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A SYSTEMATIC APPROACH TO THE HYPONATREMIC PATIENT

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SUMMARY – Hyponatremia is the most common electrolyte disorder. Sometimes it is not easy to consider the differential diagnosis and to establish a final diagnosis. Hyponatremia is acute severe (less than 115 mmol/L) when lasting for 36 to 48 hours. This condition is a medical emergency because these patients have pronounced symptoms as the result of brain edema. It should be rapidly corrected to approximately 130 mmol/L to prevent permanent brain damage. In chronic severe hyponatremia, the symptoms are mild and there is no brain edema. Many authors recommend correction to approximately 130 mmol/L at a rate of less than 0.5 mmol/h, to minimize the risk of cerebral myelinolysis. In the near future, vasopressin antagonists will become available. Preliminary experience has already demonstrated their efficacy in inducing sustained water diuresis and correction of hyponatremia.

Key words: *Hyponatremia, diagnosis; Hyponatremia, therapy; Hyponatremia, complications*

Introduction

Hyponatremia is the most common electrolyte disorder in clinical medicine. However, physicians do not always find it easy to consider the differential diagnosis and to establish a final diagnosis. In almost all cases, hyponatremia results from the intake and subsequent retention of water[1]. The water load will, in normal subjects, be rapidly excreted as the dilutional fall in plasma osmolality suppresses the release of antidiuretic hormone (ADH), thereby allowing the excretion of diluted urine.

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Causes of Hyponatremia

There are many causes of hyponatremia, however, in almost all cases it occurs because there is an impairment in the renal excretion of water, usually due to inability to suppress ADH release (Table 1).

Disorders in which ADH levels are elevated

The two most common causes of hyponatremia are effective circulating volume depletion and the syndrome of inappropriate ADH secretion, disorders in which ADH secretion is not suppressed.

Effective circulating volume depletion

Significantly decreased tissue perfusion is a potent stimulus to ADH release. This response is mediated by baroreceptors in the carotid sinus, which sense a reduction in pressure or stretch, and can overcome the inhibitory effect of hyponatremia on ADH secretion. Thus, hyponatremia may develop in patients with any of the following disorders: 1) true volume depletion due to vomiting, diarrhea; 2) bleeding or urinary losses; 3) conges-

Table 1. Major causes of hyponatremia

Disorders in which ADH levels are elevated
– Effective circulating volume depletion
True volume depletion
Congestive heart failure and cirrhosis
Thiazide diuretics
– Syndrome of inappropriate ADH secretion, including reset osmostat pattern
– Hormonal changes
Adrenal insufficiency
Hypothyroidism
Pregnancy
Disorders in which ADH levels may be appropriately suppressed
– Advanced renal failure
– Primary polydipsia
– Beer drinkers
Pseudohyponatremia
– High plasma osmolality – hyperglycemia, mannitol, urea in renal failure
– Normal plasma osmolality – hyperlipidemia, hyperproteinemia, glycine solution

tive heart failure and cirrhosis; and 4) resulting complication of therapy with thiazide diuretics[1,2].

Syndrome of inappropriate ADH secretion

Persistent ADH release and water retention can also be seen in a variety of disorders that are not associated with hypovolemia. The pattern of ADH release in these conditions is variable.

Hormonal changes

Hyponatremia can occur in patients with adrenal insufficiency (who suffer a lack of cortisol that is responsible for hyponatremia) and hypothyroidism.

Disorders in which ADH levels may be appropriately suppressed

There are two disorders in which hyponatremia can occur despite suppression of ADH release. These conditions are advanced renal failure and primary polydipsia.

Advanced renal failure

The relative ability to excrete free water (free water excretion divided by the glomerular filtration rate) is maintained in patients with mild to moderate renal failure[3]. Thus, normonatremia is usually maintained in the absence of oliguria or advanced renal failure. In the latter setting, the minimum urine osmolality rises to 200-250 mosmol/kg despite appropriate suppression of ADH. The osmotic diuresis induced by the increased solute excretion *per* functioning nephron is thought to be responsible for the inability to dilute urine[3].

Primary polydipsia

Primary polydipsia is a disorder in which there is a primary stimulation of thirst. It is most often seen in anxious, middle-aged women, and in patients with psychiatric illnesses, particularly those taking antipsychotic drugs in whom the common side effect of dry mouth leads to an increased water intake[4,5].

Low dietary solute intake

Beer drinkers or other malnourished patients (including those with low-protein, high-water diets) may have a marked reduction in the water excretory capacity that is directly mediated by poor dietary intake. Beer contains little or no sodium, potassium, or protein, and the carbohydrate load will suppress endogenous protein breakdown and therefore urea excretion. As a result, daily solute excretion may fall below 250 mosmol/kg, leading to a reduction in the maximum urine output to below 4 L/day, even though the urine being appropriately diluted. Hyponatremia will ensue if more than this amount of fluid is taken.

Pseudohyponatremia

Pseudohyponatremia refers to those disorders in which hyponatremia is associated with a plasma osmolality that is normal or elevated but not reduced.

High plasma osmolality

This condition is most often due to hyperglycemia or the administration and subsequent retention of hypertonic mannitol. In these settings, the rise in plasma osmolality induced by glucose or mannitol drives water out of cells, thereby lowering the plasma sodium concentration by dilution.

Renal failure is another disorder in which hyponatremia may be associated with high plasma osmolality (due to the retention of urea). However, urea is an ineffective osmole, since it can freely cross cell membranes. Thus, urea accumulation does not lead to water movement out of the cells, and these patients have true hyponatremia.

Normal plasma osmolality

Hyponatremia associated with normal plasma osmolality can occur when there is a reduction in the fraction of plasma that is water. In normal subjects, the plasma water is approximately 93% of the plasma volume, with fats and proteins accounting for the remaining 7%. Thus, a normal plasma sodium concentration of 142 mmol/L actually represents a concentration in the physiologically important plasma water of 154 mmol/L. However, the plasma water fraction may fall below 80% in patients with marked hyperlipidemia (as with latescent serum in uncontrolled diabetes mellitus) or hyperproteinemia (as in multiple myeloma). In these settings, the plasma water sodium concentration and plasma osmolality are unchanged, but the measured sodium concentration in the total plasma volume will be reduced (since the specimen contains less plasma water).

Symptoms of Hyponatremia

Acute severe hyponatremia and cerebral edema

Serum sodium concentration of less than 115 mmol/L is by some arbitrarily defined as severe hyponatremia, whereas the term 'acute' commonly indicates a duration of hyponatremia of less than 36-48 hours. Untreated acute severe hyponatremia is associated with high morbidity and mortality rates, both of which are primarily ascribed to brain edema.

The symptoms directly attributable to hyponatremia primarily occur with acute and marked reduction in the plasma sodium concentration, and reflect neurologic dysfunction induced by cerebral edema[1,6,7]. In this setting, the associated fall in plasma osmolality creates an osmolal gradient that favors water movement into the cells, leading in particular to brain edema.

Hyponatremia-induced cerebral edema occurs primarily with rapid (in 1-3 days) reduction in the plasma sodium concentration[7], as most often occurs in postoperative patients given large amounts of hypotonic fluid and in those treated with thiazide diuretics[5,6].

The presence of cerebral overhydration generally correlates closely with the severity of symptoms[6]. Nausea and malaise are the earliest symptoms, and may be seen when the plasma sodium concentration falls below 125-130 mmol/L. These may be followed by headache, lethargy and obtundation, and eventually seizures, coma and respiratory arrest if the plasma sodium concentration falls below 115-120 mmol/L[6,8].

Animal experiments have facilitated analysis of the probable causes of cerebral edema in severe acute hyponatremia. That work has demonstrated that brain cells have the ability to adapt to hypo-osmolality-induced cell swelling, as most other cells do[9]. However, this process requires 48-72 hours to reach completion[9]. An initial phase of rapid extrusion of ions (Na^+, K^+, and Cl^-) from the cells is followed by a slow phase during which the intracellular concentrations of osmotically active organic osmolytes are reduced[10,11]. This regulatory process serves to return the initially swollen cells to normal cell volume (Fig. 1). During the transitional phase, before the cell volume adaptation is complete, brain edema is present (Fig. 2). Because of the rigid skull surrounding the brain, cerebral edema can lead to decreased brain perfusion and herniation of the brainstem into the foramen magnum. These changes are preventable by rapid correction of acute severe hyponatremia.

Chronic severe hyponatremia and risk of myelinolysis

Chronic severe hyponatremia often involves mild to moderate hyponatremic symptoms. It is commonly observed in the advanced stages of the syndrome of inappropriate secretion of antidiuretic hormone, cardiac failure, and liver cirrhosis. It does not appear to cause major problems by itself. In chronic hyponatremia, brain volume regulation is intact, and thus there is no evidence of brain edema.

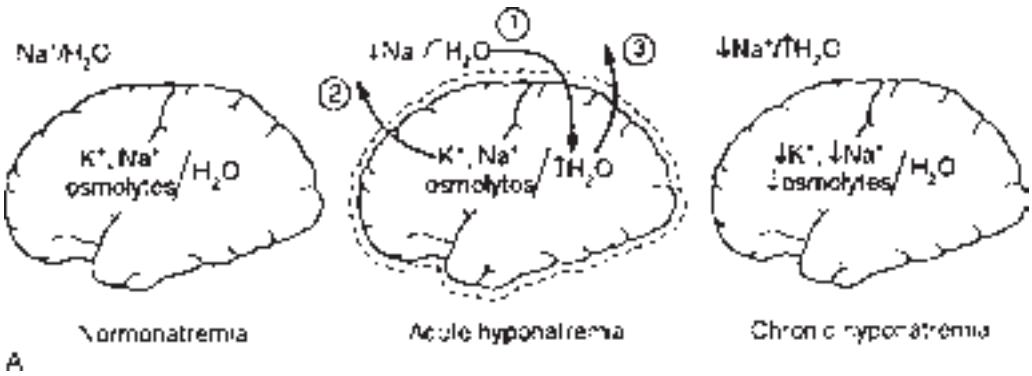

Fig. 1. Cerebral adaptation to hyponatremia

Decrease in extracellular osmolality causes movement of water (H_2O) into the cells, increasing intracellular volume and thus causing tissue edema. To prevent this, the mechanisms geared towards volume regulation come into operation. Soon after the induction of extracellular fluid hypo-osmolality, H_2O moves into the brain in response to osmotic gradient. The result is cerebral edema. Within 1-3 hours, a decrease in cerebral extracellular volume occurs by fluid movement into the cerebrospinal fluid, which is then shunted back into the systemic circulation. This happens very promptly, as early as 30 minutes after the onset of hyponatremia. As H_2O losses accompany the losses of brain solute, the expanded brain volume decreases back towards normal.

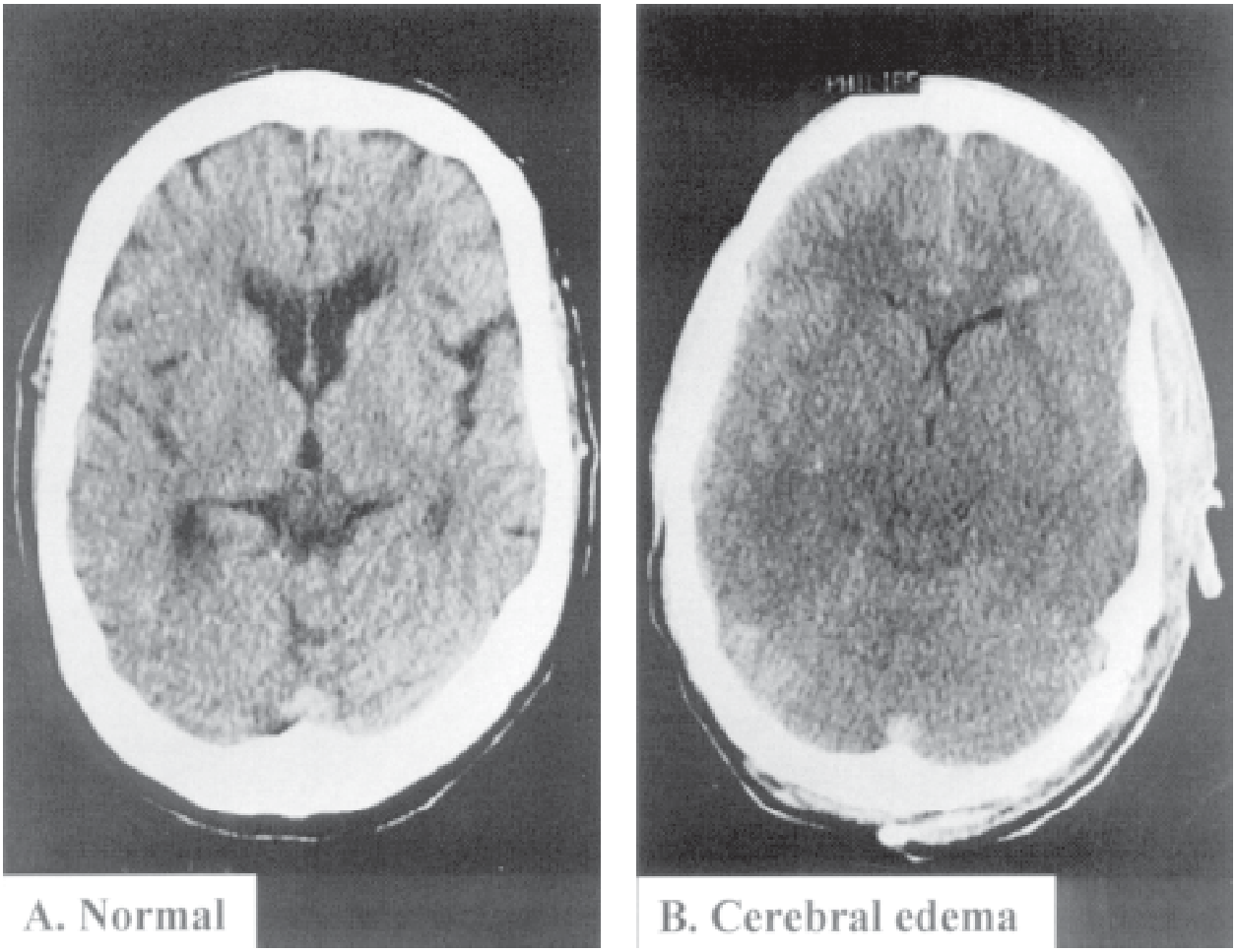

Fig. 2. Computer tomography scans of the brain

(A) A normal appearing brain on CT scan; (B) diffuse cerebral edema in a patient with acute severe hyponatremia.

Problems may arise when chronic hyponatremia is corrected, especially when it is corrected faster than 0.5 mmol/h, and when the correction process eventually reaches the normonatremic or even hypernatremic range. An overly rapid increase in the plasma sodium concentration may lead to the osmotic demyelination syndrome (also called central pontine myelinolysis, although demylination is often more diffuse and does not necessarily involve the pons)[6,7,12,13] (Fig. 3). These changes may lead to potentially severe neurologic symptoms that are delayed by 2-6 days after correction and may be irreversible[13].

It should be pointed out that correction of chronic hyponatremia is often an elective procedure, because there are no pernicious symptoms or adverse events related to this form of hyponatremia. Although data are incomplete, there is more evidence favoring slow correction of chronic severe hyponatremia than those favoring rapid correction.

Pontine and central pontine myelinolysis involves changes that produce the clinical signs of bulbar and pseudobulbar palsy. Imaging studies such as computed tomography (CT) and magnetic resonance imaging (MRI) are helpful in actually demonstrating that myelinolysis has occurred[14]. However, CT and MRI results become positive only 6 to 10 days after the clinical signs of myelinolysis have become manifest. There is no known treatment for this demyelination syndrome.

In fact, as the term 'osmotic demyelination' suggests, in animal studies it was possible to directly relate myelinolysis to local osmotic imbalances that occur in the brain during rapid correction of chronic hyponatremia[15]. These imbalances have been attributed to slow reaccumulation of cell protective organic osmolytes, as opposed to rapid and overshooting reaccumulation of ionic osmolytes. In experimental animals, it has been demonstrated that disruption of the blood – brain barrier may occur in situations such as this, leading to myelinolysis. Because of regional differences in the brain, the pons is a preferred site for the blood – brain barrier disruption and associated myelinolysis.

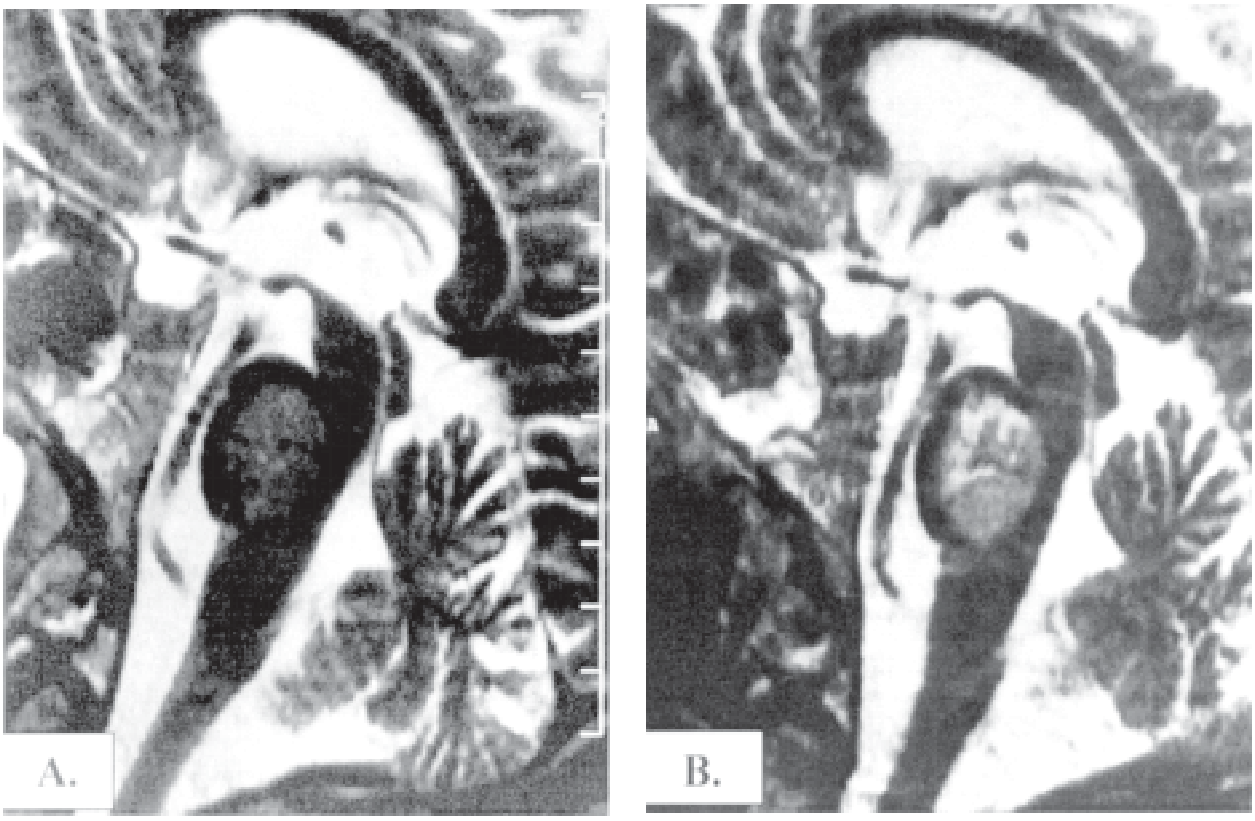

Fig. 3. Magnetic resonance imaging

(A) A normal appearing pons on MRI; (B) image of central pontine myelinolysis. MRI is the most useful diagnostic technique for central pontine myelinolysis.

Diagnosis of Hyponatremia

The diagnostic process in hyponatremia involves thorough history and physical examination along with three basic laboratory values: serum osmolality, urine osmolality, and urine sodium[1] (Fig. 4). This information is used to determine the cause of hyponatremia and to help guide therapy. It is necessary to ask patients about the use of medications (particularly thiazide diuretics), recent vomiting, diarrhea, or excessive sweating with hypotonic fluid ingestion, recent surgery, a history of physiatric illness, congestive heart failure (CHF), cirrhosis, or nephrotic syndrome with renal failure. Physical examination should focus on assessment of volume status and include orthostatic vital signs, skin turgor, mucous membrane appearance, jugular vein distention, findings of edema, and wedge pressure and central venous pressure if available.

The initial laboratory measurement needed in the evaluation of hyponatremia is serum osmolality. A common cause of hyperosmolar hyponatremia (serum osmolality below 290 mmol/L) is hyperglycemia. The infusion of hypertonic mannitol is a less common cause. Isoosmolar hyponatremia (normal serum osmolality of 275 to 290 mmol/L) may rarely be caused by pseudohyponatremia from either severe hyperlipidemia or hyperproteinemia. The findings result from the method used to measure serum sodium concentration and do not represent true hyponatremia.

Hypo-osmolar hyponatremia (serum osmolality less than 275 mmol/L) is the most common type.

The next laboratory measurement is urine osmolality. This value indicates whether water excretion is impaired. Patients with hyponatremia and urine osmolality less than 100 mmol/L are appropriately excreting very diluted urine, as in primary polydipsia and resetting of the osmostat (i.e. a form of the syndrome of inappropriate ADH in which serum osmolality is reset downward to a new threshold). In patients with resetting of the osmotat, a serum sodium concentration between 125 and 130 mmol/L is usually maintained, with appropriate excretion of diluted urine during water loading. However, most patients with hyponatremia have urine osmolality of more than 200 mmol/L, reflecting impairment in water excretion.

The final step in the evaluation of hyponatremia is to measure the urine sodium concentration and to use this

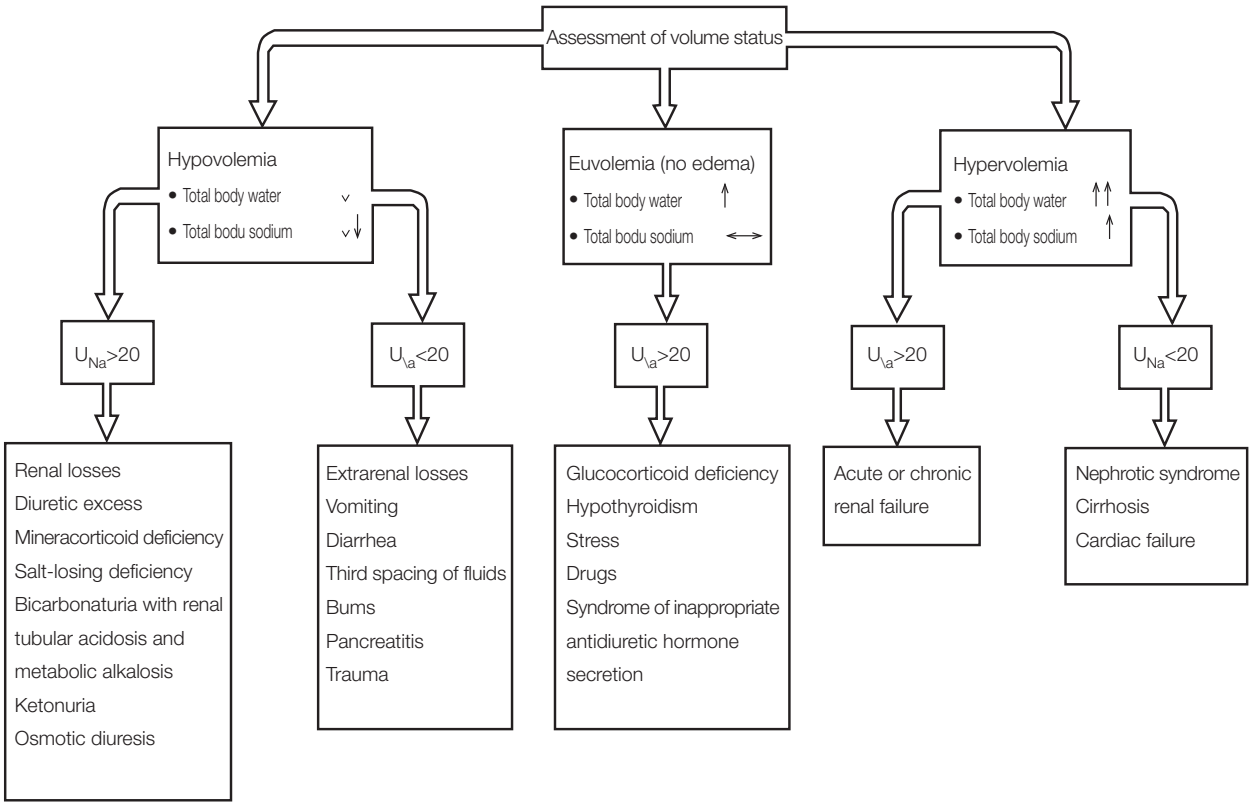

Fig. 4. Diagnostic algorithm for hyponatremia

finding in conjunction with volume status to determine the cause of hyponatremia. A spot test showing a urine sodium concentration of less than 30 mmol/L differentiates patients with hypovolemic hyponatremia from patients with euvolemic hyponatremia.

A high urine sodium concentration may be found in patients with volume depletion secondary to a renal cause of salt wasting (e.g., adrenal insufficiency, use of thiazide diuretics), metabolic alkalosis, or osmotic diuresis (e.g., from hyperglycemia). The so-called sodium-avid states of CHF, cirrhosis, and nephrotic syndrome all typically have a low urine sodium concentration unless patients are taking a diuretic, whereas renal failure tends to cause a high urine sodium concentration.

Treatment of Hyponatremia

The preferred rate at which the plasma sodium concentration should be elevated varies with the clinical presentation (Fig. 5). Acute symptomatic hyponatremia primarily results from cerebral edema due to water movement into the brain. Rapid initial correction of hyponatremia is warranted in symptomatic patients, but overly rapid correction can be deleterious in any patient, particularly those with chronic hyponatremia (Tables 2 and 3).

Asymptomatic hyponatremia

Untreated patients with chronic asymptomatic hyponatremia are generally at a low risk of neurologic symptoms owing to the cerebral adaptation. In this setting, rapid correction is not indicated and may be harmful. The focus of therapy should be on identifying and correcting

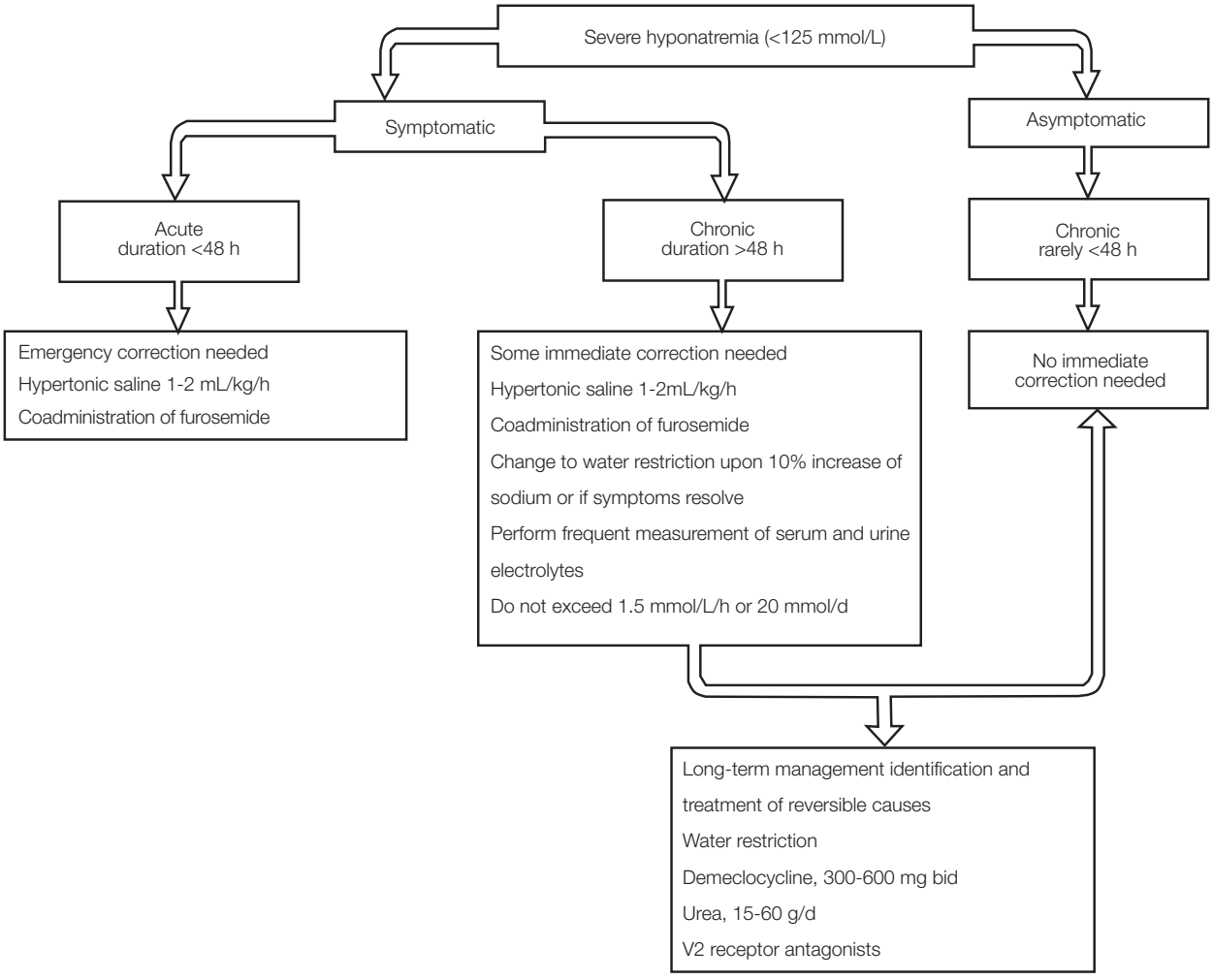

Fig. 5. Treatment algorithm for severe hyponatremia (<125 mmol/L)

Table 2. General guidelines for the treatment of symptomatic hyponatremia

Acute hyponatremia (duration less than 48 hours)
Increase serum sodium rapidly by approximately 2 mmol/L/h until symptoms resolve
Full correction probably safe but not necessary
Chronic hyponatremia (duration of more than 48 hours)
Initial increase in serum sodium by 10% or 10 mmol/L
Perform frequent neurologic evaluations; correction rate may be reduced with improvement of symptoms
At no time should correction exceed the rate of 1.5 mmol/L/h, or increments of 15 mmol/d
Measure serum and urine electrolytes every 1-2 h

*The sum of urinary cations (U_{Na} + U_K) should be less than the concentration of infused sodium to ensure excretion of electrolyte-free water.

Table 3. Treatment of chronic symptomatic hyponatremia

– Calculate the net water loss needed to raise serum sodium (S_{Na}) from 110 mmol/L to 120 mmol/L in a 50-kg person.
Example
Current S_{Na} x Total body water (TBW) = Desired S_{Na} x New TBW
Assume that TBW = 60% of body weight
Therefore TBW of patient = 50 x 0.6 = 30 L
New TBW = 110 mmol/Lx30 L/120 mmol/L = 27.5 L
Thus, the electrolyte-free water loss needed to raise S_{Na} to 120 mmol/L = Present TBW – New TBW = 2.5 L
– Calculate the time course in which to achieve the desired correction (1 mmol/h) – in this case, 250 mmol/h
– Administer furosemide, monitor urine output, and replace sodium, potassium, and excess free water lost in urine
– Continue monitoring urine output and replace sodium, potassium, and excess free water lost in urine

the underlying cause of hyponatremia. It the patient is judged to be hypovolemic on the basis of clinical assessment and urine sodium concentration, normal saline solution should be administered initially to correct the extracellular fluid volume deficit. Hypovolemic patients should restrict salt and water.

Most patients with CHF or nephrotic syndrome maintain a serum sodium concentration of more than 125 mmol/L, even with a marked increase in ADH levels. Patients with CHF can be treated with inotropes, afterload reduction, and loop diuretics in addition to salt and water restriction. Loop diuretics are the mainstay of therapy in patients with nephrotic syndrome, and if these agents are unsuccessful, dialysis may be warranted.

For patients who are euvolemic and hyponatremic, therapy consists primarily of water restriction.

Symptomatic hyponatremia

More aggressive initial correction, at a rate of 1.5 to 2 mmol/L *per* hour, is indicated for the first three to four hours (or until the symptoms resolve) in the patients who present with seizures or other severe neurologic abnormalities due to untreated and usually acute hyponatremia[7,15,16]. The primary problem in these patients is cerebral edema, and the risk of delayed therapy is greater than the potential risk of too rapid correction.

Hyponatremia can be corrected with the administration of hypertonic saline solution (3%) at a rate of about 1 ml/kg *per* hour. A loop diuretic may be added to enhance water excretion if urine osmolality is greater than 300 mOsm/kg. With the use of this combination therapy, the sodium lost in the urine is replaced with an equal amount of sodium in a smaller volume. The serum sodium con-

centration should be raised by no more than 25 mmol/L in the first 48 hours, at a rate of no more than 2 mmol/L *per* hour, and the target goal should be 120 to 125 mmol/L. Treatment with hypertonic saline solution is advocated only for patients with severe hyponatremia who have profound neurologic symptoms.

Vasopressin antagonists

It is expected that V_2 and $V_{1/2}$ receptor antagonists will make the treatment of hyponatremia more predictable, more 'titratable', and less burdensome to patients, in comparison with the current therapeutic approach. Current treatment usually consists primarily of fluid restriction, and may be unacceptable to patients. Until now, five different oral, competitive, V_2 and $V_{1/2}$ vasopressin receptor antagonists have been developed to the stage of clinical testing[17].

The treatment of hyponatremia will become more promising when new oral vasopressin antagonists are available. Whether such agents will also have an effect on thirst, remains to be determined. Work must also be performed to investigate the predictability of the correction rate for given cases of hyponatremia when vasopressin antagonists are used. No guidelines for prediction are currently available. Another question is whether vasopressin antagonists would lower the portal pressure in cirrhosis of the liver and whether they would increase the glomerular filtration rate in patients with renal insufficiency. The final point concerns the role of hyponatremia in the prognosis of advanced congestive cardiac failure. On the basis of the potential reductions in cardiac pre- and afterloads by $V_{1/2}$ receptor antagonists, it is now conceivable that hyponatremia may contribute to the severity of congestive heart failure. In that case, vasopressin antagonists would accomplish substantially more than simply the improvement of some cerebral symptoms. It will be necessary to keep an open mind regarding the progress to be expected in the clinical applications of oral vasopressin antagonists[17-19].

Prognosis

The prognosis depends on the underlying condition.

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Sažetak

SUSTAVNI PRISTUP BOLESNIKU S HIPONATRIJEMIJOM

I. Ratković-Gusić, P. Kes i V. Bašić-Kes

Hiponatrijemija spada u najčešće poremećaje elektrolita. Diferencijalna i konačna dijagnoza su ponekad vrlo složene. Teška akutna hiponatrijemija je stanje s koncentracijom natrija nižom od 115 mmol/L, koje traje između 36 i 48 sati. Ovo stanje spada u hitna medicinska stanja, jer su bolesnici u opasnosti od prijetećeg edema mozga. Brzim ispravljanjem hiponatrijemije do koncentracije od 130 mmol/L može se spriječiti trajno oštećenje mozga. Kronična teška hiponatrijemija praćena je blažim simptomima i kod nje nema opasnosti od edema mozga. Mnogi autori preporučuju ispravljanje po stopi od 0,5 mmol/sat do konačne koncentracije od 130 mmol/L. Na taj se način spriječava nastanak moždane mijelinolize, do koje može doći zbog prebrzog ispravljanja kronične hiponatrijemije. U tijeku su brojni klinički pokusi o primjeni antagonista vazopresina u liječenju hiponatrijemije. Početni rezultati su ohrabrujući i ukazuju na njihovu učinkovitost u poticanju izlučivanja tekućine iz tijela, kao i na ispravljanje hiponatrijemije.

Ključne riječi: *Hiponatrijemija, dijagnostika; Hiponatrijemija, liječenje; Hiponatrijemija, komplikacije*