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REVIEW

Hyponatremia: Clinical Diagnosis and Management

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ABSTRACT

Hyponatremia is a common clinical problem in hospitalized patients and nursing home residents. It also may occur in healthy athletes after endurance exercise. The majority of patients with hyponatremia are asymptomatic and do not require immediate correction of hyponatremia. Symptomatic hyponatremia is a medical emergency requiring rapid correction to prevent the worsening of brain edema. How fast we should increase the serum sodium levels depends on the onset of hyponatremia and still remains controversial. If the serum sodium levels are corrected too rapidly, patients may develop central pontine myelinolysis, but if they are corrected too slowly, patients may die of brain herniation. We review the epidemiology and mechanisms of hyponatremia, the sensitivity of women to hyponatremic injury, the adaptation and maladaptation of brain cells to hyponatremia and its correction, and the practical ways of managing hyponatremia. Because the majority of hyponatremia is caused by the non-osmotic release of vasopressin, the recent approval of the vasopressin receptor antagonist conivaptan for euvolemic hyponatremia may simplify hyponatremia management. However, physicians should be aware of the risk of rapid correction of hyponatremia, hypotension, and excessive fluid intake.

KEYWORDS: Acute hyponatremia; Brain edema; Central pontine myelinolysis; Chronic hyponatremia; Exercise-associated hyponatremia; Organic osmolytes; Vasopressin; Vasopressin receptor antagonist

Hyponatremia is a common and serious problem in clinical medicine. Anderson et al[1] noted that the prevalence of hyponatremia (serum sodium concentration [SNa] $<$ 130 meq/L) in hospitalized patients was approximately 2.5%. Two thirds of the patients with hyponatremia developed it while in the hospital. The daily incidence rate was approximately 1%. Hyponatremia is, in general, less common in the outpatient setting, but the prevalence can be substantial in high-risk populations. Such high-risk patients include those with various diseases (vida infra) and the elderly population.[2-6] Miller et al[7] measured the prevalence of hyponatremia to be 18% in a nursing home population. Approximately one half of all residents of this nursing home had hyponatremia at least 1 time during a 1-year period.

The prognosis associated with hyponatremia is fairly severe.[1,3,8-13] Anderson et al[1] noted that the fatality rate in hyponatremic patients was 60 times that of patients in whom hyponatremia did not develop. The reason for this dire prognosis may be found in the cause (see below). Most series observe that the non-osmotic release of vasopressin is the predominant cause of hyponatremia, and because severe stress is one of the (many) causes of non-osmotic release of vasopressin, it may be that hyponatremia simply selects those patients who are under substantial stress.[1,3,8-13]

Significant hyponatremia also can be found in healthy individuals who participate in high-endurance exercises, such as marathon and iron man triathlons. Hyponatremia (SNa $<$ 135) was found in 13% of randomly selected runners of the 2002 Boston Marathon. A small fraction (0.6%) of these runners had critical hyponatremia (SNa $<$ 120).[14] There have been a few exercise-associated hyponatremia (EAH)-related fatalities resulting from brain edema reported in the last 8 years.[15] EAH can be avoided by limiting fluid intake to less than 800 mL per hour, as recommended by the International Marathon Medical Directors Association. This guideline should be adjusted according to individual and environmental factors.[16]

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PHYSIOLOGY OF WATER METABOLISM

The mechanisms involved in producing concentrated or dilute urine have been enumerated in great detail elsewhere,[17] and we will review these mechanisms only briefly so as to provide a context for the clinical categorization of patients with hyponatremia. Humans with normal kidney function can produce urine with a solute concentration range from less than 100 mosm/L to more than 1000 mosm/L. This allows for a more than 10× range in urine volume and, by extension, fluid intake while preserving osmolar equilibrium. The physiologic mechanisms involved in producing dilute or concentrated urine can be enumerated simplistically through the Kokko-Rector model of the kidney.[18] Briefly, solute and water are filtered at the level of the glomerulus and a variable portion of both are reabsorbed in the proximal tubule and thin loop of Henle. Up until this nephron segment, solute handling is performed by the tubular cells, and water transport can be considered as passive. However, the thick portion of the ascending limb of the loop of Henle (TAL) is rather impermeant to water, and pumping of solute in this nephron segment allows for both trapping of solute in the renal medulla, a function aided by the countercurrent architecture of medullary blood perfusion and dilution of fluid within the tubular lumen. Most of the features described to this point, namely, distal delivery of solute and function of TAL, are necessary for the production of both dilute and concentrated urine. The final steps in urine concentration occur in the collecting duct. If concentrated urine is to be excreted, vasopressin must be present in the circulation and the collecting duct epithelium must respond to this vasopressin. The normal collecting duct epithelium responds to vasopressin by a classic G-protein–regulated signal cascade that involves cyclic adenosine monophosphate as the "second messenger" and results in the insertion of water channels (aqueporin 2), which allows water to easily transverse the collecting duct epithelium. As the interstitial fluid is concentrated, especially in the medulla, the remaining fluid in the tubular lumen becomes concentrated and the resultant urine achieves a high osmolarity. However, in the absence of vasopressin, or if the collecting duct fails to respond to vasopressin, the tubular fluid and ultimately the urine remains dilute.[19] These concepts are demonstrated graphically in Figure 1.

Vasopressin is a decapeptide synthesized largely in the superoptic nucleus of the hypothalamus and secreted from the posterior pituitary. The synthesis and release of vasopressin are regulated by both osmotic and non-osmotic mechanisms.[20,21] The non-osmotic mechanisms are multiple and include opiates, angiotensin, and endothelin, as well as a number of cytokines and neurotransmitters.[22-25]

CLINICAL SIGNIFICANCE

- Hyponatremia is commonly caused by non-osmotic release of vasopressin.
- Premenopausal females are sensitive to hyponatremic brain injury.
- Treatment of hyponatremia should focus on removal of free water.
- Vasopressin receptor antagonists are promising for treating SIADH.

MECHANISMS OF HYPONATREMIA

The clinical approach to hyponatremia (Figure 2) generally begins by excluding conditions in which the osmolarity is not reduced. In fact, because sodium is the predominant osmole in the extracellular fluid (ECF) compartment and serum, physicians consider hyponatremia to be essentially synonymous with a reduction in osmolarity. This rather casual association has led to the characterizations of all situations in which hyponatremia does not reflect hypo-osmolarity as "pseudohyponatremia." This is unfortunate because there are 2 conditions in which pseudohyponatremia is really a laboratory artifact, namely, severe hyperlipidemia and hyperproteinemia. In these conditions, the lipid or protein component of the serum volume becomes considerable, whereas the sodium is essentially eliminated from this compartment. Sodium measurement devices that measure sodium amount in a given volume then measure the sodium concentration as low because they estimate the serum water content too high. Again, this really is pseudohyponatremia. In contrast, conditions in which an osmotically active substance such as glucose or mannitol accumulates in the serum and draws water out of the intracellular space also is referred to as a kind of "pseudohyponatremia." However, in this case, the SNa concentration and chemical activity are truly depressed.

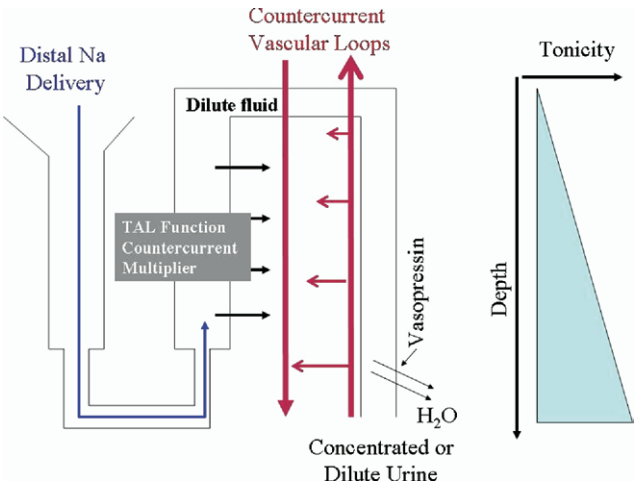

Figure 1 Roles of distal sodium delivery, solute transport in the thick ascending limb of Henle, and vasopressin action or inaction in the production of concentrated or dilute urine. TAL = thick ascending limb of Henle.

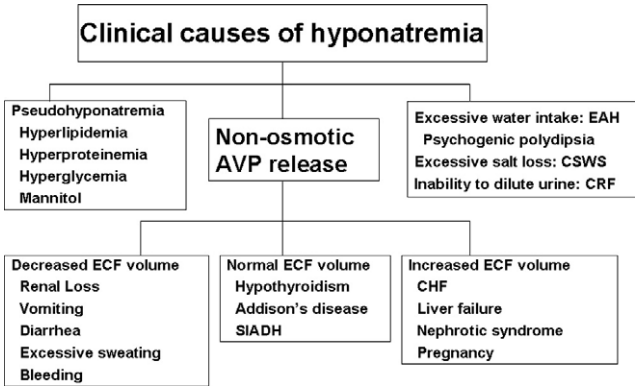

Figure 2 Clinical approach to hyponatremia based on clinical assessment of ECF volume. AVP = arginine vasopressin; CSWS = cerebral salt wasting syndrome; EAH = exercise-associated hyponatremia; CRF = chronic renal failure; SIADH = syndrome of inappropriate antidiuretic hormone; ECF = extracellular fluid; CHF = congestive heart failure.

Once the above conditions are excluded, clinicians generally determine whether non-osmotic release of vasopressin is involved and, because it usually is involved, why non-osmotic release of vasopressin occurs. Clinically, these situations are generally grouped on the basis of ECF volume status (Figure 2). Hyponatremia in patients with increased ECF volume is generally attributable to congestive heart failure, liver failure, nephritic syndrome, or pregnancy. Patients who have hyponatremia with decreased ECF volume generally have excessive sweating, gastrointestinal losses, renal losses, or bleeding as causes. Patients with normal ECF volume develop hyponatremia from cortisol deficiency, thyroid hormone deficiency, or the syndrome of inappropriate antidiuretic hormone release, which, in turn, can be caused by a variety of conditions (Figure 3). Occasionally, more than 1 mechanism may be implicated. For instance, patients with paraplegia or quadriplegia are prone to develop hyponatremia, particularly when they have pneumonia or urinary tract infection. These patients tend to have decreased ECF volume and "appropriate" antidiuretic hormone secretion. With infection and stress, additional vasopressin may be released "inappropriately" and results in severe hyponatremia.[26]

There are a few settings in which the non-osmotic release of vasopressin is not involved or does not play a major role:

- Cerebral salt wasting syndrome is a condition associated with severe sodium deficit caused by excessive release of brain natriuretic peptide. It has been reported in a variety of central nervous system pathologies, particularly subarachnoid hemorrhage, tuberculous meningitis, and brain surgeries.[27]
- Chronic renal failure may cause hyponatremia because of the inability to dilute or concentrate urine because of decreases (sometimes to zero) in the delivery of solute and water to the TAL. In this setting, a patient's osmolarity becomes almost totally dependent in the short term on what fluid and solute are ingested.
- Psychogenic polydipsia/potomania refers to a condition in which kidney function is normal and dilute urine is produced, but free water intake overwhelms the kidney's capabilities and the SNa becomes diluted. These generally (but not always) occur in patients with severe psychiatric problems or in the setting of ethanol consumption. In the latter case, decreases in obligate osmolar excretion play an important pathogenetic role.[28] Only moderately excessive water intake in the absence of ethanol consumption has been reported to cause SNa dilution in the setting of very low dietary solute consumption and small stature.[29]
- Exercise-associated hyponatremia is mainly caused by excessive consumption of fluid. The substantial weight gain during running is the single most important factor associated with hyponatremia.[14] However, not all hyponatremic athletes had weight gain; non-osmotic release of vasopressin may play a role in the development of EAH. For instance, pain and stress during the race may induce the release of vasopressin. Siegel et al reported that 43% of patients with EAH had measurable AVP levels consistent with SIADH. The authors speculated that the release of muscle derived interleukin-6 during rhabdomyolysis may stimulate secretion of AVP.[30] Noakes et al[15] proposed that failure to mobilize osmotically inactive Na from internal stores, such as bone, also may contribute to EAH. However, so far there is no evidence to support this hypothesis.

SENSITIVITY OF WOMEN TO HYPONATREMIC INJURY

Patients with hyponatremia may present with decreased levels of consciousness and even seizures. The severity of these symptoms and signs seems to be related to both the

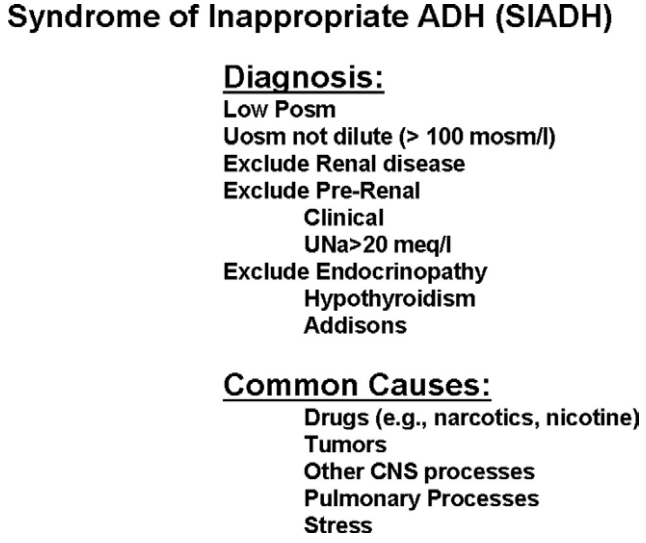

Figure 3 Clinical diagnosis and common causes of the syndrome of inappropriate antidiuretic hormone. ADH = antidiuretic hormone; UNa = urinary sodium; CNS = central nervous system.

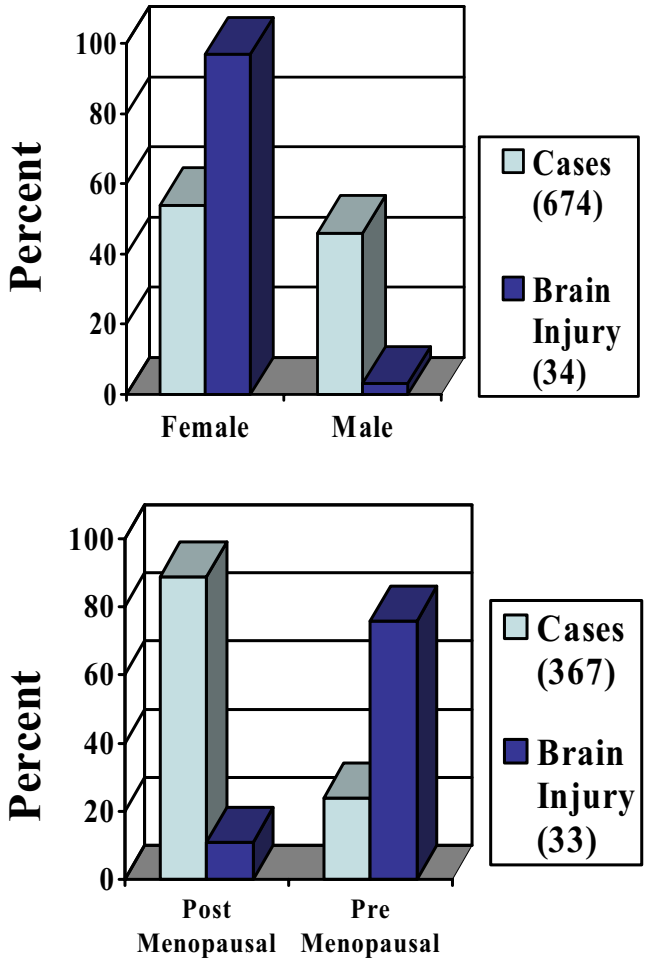

Figure 4 Data from Ayus and colleagues[32] demonstrating that although the incidence of significant hyponatremia is similar in males and females, the incidence of significant brain injury is largely confined to females (*top*). Further analysis of the females demonstrated that most brain injury cases occurred in premenopausal women (*bottom*).

acuity and the severity of the hyponatremia.[31] The gender and age of the afflicted individual also seems to be important.

In a landmark article in 1986, Arieff[32] described 15 previously healthy women who developed acute hyponatremia (average SNa decreased to 108 mmol/L) after elective surgery. The outcomes in these patients were poor (27% mortality, 60% persistent vegetative state). In a follow-up study, it was demonstrated that although men and women seemed equally likely to develop hyponatremia and hyponatremic encephalopathy after surgery, women were 25 times more likely to die or have permanent brain injury. On further analysis, most of the risk in females was confined to women of menstruant age[33] (Figure 4). Increased sensitivity to hyponatremic injury in women also is observed in the setting of EAH. In a series of 7 cases of EAH with cerebral edema and noncardiogenic pulmonary edema, 5 were females.[34] In another study, Davis and coworkers reported 15 marathon runners who developed symptomatic hyponatremia (SNa $<$ 122); only 1 was male.[35]

In view of these observations, considerable interest has developed regarding the mechanisms underlying the gender difference in susceptibility to hyponatremic injury.[36] At the present time, it seems that female sex hormones both alter neuronal volume regulation in response to hypo-osmolarity and sensitize the cerebral vasculature to the constrictive actions of vasopressin.[37,38]

BRAIN OSMOLES AND HYPONATREMIA

The brain is the organ that is most susceptible to the sudden decrease of SNa in the body because it is confined within the rigid skull. In the setting of EAH, symptoms such as nausea, vomiting, and confusion begin when SNa decreases to less than 129 mEq/L.[15] If hyponatremia develops slowly over several days, brain cells are capable of adapting by releasing intracellular K and other solutes to maintain the cell volume. We have shown that in chronically hyponatremic rats, the decrease in brain osmolality is accounted for by the decrease in electrolytes (K 36%, Na 18%, and Cl 18%) and organic osmolytes (23%), including amino acids, myoinositol, creatine/creatine phosphate, and others. The contribution of organic osmolytes is higher, approximately 35%, if only intracellular solutes are considered.[39]

Another serious brain complication related to hyponatremia is central pontine myelinolysis (CPM). CPM was first described by Adams et al[40] in 1959 in alcoholic patients with malnutrition. It is characterized by a loss of oligodendrocytes and myelin with relatively well-reserved neurons in the central basis of pontis, as well as extrapontine sites such as basal ganglia and cerebellum.[41] The association between rapid correction of hyponatremia and CPM was initially reported by Kleinschmidt-DeMasters and Norenberg,[42] and Norenberg et al.[43] The risk for development of CPM is associated with severity and chronicity of the hyponatremia and the correction rate of hyponatremia. It rarely occurs if SNa is greater than 120 and the hyponatremia is acute in onset.

The pathogenesis of CPM is still not fully understood. During correction of chronic hyponatremia, a rapid increase in SNa will lead to brain cell shrinkage. To maintain proper cell volume, brain cells take up Na, K, and Cl first, and then organic osmolytes. These organic osmolytes are protective against damages to proteins or DNA from increased ion strength inside cells.[44] The reaccumulation of certain organic osmolytes, such as myoinositol and amino acids, is a slow process because it takes time to synthesize new transporters and reinsert them into cell membrane. In addition, the ability to reaccumulate organic osmolytes in different brain regions varies. In rats, the midbrain is the area with the least ability to reaccumulate organic osmolytes. It also is the area where demyelination is most severe after rapid correction of hyponatremia.[45]

THERAPY OF HYPONATREMIA

The treatment of hyponatremia is determined by 3 major factors: severity of hyponatremia, that is, the presence or

absence of severe central nervous system symptoms such as lethargy, delirium, seizure, and coma; onset of hyponatremia: acute (within 48 hours) or chronic (>48 hours); and volume status. Symptomatic hyponatremia, particularly if associated with hypoxia, is a medical emergency. An immediate increase in SNa level by 8 to 10 meq/L in 4 to 6 hours with hypertonic saline is recommended.[46] The biggest challenge of treating symptomatic hyponatremia is how to prescribe saline therapy and maintain the correction rate in the target range. Because free water excess (FWE) is the most common cause of hyponatremia, it is generally agreed that the first step is to calculate the FWE. Note that we do not refer to a "sodium deficit" because it is possible, in fact it is likely, that there is not a sodium deficit. Rather, it is an excess of water that must be addressed by the clinician.

If we assume that total body water (TBW) = 0.6 × body weight (kilograms, use 0.5 for females), that the patient is euvolemic (ie, has no true sodium deficit), and that the SNa is the only determinant of osmolarity we will consider, the FWE can be calculated as: FWE = TBW × (140 − SNa)/140.

Once the FWE is calculated, we next decide what our desired correction rate should be. For acute hyponatremia, more rapid correction may be possible, but for chronic hyponatremia, slower rates of correction (eg, 12 meq/L in 24 hours)[47] have been advocated. By matching the FWE to the decrease in SNa, one can estimate how much free water removal will correspond with this 12 meq/L in 24 hours. For example, a 50-kg patient with an SNa of 100 meq/L would have an estimated FWE of 8.6 liters; it follows that one would want to remove approximately 2.6 liters in the first 24 hours to avoid a correction rate exceeding 12 meq of Na/L/24 hours. If we administer an adequate dose of furosemide, the urine sodium + urine potassium should be approximately 70 to 80 meq/L, and the urine will be essentially one half free water. Ergo, if we replace the urine electrolyte losses (milliequivalent of Na and K with milliequivalent of Na) with 0.9% saline (ie, ½ mL/mL of urine), the net free water clearance is one half of the urine output. If we replace the urine electrolyte losses with 3% saline (0.15 mL/mL of urine), the net free water clearance = 0.85× urine output. Measurements of urine electrolytes can (and should) be performed to monitor furosemide effect and to aid in more accurate measurements. Depending on the urine flow rate, 3% saline, 0.9% saline, combinations of the above, or even more dilute infusion solutions can be administered to achieve the desired rate of free water clearance. If hypokalemia is present (and/or develops), some potassium should be added to the infusion solution and tracked as an added osmolyte.

Another approach is to estimate SNa change on the basis of the amount of Na in the infusate using the formula described by Adrogue and Madias:[48] $\Delta SNa = \{[Na + K]_{inf} - SNa\} \div (TBW + 1)$; where ΔSNa is a change in SNa, $[Na + K]_{inf}$ is infusate Na and K concentration in 1 liter of solution. Although this formula is relatively simple and widely used, we believe that the focus on Na rather than water may create some confusion and could result in unintended changes in total body sodium and water (eg, pulmonary edema) if urine output is not carefully monitored.

We believe that it cannot be overstated that frequent measurements of the SNa *must* be performed in concert with whichever calculations are used; as we reemphasize, clinical estimates of TBW are rather crude. Nguyen and Kurtz[49] reviewed potential errors with simplified formulae. If the rate of correction is too fast or too slow, alterations in the infusion rate and/or furosemide dose may be necessary.

NEW THERAPIES FOR HYPONATREMIA

Recently, conivaptan, a V1A/V2-receptor antagonist, was approved for treating hospitalized patients with euvolemic hyponatremia. Because most hyponatremia is caused by the non-osmotic release of vasopressin, the availability of vasopressin antagonists is exciting and may change the management of hyponatremia completely. Ghali et al[50] reported the efficacy and safety of 5-day oral conivaptan therapy (40 or 80 mg/day) for euvolemic or hypervolemic hyponatremia. In 1 day, SNa was increased by 4 and 7 mEq/L, and free water clearance was 0.4 and 1.3 liters for the groups receiving 40 or 80 mg/day, respectively. Rapid correction of hyponatremia was reported in 10% of subjects receiving conivaptan; however, none of them had serious neurologic complications associated with rapid correction. However, conivaptan-related hypotension, polydipsia, and hypovolemia were reported in this study.

From a pathogenesis point of view, V2-receptor antagonists are ideal drugs for hyponatremia involved in the non-osmotic release of vasopressin, except those with volume depletion. With this therapy, the risk of rapid correction is still present; therefore, frequent checks of SNa are needed. In addition, V2-receptor antagonists are not suitable for certain causes of hyponatremia, such as cerebral salt wasting syndrome, psychogenic polydipsia/potomania, and others. It is critical to identify the mechanisms of hyponatremia before selecting the treatment of hyponatremia.

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