast, patients with acutely developing hyponatremia are typically symptomatic at a level of approximately 120 mEq/L and are at higher risk for developing severe cerebral edema, coma or brainstem herniation (5).

Causes and types of hyponatremia

Depending on the state of hydration, the hyponatremia may be associated with decreased increased or near-normal amounts of total body sodium (6).

Euvolemic hyponatremia

In euvolemic hyponatremia there is a relative excess of water compared with sodium (1, 2). The excess total body water may not be clinically apparent, because it is mainly intracellular. Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is the most common cause of nonosmotic AVP release in euvolemic hyponatremic patients (7). The diagnostic features include hyponatremia with inappropriately raised urine osmolarity (>100 mmol/L), increased urinary sodium excretion (>20 mmol/L), hypouricemia, in the presence of normal renal and endocrine functions (8). Patients with SIADH appear to have thirst and daily fluid intake similar to that of healthy individuals despite plasma osmolalities well below the physiologic osmotic threshold for thirst appreciation. The persistent of thirst at such low plasma osmolalities is believed to be the prime reason for the hyponatremia in SIADH (9). Hypouricemia in SIADH is caused by increased urinary uric acid excretion (10).

SIADH must be considered in patients with pneumonia, active tuberculosis, pulmonary abscess, neoplasm or asthma, as well as in patients with central nervous system infection. Patients with carcinoma of the nasopharynx, duodenum, stomach, pancreas, ureter, prostate or uterus also have an increased risk (7). Postoperative patients who experience pain, nausea and vomiting and are being treated with analgesics and hypotonic solution are particularly prone to develop SIADH. SIADH in these patients develops as a consequence of elevated levels of hormone AVP secretion secondary to surgical stimulus (nausea and pain) and analgesic and hypotonic fluid administration.

Other potential causes of euvolemic hyponatremia are primary polydipsia (11), exercise-induced hyponatremia (12),

low solute intake, reset osmostat (13), hypothyroidism (14), glucocorticoid deficiency (15) and nephrogenic syndrome of inappropriate antidiuresis (16). Excess water intake by itself almost never causes hyponatremia unless there is a subclinical nonosmotic release of AVP. Nonosmotic AVP secretion combined with high fluid intakes that exceed the urine output has been hypothesized to lead to exercise-associated hyponatremia (13).

The amount of solute intake determines the amount of water that can be excreted by the kidney. In conditions such as "beer-drinker syndrome (beer potomania)," there is not much solute in the patient who is drinking only beer. If one can even maximally dilute the urine down to 50 mmol/L, and the solute intake is only 200 mmol per day, that individual can only excrete 4 L of water per day (200/50). Thus, if the person is drinking 6 or 7 L per day, he/she becomes hyponatremic because of an inability to maximally excrete excess free water in presence of inadequate urinary solute excretion (17).

The diagnostic criteria for reset osmostat include normovolemic hypotonic hyponatremia; normal renal, adrenal and thyroid function; ability to concentrate the urine when serum tonicity is raised above the reset level of serum osmolality; ability to excrete more than 80% of a standard oral water-loading test (10-15 ml/kg) within 4 hours, and maintenance of urine osmolarity below 100 mmol/L during water diuresis (12).

Nephrogenic syndrome of inappropriate antidiuresis should be suspected in any patient with therapy-resistant hyponatremia, undetectable vasopressin levels, who is unresponsive to vasopressin-receptor antagonist, and has an abnormal response to a water-loading test (15).

Hypovolemic hyponatremia

Hypovolemic hyponatremia is characterized by deficits of both total body sodium and total body water, with the sodium deficit greater than the water deficit (1, 2). With ECF volume depletion from any cause, the AVP secretion is increased to defend ECF volume. Hypovolemic hypotonic hyponatremia can be due to renal sodium-wasting including diuretic use (18), cerebral salt-wasting (urine sodium >20 mmol/L) (19), interstitial nephritis or mineralocorticoid deficiency, or extra renal losses such as diarrhea, vomiting, excessive sweating or third-spacing (urine sodium <10 mmol/L) (1).

Cerebral salt-wasting has been described in patients with subarachnoid hemorrhage (19). These patients manifest the diagnostic criteria of SIADH, except that renal salt-wasting is the primary defect leading to ECF volume depletion, which stimulates AVP release (18, 19). The high urine sodium excretion seems to be likely due to a brain natriuretic peptide and not due to volume expansion (19).There is also evidence that hypouricemia and increased urine uric acid excretion coexist in patients with cerebral salt-wasting syndrome due to a tubular transport abnormality for uric acid (19). Correction of hyponatremia lowers the urine uric acid excretion in SIADH leading to normalization of serum uric acid level, but in cerebral salt-wasting syndrome, hypouricemia and increased urine uric acid excretion persist (19).

Hypervolemic hyponatremia

Hypervolemic hypernatremic patients have an excess of both total body sodium and total body water, with the water excess greater than the sodium gain (1, 2). The hyponatremia is usually caused by fluid overload associated with elevated AVP secretion, such as with patients who have advanced kidney failure, congestive heart failure or cirrhosis (20).

The hyponatremia in heart failure patients is associated with the nonosmotic release of AVP. In a state of congestive heart failure, a decrease in cardiac output initiates a baroreceptor response which in turn triggers the secretion of the 3 hormones renin-angiotensin-aldosterone system (RAAS), AVP and norepinephrine. Beta-adrenergic stimulation and RAAS activation further contribute to water retention and hyponatremia because of severe renal vasoconstriction and reduced glomerular filtration. The severity of the defect in water excretion due to the neurohumoral activation parallels the severity of the heart disease. A low serum sodium concentration below 125 mmol/L represents near end-stage disease (20). The same mechanism also applies in cirrhosis, except the arterial underfilling is not due to a decrease in cardiac output, but is secondary to primary systemic arterial vasodilatation that initially occurs in the splanchnic bed. The arterial baroreceptors sense the arterial underfilling, which in turn triggers the activation of the neurohumoral axis.

Diagnostic approach to the patient with hyponatremia

A history of concurrent illness and medication use, as well as the assessment of ECF volume on physical examination, and certain laboratory tests, such as blood and urine osmolality levels, urine sodium concentration and serum uric acid level, usually provide useful information to establish the correct diagnosis (1, 2).

Pseudohyponatremia and hyperglycemia-induced hyponatremia should be considered early during the diagnostic process. A normal serum osmolarity (280 mmol/L) suggests the presence of pseudohyponatremia secondary to

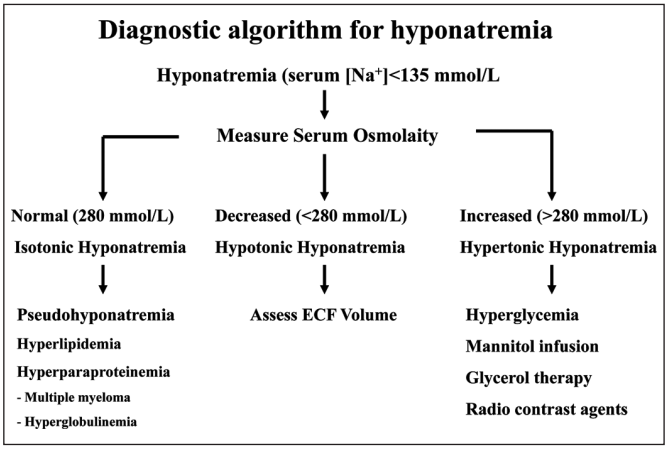

Fig. 1 - Diagnostic algorithm for hyponatremia: hyponatremia (serum [Na^+] <135 mmol/L. ECF = extracellular fluid.

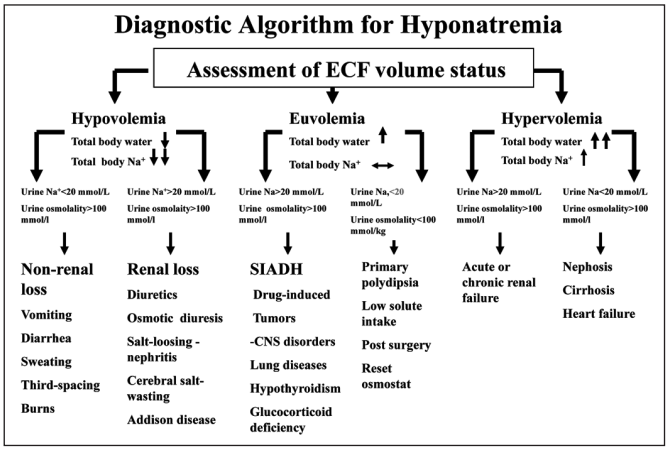

Fig. 2 - Diagnostic algorithm for hyponatremia. CNS = central nervous system; ECF = extracellular fluid.

hyperparaproteinemia (multiple myeloma or Waldenström's macroglobulinemia) or hyperlipidemia. An elevated serum osmolarity (>280 mmol/L) is found in patients with hyperglycemia or mannitol infusion (1, 2) (Fig. 1).

In euvolemic hyponatremia, there is no clinical evidence of ECF volume depletion or expansion. The opposite occurs in hypovolemic hyponatremia. There is clinical evidence of ECF volume depletion (weight loss, decreased skin turgor and/or orthostatic fall in blood pressure). The patient has diarrhea, vomiting or is on a diuretic. With hypervolemic hyponatremia, patients have peripheral edema, ascites or pulmonary congestion. The hyponatremia is probably associated with heart failure, cirrhosis and advanced kidney failure.

Urine osmolality helps to differentiate between conditions associated with impaired free water excretion (SIADH) and primary polydipsia or reset osmostat, in which water excretion is normal (<100 mmol/L). A urine osmolality greater than 100 mmol/kg indicates impaired ability of the kidneys to dilute urine in the presence of increased total body water. A urine osmolarity <100 mmol/L and urinary sodium concentration <20 mmol/L in patients with normovolemic hyponatremia suggests primary polydipsia, exercise-associated hyponatremia (marathon runners) or low dietary solute intake (beer drinkers [beer potomania]). With SIADH, the urine sodium is >20 mmol/L. However, if sodium intake is inadequate, then urine sodium may be <20 mmol/L (Fig. 2).

In hypovolemic patients, a urinary sodium concentration >20 mmol/L predicts renal losses of sodium (diuretic use or mineralocorticoid deficiency). When the urinary sodium excretion is <20 mmol/L, extra renal losses including vomiting, diarrhea, excessive sweating or third-spacing losses should be suspected.

In hypervolemic (edematous) patients, a urinary sodium excretion >20 mmol/L suggests the presence of acute or chronic kidney disease. In contrast, when the urinary sodium excretion is <20 mmol/L, nephrotic syndrome, cirrhosis of liver or congestive heart failure are clinically apparent (Fig. 2).

Treatment

Appropriate treatment of hyponatremia depends on the correct classification of hyponatremia, the concomitant disease state, the severity of symptoms and the severity of hyponatremia. To mange hyponatremia, one must definitely differentiate acute from chronic hyponatremia in terms of therapy and search for the source of electrolyte-free water (water without Na^+ and K^+) in acute hyponatremia and the underlying cause of antidiuretic hormone (ADH) action to retain this electrolyte-free water in chronic hyponatremia.

Acute hyponatremia

Acute hyponatremia (duration <48 hours) should be treated aggressively to prevent cerebral edema, while chronic hyponatremia should be treated slowly to avoid the osmotic demyelination syndrome (21). The single most important factor guiding initial therapy is the presence of neurologic symptoms. Cases of acute hyponatremia (defined as <48 hours in duration) are usually symptomatic if the hyponatremia is severe (serum sodium <120 mmol/L) (21). Untreated acute or improperly treated severe hyponatremia can result in cerebral edema, irreversible neurologic damage, respiratory arrest, brain stem herniation and death (21). Patients with symptomatic hyponatremia are at greater risk of cerebral edema due to hyponatremia itself (21) and should be treated with hypertonic 3% saline to promptly increase

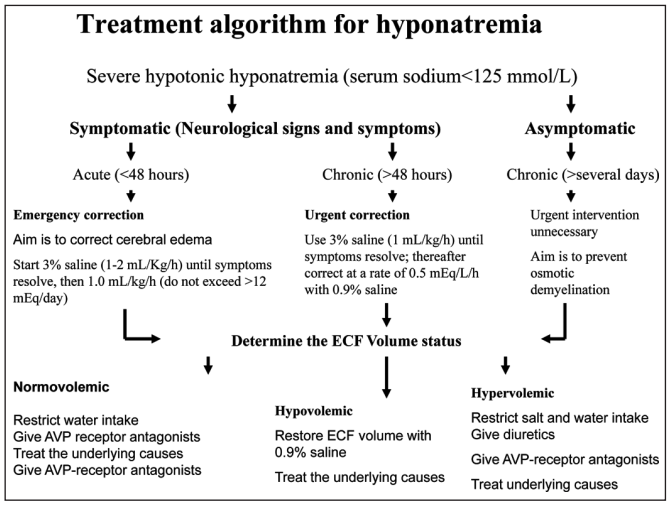

Fig. 3 - Treatment algorithm for hyponatremia: severe hypotonic hyponatremia (serum sodium <125 mmol/L). AVP = arginine vasopressin; ECF = extracellular fluid.

sodium by 1-2 mmol/L per hour until symptoms abate or a safe level of sodium is achieved (≥120 mmol/L); thereafter, hyponatremia should be corrected at a rate of 0.5 mmol/L per hour, not exceeding 12 mmol/L in 24 hours or 18 mmol/L in 48 hours (22) (Fig. 3). The aim of treatment is to prevent cerebral edema. The initial infusion rate of hypertonic 3% saline can also be estimated by multiplying the patient's body weight (kg) by the desired rate of increase in serum sodium (mmol/L per hour) (21).

Chronic hyponatremia

Patients with chronic hyponatremia (≥48 hours in duration) who are asymptomatic or have mild symptoms are at lower risk of cerebral edema due to hyponatremia; however, they are at greater risk of osmotic demyelination resulting from overly rapid correction (23). Osmotic demyelination is a severe neurologic disorder that is characterized by hemiplegia or paraplegia, respiratory paralysis, coma or even death.

If the patient has mild to moderate symptoms, the hyponatremia should be corrected with 0.9% saline at a rate of <0.5 mmol/L per hour to a maximum serum sodium concentration of 125 mmol/L over 24 hours to avoid the risk of neurologic injury from osmotic demyelination (21).

Euvolemic hyponatremia

In SIADH patients, a trial of water restriction is initially employed. Sodium should not be restricted, and drugs known to cause SIADH should be discontinued. If the serum sodium level continues to fall, a trial of intravenous normal saline may clarify diagnosis. If the patients have SIADH, hyponatremia will worsen, and if they are ECF volume contracted, serum sodium will improve. Demeclocycline, lithium and urea have been used in cases of chronic asymptomatic hyponatremia with variable efficacy and toxicity (22, 24).

Patients with glucocorticoid deficiency or hypothyroidism should be treated with glucosteroids and L-thyroxin, respectively. The treatment of patients with low solute intake is to increase their sodium as well as protein intake. In patients with primary polydipsia, hyponatremia can be corrected rapidly by simply withholding their fluid without the need to superimpose hypertonic saline. Treatment of patients with beer potomania is to increase dietary sodium and protein intake (1).

The vasopressin-receptor antagonists are now approved for use in hospitalized patients with euvolemic and hypovolemic hyponatremia (25). These agents treat hyponatremia through V2-receptor antagonism of AVP in the renal collecting ducts, resulting in excretion of free water (aquaresis). These agents are indicated for severe hypervolemic and euvolemic hyponatremia (serum sodium level <125 mEq/L) or for less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction.

Hypovolemic hyponatremia

In a hypovolemic patient who is symptomatic, the major emphasis should be on restoring the blood volume. Intravenous boluses of 0.9% saline are first used to restore the circulation. After the initial fluid resuscitation, the ECF sodium and volume deficits should be corrected over 24 hours using either 0.9% saline or 0.45% saline (26).

Hypervolemic hyponatremia

The standard approach toward management of hypervolemic hyponatremia very much depends on the underlying disease process. In patients with congestive heart failure, the primary treatment is aimed to improve the cardiac function with angiotensin-converting enzyme inhibitors and beta blockers. Patients should be treated with water restriction and loop diuretic to promote sodium and water excretion by the kidneys (27). In both congestive heart failure and cirrhosis, the addition of a potassium-sparing diuretic is useful to prevent hypokalemia and lessen edema. Tolvaptan, a selective vasopressin V_2-receptor antagonist, has now become a safe and effective therapeutic agent to correct hyponatremia associated with congestive heart failure, liver cirrhosis and SIADH (25).

Conclusion

Hyponatremia is a common disorder and can lead to neurologic complications. The presence or absence of significant neurologic signs and symptoms must guide therapy. Neurologic disease can follow both the failure to treat promptly as well as the overly rapid treatment of hyponatremia. An overly rapid increase in serum Na^+ (>12 mEq/L per 24 hours) may result in serious brain injury. Hypertonic saline provides rapid correction of serum sodium in acute, severe and symptomatic hyponatremic patients. Fluid restriction is frequently employed for chronic hyponatremia. AVP receptor antagonists provide prompt and effective water diuresis in patients with euvolemic and hypervolemic hyponatremia. Furosemide can be used to treat volume overload.

Case 1

A previously healthy 19-year-old woman was admitted to a university teaching hospital for kidney transplant donation. Past medical history was unremarkable. The physical examination was normal. Her blood pressure was 120/76 mm Hg, weight 58 kg and the preoperative tests for renal function, urinalysis and chest X-ray were all normal. The patient's intraoperative course was uneventful. The estimated blood loss during the 2-hour surgery was 150 mL.

Immediately after the surgery, she complained of pain and severe nausea. She was treated with intravenous morphine for pain and Phenergan for nausea. She received a total of 5.8 L of 0.2% saline in 5% dextrose in water during the first day of surgery. On postoperative day 2, she was noted to be confused and combative and had a brief apnea spell. Her serum sodium was 114 mmol/L. The patient was transferred to the pediatric intensive care unit.

Physical examination revealed blood pressure of 142/87 mm Hg, heart rate 60 bpm, nuchal rigidity, unisocoria but no other focal neurologic findings. Two hours later, serum electrolytes were sodium 110, potassium 3.8, chloride 84, bicarbonate 25, blood urea nitrogen (BUN) 2.9, glucose 5.1 mmol/L, creatinine 53 µmol/L, uric acid 148 µmol/L, serum osmolality 250 mmol/kg and urine osmolality 625 mmol/kg. Arterial blood gas analysis showed pH 7.34, pO_2 7.58 kPa, and pCO_2 6.3 kPa. Hemoglobin was 82 g/L. Chest X-ray showed evidence of pulmonary edema. The pulmonary wedge pressure was 8 mm Hg. A computed tomography (CT) scan of the brain was ordered.

En route to the CT the patient had a seizure and respiratory arrest. She was resuscitated, her pupils were dilated. Six hours later, the urine output increased to 300 ml/hour, urine osmolarity fell to 60 mmol/L, serum sodium rose to 162 mmol/L and she developed central diabetes insipidus. She died 12 hours later, and the autopsy showed massive cerebral edema, uncal herniation, intact basilar artery and patent pulmonary arteries.

Why did this patient develop pulmonary edema and hypoxia?

A. Congestive heart failure
B. Adrenal insufficiency
C. Hyponatremic encephalopathy
D. Reset hyponatremia
E. Cerebral salt-wasting syndrome

The correct answer is C. The lethal combination of being in surgery (excess vasopressin release) and use of hypotonic solution postoperatively resulted in severe hyponatremia, cerebral edema and neurogenic pulmonary edema. Pulmonary edema may be the first manifestation of hyponatremic encephalopathy (1, 7, 27-29).

Case 2

A 10-month-old white male was admitted to the hospital for the repair of cleft lip. His weight was 7.5 kg, temperature 99°F, pulse 140/min and respiratory rate 45/min. Physical examination was otherwise unremarkable. Laboratory data on admission included a hematocrit of 0.41%, sodium 121, potassium 4.2, chloride 91, bicarbonate 24, glucose 4.9 and BUN 4.3 mmol/L. Serum creatinine was 35.5 µmol/L. Urinalysis revealed the following: pH 5.5, specific gravity 1.019, trace protein and no cells. Urinary sodium, chloride and potassium were 43, 34 and 18 mmol/L, respectively. Liver function studies were normal. Serum cortisol, thyroxin and aldosterone levels were also normal.

Hyponatremia was unresponsive to high sodium intake (10 mmol/kg per 24 hours) or administration of fludrocortisone orally at 0.05 mg/day. Serum electrolyte values, while receiving salt supplements and fludrocortisones, were as follows: sodium 127, potassium 4.3, chloride 98 and bicarbonate 25 mmol/L. Urine sodium concentrations ranged between 128 and 178 mmol/L. Urine osmolality was 689 mmol/kg during the initial presentation and fell to an average of 56 mmol/kg after the ECF volume contraction was corrected. CT and nuclear magnetic resonance of the brain showed no abnormality in the hypothalamic area.

What is the most likely cause for this patient's hyponatremia?

A. Reset osmostat
B. SIADH
C. Hypoaldosteronism
D. Primary polydipsia
E. Hypothyroidism

The correct answer is A. In a patient with normovolemic hyponatremia, the diagnosis of reset osmostat should be considered after exclusion of the diagnosis of SIADH and other endocrine disorders (13). In this type of hyponatremia, renal diluting capacity is normal, but the normal regulation of serum tonicity takes place at a lower serum osmolality threshold (13). The diagnosis of reset osmostat can be confirmed by challenging these patients with a water load and measuring the ability to maximally dilute the urine osmolality (13). The mechanism responsible for resetting of the osmostat is not understood. Differentiation between the patients with hyponatremia resulting from reset osmostat and those with alterations in total body sodium and water content is important, because management differs according to diagnosis. The hyponatremia in patients with reset osmostat is asymptomatic and requires no specific therapy.

Case 3

An 18-year-old man developed polyuria following resection of recurrent craniopharyngioma. His brain tumor was first detected when he was 10 years old. Surgical resection at that time was followed by the development of panhypopituitarism and diabetes insipidus requiring chronic hormonal replacement therapy. At 18 years of age, a recurrent tumor growth led to another surgical resection 6 days ago. Five days after the surgery, he developed polyuria followed by headache and increasing lethargy and experienced a generalized tonic-clonic seizure. His medications included Synthroid (levothyroxine sodium), Carafate, hydrocortisone and desmopressin acetate. Examination revealed an obese, adolescent male who was found to have tachycardia (pulse 102/min), ECF volume depletion and hypotension (blood pressure 94/56 mm Hg). His chest was clear, and cardiac exam was normal. He appeared to have adequate peripheral perfusion. Urinalysis showed specific gravity 1.012, pH 6, negative dipstick and unremarkable microscopy. Serum electrolytes were sodium 123, potassium 3.4, chloride 92, bicarbonate 25, glucose 6.5 and BUN 6 mmol/L. Serum creatinine was 53.2 μmol/L, uric acid 190.3 μmol/L and osmolarity 259 mmol/L. Urine sodium was 224, potassium 22, chloride 261 mmol/L, creatinine 3,978 μmol/L and osmolality 509 mmol/kg. Fractional sodium excretion was 2.5%. His urine output over the last 3 days averaged 290 ml/hour, exceeding his fluid intake.

Which ONE of the following is the MOST likely cause of hyponatremia in this patient?

A. SIADH
B. Diabetes insipidus
C. Hypoaldosteronism
D. Cerebral salt-wasting syndrome
E. Interstitial nephritis

The correct answer is D. This patient abruptly developed polyuria, hypovolemia and symptomatic hyponatremia 5 days after intracranial surgery. The differential diagnosis of his polyuria can be narrowed by examining the urine osmolality. Urine osmolality <100 mmol/kg indicates deficiency or resistance to vasopressin, while hyperosmolar urine indicates a solute diuresis. This patient's urine osmolarity exceeded 500 mmol/L, demonstrating that desmopressin was effective enough to produce a high rate of free water absorption (high urine flow rate on postoperative days) that undoubtedly contributed to his hyponatremia. Diabetes insipidus doe not appear to be a major factor in this patient's decompensations. This case may be also due to desalination hyponatremia related to ECF overexpansion with normal saline in the setting of ADH action (high urine osmolality, Na^+ and K^+) or SIADH. The etiology of a solute diuresis can be determined by measuring urine electrolyte concentrations (2). The sum of this patient's urine sodium and chloride levels approximated his urine osmolality. Therefore, he was experiencing a saline diuresis that, in the presence of hypovolemia and hyponatremia, reflected inappropriate renal salt-wasting. The development of excessive natriuresis and hyponatremia shortly following brain surgery is consistent with the syndrome of cerebral salt-wasting (19). This disorder can be differentiated from the syndrome of inappropriate ADH secretion by the presence of markedly negative water and sodium balance, higher rates of urine flow and sodium excretion, as well as a normal serum uric acid level (19). Treatment consists of vigorous saline replacement and, possibly, pharmacologic doses of mineralocorticoids.

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