

Cerebral Salt Wasting: Pathophysiology, Diagnosis, and Treatment

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KEYWORDS

• Natriuresis • Natriuretic factors • Hyponatremia • SIADH

Hyponatremia can be a vexing problem for those who care for critically ill neurologic patients. Although seemingly simple at first glance, the accurate diagnosis and effective treatment of hyponatremia can be complex. The chief difficulty in this setting often lies in determining what is driving the fall in serum sodium concentration. **Cerebral salt wasting (CSW) is a disorder of sodium and water handling that occurs as a result of cerebral disease in the setting of normal kidney function. It is characterized by hyponatremia in association with hypovolemia and, as the name implies, is caused by natriuresis.** In routine clinical practice, distinguishing this condition from the more familiar syndrome of inappropriate secretion of antidiuretic hormone (SIADH) can be quite difficult. Nonetheless, this task is crucial because treatments for the two conditions are fundamentally different. Accordingly, it is important for physicians caring for critically ill neurologic patients to have a thorough understanding of this disorder. This article reviews the pathophysiology of CSW. Building on these basic concepts, a rational approach to its diagnosis and treatment is outlined.

HISTORICAL ASPECTS

Early studies of hyponatremia in patients with cerebral disease published in the 1950s described the presence of polyuria, elevated urinary sodium levels, and dehydration despite the presence of a low serum sodium concentration and adequate

fluid intake. This syndrome was termed “cerebral salt wasting.” At the time, CSW was suspected to be the major cause of hyponatremia in patients with central nervous system (CNS) injury. Shortly after its original description, however, a syndrome of euvolemic hyponatremia associated with normal urine output and inappropriately high levels of antidiuretic hormone (ADH) was described in a patient with bronchogenic carcinoma.¹ This was later termed as the “syndrome of inappropriate antidiuretic hormone release.” Following this discovery and over the subsequent 30 years, hyponatremia that developed in patients with neurologic diseases, such as subarachnoid hemorrhage (SAH), was generally attributed to SIADH.^{2–6} Beginning in the 1980s, several key studies^{7–9} challenged this concept by demonstrating in patients with aneurysmal SAH a syndrome of low blood volume, natriuresis with a net negative sodium balance, and high urinary output, which was consistent with CSW and not SIADH. These publications led to the modern acceptance of CSW as an important cause of hyponatremia in patients with brain injury and to important research that followed investigating the pathophysiologic disturbances of salt and water homeostasis in patients with neurologic disease.

CLINICAL RELEVANCE

Hyponatremia is frequently encountered in patients with neurologic disease. A recent analysis

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of 316 patients with aneurysmal SAH detected hyponatremia in 57% of patients.¹⁰ Although previous investigators have reported lower frequencies,^{11–13} it is still the most commonly encountered electrolyte disturbance in the neurologic intensive care unit. Adding to its importance are the occasional serious consequences of severe hyponatremia, which include seizures and worsening of cerebral edema. Although hyponatremia is most reliably encountered in patients with aneurysmal SAH,^{7,11,14–30} it occurs not infrequently in a variety of other conditions affecting the CNS, such as head trauma,^{31–43} malignancy,^{44–51} and CNS infections,^{14,52–60} and it has been reported in the postoperative neurosurgical setting.^{61–64}

The proportion of patients with hyponatremia related to neurologic disease who have CSW, as opposed to SIADH or some other etiology of hyponatremia, is substantial, although the exact frequency is not clear. This issue has been studied most rigorously in patients with aneurysmal SAH.^{7,11,14–30} In one study, up to 67% (six of nine) of patients with hyponatremia after rupture of an intracranial aneurysm had CSW as the etiology of low sodium levels⁷ and 75% (six of eight) of SAH cases in other reports.⁸ A study by Sherlock and colleagues,¹⁰ however, found that only 6.5% (4 of 62) of patients who presented with spontaneous SAH and subsequent hyponatremia had CSW as the cause of abnormally low sodium levels in their unselected cohort.

The discrepancy between reported prevalence rates may be a result of differences in study population size. Much has to do with how CSW and volume depletion are defined, however, when comparing the available data. There is no universally accepted gold standard in defining extracellular volume status or the specific parameters that classify cerebral-induced salt wasting, leading to significant variability between studies in the definition of low intravascular volume. For example, some authors have measured central venous pressure (CVP),¹⁰ whereas others have used isotope-labeled albumin.⁶⁵ This difference in method of volume assessment and inclusion criteria could result in varying frequencies of affected subjects among studies, and it is unclear whether direct comparisons can be made between such trials when identifying CSW as an underlying etiology in hypovolemic hyponatremic patients. An additional confounding variable underlying the variability of CSW frequency in the literature is the manner in which sodium depletion is defined. Single versus multiple day cumulative sodium balance measurements often yield significantly different results.⁶⁶

CSW has been associated with a host of other CNS diseases in addition to aneurysmal SAH. Although the precise frequency of CSW in traumatic brain injury is unknown, an association has been described in a number of case reports, small case series, and studies with greater sample size that incorporate several categories of neurologically injured patients of which small numbers of traumatic brain injury patients are included.^{8,31–33,67,68}

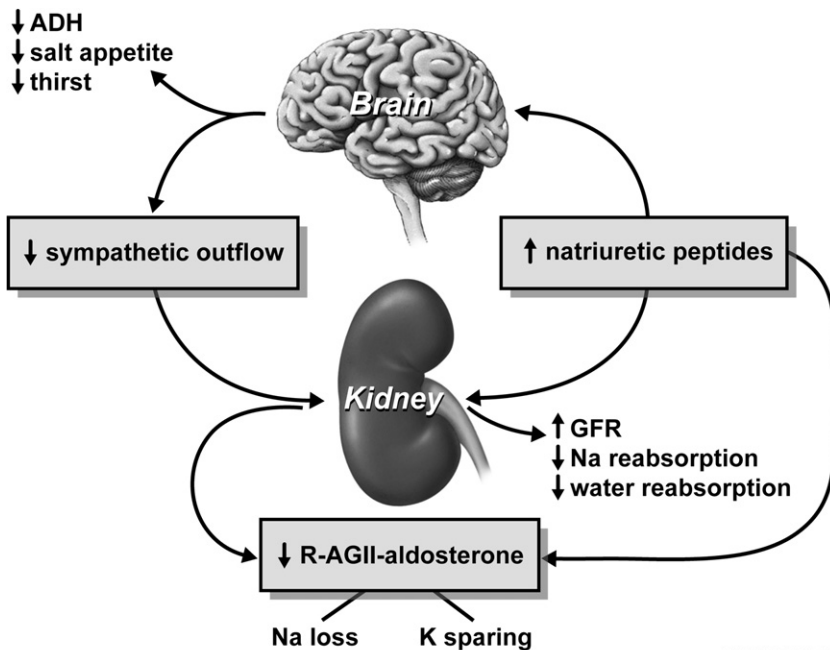
The best estimate can be found in a study by Vespa,³⁵ in which 5% to 10% of traumatic brain injury patients were found to have salt wasting. The hyponatremia that frequently occurs in patients with infectious meningitis is most often attributed to SIADH. In several studies of this condition, however, a number of patients with moderate to severe volume contraction in association with decreased serum sodium levels, a combination that is most consistent with CSW, were identified. Further proof of an association between CSW and meningitis is provided by the observation of a trend toward more adverse outcomes in children with meningitis-associated hyponatremia who were treated with fluid restriction.^{52,59,69,70} Other conditions in which natriuresis with volume contraction and hyponatremia occur include transphenoidal pituitary surgery and cerebral malignancies, such as primitive neuroectodermal tumors with intraventricular dissemination, carcinomatous meningitis, glioma, and primary CNS lymphoma.^{44–51,61,62}

PATHOPHYSIOLOGY OF CSW

Despite the clear association between the presence of CSW and severe neurologic disease, the mechanism underlying this association has not yet been clearly identified. Maintenance of body sodium and water homeostasis is a vital physiologic process. It is largely governed by intricate interactions between the autonomic nervous system and humoral factors that influence the kidney's handling of sodium and water. Disruption of the normal interactions between these systems can generate sodium and water dysregulation at the level of the nephron, thereby leading to more global alterations in sodium and water homeostasis. It has been postulated that interference of sympathetic input to the kidney and the presence of abnormally elevated circulating natriuretic factors noted after cerebral injury can lead to CSW (Fig. 1).

Physiology of the Renin-Angiotensin-Aldosterone System

The renin-angiotensin-aldosterone system (RAAS) is a hormonal pathway involving several enzymatic



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Fig. 1. Proposed mechanisms responsible for the production of CSW syndrome. ADH, antidiuretic hormone; GFR, glomerular filtration rate; K, potassium; Na, sodium; R-AG II, renin-angiotensin II. (From Rabinstein A, Wijdicks E. Hyponatremia in critically ill neurologic patients. *Neurologist* 2003;9:6; with permission.)

steps and humoral factors that serve a central role in maintaining whole-body sodium and water homeostasis. Renin is a circulating enzyme produced and stored within the kidney and released in response to low systemic and renal arterial perfusion. Once released, it initiates a series of intricate sequential enzymatic steps involving the well known angiotensin-converting enzyme, the ultimate product of which is the formation of angiotensin II (AT II). This potent vasoconstrictor agent has immediate effects on blood pressure by influencing the constrictive properties of peripheral vasculature, increasing sympathetic tone, and stimulating the release of ADH.⁷¹ Moreover, AT II augments renal blood flow to maintain an appropriate rate of glomerular filtration and the percentage of sodium to be filtered. AT II activity is not only critical in the immediate phases of hemodynamic control but is also instrumental in maintaining serum sodium homeostasis by stimulating the release of aldosterone, a key mineralocorticoid released from the adrenal gland that regulates extracellular fluid volume and serum potassium concentration (eg, nephrogenic excretion). Aldosterone ultimately causes sodium retention and a subsequent increase in serum sodium concentration by binding to specific intracellular receptors at the distal tubule and collecting ducts, leading to a cascade of protein synthesis of sodium channels, sodium-potassium pumps, and

their regulatory proteins all of which are critical in transepithelial sodium transport.⁷²

In large part, effective extracellular fluid volume and sodium concentration are maintained by the degree of RAAS activity and aldosterone bioavailability. These are increased during periods of low circulating fluid volume and decreased when total circulating volume is sufficient or elevated. A cerebrally mediated mechanism for influencing the RAAS system, and renal salt and water handling, may exist.^{73–75} Several publications have documented the scientific progress and understanding of a local intrinsic tissue-specific RAAS model within the CNS and its influence on renal physiology.^{71,76,77} As detailed in a key review by DiBona,⁷⁸ intrinsic cerebral AT II production likely exists and its presence within the CNS conceivably can influence renal sympathetic nerve activity and baroreflex control. More specifically, neuronal synthesis of this hormone within the paraventricular nucleus is released in the rostral ventrolateral medulla, a critical structure in the autonomic neural control of circulation. Tonic excitation of the rostral ventrolateral medulla influenced by endogenous AT II has been postulated to result in increased peripheral sympathetic tone.

Sympathetic Nervous System Hypothesis

The sympathetic nervous system plays an important role in the regulation of sodium and water

handling in the kidney.^{78–80} In the face of intravascular volume contraction, the autonomic nervous system responds by increasing sympathetic nervous system tone. This in turn induces secretion of renin from the kidneys, subsequently leading to elevations in the bioavailability of AT II and aldosterone, stimulating sodium and water retention. By way of a positive feedback mechanism, AT II itself may have a role in regulating sympathetic nervous system activity.^{71,72} Data from animal studies suggest that this circulating hormone can directly affect the sympathetic nervous system by binding to specific receptors located within discrete subcortical brain structures, specifically the subfornical organ and area postrema.^{78,81,82} Direct projections from the subfornical organ to the paraventricular nucleus are thought to influence rostral ventrolateral medulla activity indirectly. Activation of these circumventricular regulatory centers leads to an increase in the activity of the sympathetic nervous system by their projections to preganglionic sympathetic neurons within the intermediolateral cell column of the spinal cord^{82,83}; the ultimate effect is an increase in mean arterial pressure and retention of sodium and water by the kidney.

Peters and coworkers¹⁴ originally hypothesized that disruption of CNS influence on renal salt and water balance mechanisms could potentially disturb the kidney's ability to maintain proper sodium homeostasis. Specific renal innervation by the sympathetic nervous system, however, was not discovered until nearly 20 years later.⁷⁹ Peters' theory was then expanded on to explain more specifically the mechanism underlying CSW.^{15,21,22,84} According to this theory, loss of adrenergic tone to the nephron has two important consequences. First, it leads to a decrease in renin secretion by the juxtaglomerular cells, thereby causing decreased levels of aldosterone and decreased sodium reabsorption at the proximal convoluted tubule. Second, it causes dilatation of the afferent arteriole, leading to increased glomerular filtration of plasma and sodium. The failure of renin and aldosterone levels to rise in the setting of CSW-associated volume contraction has been considered to be evidence in favor of this hypothesis. This hypothesis has one crucial flaw: acute CNS injury typically leads to a surge and not a decrease in sympathetic tone during the immediate phases of injury. This is demonstrated by such phenomena as neurogenic pulmonary edema and myocardial dysfunction, which occur because of dramatic sympathetic outflow during periods of severe CNS stress.⁸⁵ It has yet to be demonstrated that the changes in the interactions between the autonomic nervous system and the

kidneys that are needed to produce a salt-wasting state actually occur in the setting of acute cerebral injury.

Natriuretic Peptide Theory

Natriuretic peptides were initially discovered in the early 1980s after it was demonstrated that atrial myocardial extracts induced a potent natriuretic response when infused into rats.⁸⁶ At about the same time, early studies investigating the pathogenesis of sodium and extracellular volume disturbances in patients with SAH led to the hypothesis that a natriuretic factor may be involved.^{8,9,17} Subsequently, a number of specific natriuretic substances were identified and their biologic effects have been intensely studied.

Natriuretic peptides are molecules that normally defend against periods of excess water and salt retention by antagonizing the RAAS system, promoting vascular relaxation, and inhibiting excess sympathetic outflow and the generation of vasoconstrictor peptides.⁸⁷ Four main natriuretic peptides with purported associations with CSW have been identified: (1) atrial natriuretic peptide (ANP); (2) brain-natriuretic peptide (BNP); (3) C-type natriuretic peptide (CNP); and (4) the more recently discovered dendroaspis natriuretic peptide (DNP).^{88,89} Although the former three natriuretic peptides have shown some expressivity within the CNS, each peptide has a unique predominant tissue-specific site of production: ANP and DNP from the myocardial atria; BNP from within the ventricles of the heart; and CNP from the telencephalon, hypothalamus, and endothelium.^{90–93}

The natriuretic peptides all have similar, potent effects on the regulation of cardiovascular homeostasis by influencing vascular tone and sodium and water homeostasis. They cause relaxation of vascular smooth muscle thereby leading to dilatation of arteries and veins, most likely by dampening vascular sympathetic tone.^{94–96} A similar effect on the nephron's afferent tubule leads to increased filtration of water and sodium through the glomerulus. These molecules also have direct renal tubule natriuretic and diuretic effects by inhibiting angiotensin-induced sodium reabsorption at the proximal convoluted tubule and antagonizing the action of vasopressin at the collecting ducts, respectively.^{97,98} Interestingly, local production of natriuretic peptides within the adrenal medulla^{99,100} has been demonstrated and might have paracrine inhibitory effects on mineralocorticoid synthesis.¹⁰⁰ This paracrine mechanism might explain why in patients with CSW aldosterone and renin levels fail to rise

despite the presence of hypovolemia. Clearance and inactivation of circulating natriuretic peptides occurs by two main mechanisms: endocytosis once bound to a C-type natriuretic receptor (which has equal affinity for the family of peptides),^{101,102} and degradation and cleavage by endopeptidases within the vasculature and renal tubular system.⁸⁷

These characteristics of natriuretic peptides make them ideal candidate mediators that may serve as a key link between CNS injury and the development of CSW. Several studies have demonstrated that a rise in serum BNP concentration is evident after SAH.^{19–21,103,104} McGirt and colleagues¹⁹ demonstrated the existence of a temporal relationship between elevated BNP levels and the presence of hyponatremia in patients with SAH. Interestingly, in this same study abnormally high levels of BNP correlated well with the presence of cerebral vasospasm, suggesting that BNP may have a direct causal link to the secondary complications often observed in SAH. Besides BNP, other members within this peptide family, ANP in particular, have also been suspected to contribute to the development of CSW.^{16,17,28} The caveat to this, however, is that BNP was not measured in these earlier studies, leaving open the possibility that it, rather than ANP, was responsible for the CSW.^{28,105} Additionally, more recent evidence has shed light on a new member of the natriuretic peptide family, DNP, as a potential additional causative agent of hyponatremia in patients with aneurysmal SAH.²⁴ Further investigation is needed to better define the roles played by the different natriuretic peptides in the pathogenesis of CSW.

Several hypotheses have been offered to explain how an intracranial insult could lead to elevations of serum concentrations of these peptides. One plausible hypothesis is that direct damage to cortical and subcortical structures where BNP exists¹⁰⁶ leads to inadvertent release of hormone directly into the circulation.¹⁴ Some investigators have proposed that generation and release of natriuretic peptides from the hypothalamus in disease states, such as SAH, may serve a protective role against elevated intracranial pressure. This cerebral induction of natriuresis could limit further impending rise in intracranial pressure and its subsequent potential unfavorable outcomes.^{21,107}

Myocardial tissue has also been proposed to be a source of elevated natriuretic peptide levels in CSW.^{104,105} Surges in sympathetic outflow typically occur as a result of acute CNS injury.⁸⁵ This increase in sympathetic tone may lead to catecholamine-induced myocardial ventricular strain, thereby causing release of BNP from the atrial

myocardium.^{85,103} Additionally, the presence of excess catecholamine as a result of acute intracranial disease may be excitotoxic to cardiac myocytes,⁸⁵ also potentially causing transient myocardial dysfunction. Related neurohumoral findings have also been demonstrated in other forms of acute cerebral injury, such as ischemic stroke, also implying that like mechanisms are at play.¹⁰⁸ Some authors have speculated that hypervolemic therapy itself, which is frequently administered after SAH, can lead to myocardial chamber stretch with resultant peptide release.²³ Regardless of which individual or combination of molecules is responsible, the mechanistic cause-and-effect link between cerebral damage and natriuretic peptide release with ensuing renal sodium loss has yet to be identified.

Miscellaneous Hypotheses

Kojima and colleagues²⁶ suggest that a mechanism or mechanisms other than one involving ANP, BNP, or ADH exists that may be responsible for CSW. In an experimental rat model, they measured serum concentrations of these hormones and urinary volume and sodium excretion at several time intervals after induction of SAH while controlling the degree of volume therapy to exclude this as a confounding variable. Findings consistent with CSW occurred in the SAH rats: a significant elevation in urinary volume and sodium excretion, decreased body weight, and an increase in hematocrit. Interestingly, levels of ANP decreased, whereas the BNP and ADH concentrations were unchanged. They concluded that a novel, undefined mechanism, or one that involves DNP, likely underlies the etiology of CSW.

Adrenomedullin (AM) is a more recently discovered endogenous peptide that has been proposed as a mediator of CSW.^{30,109,110} Originally discovered in pheochromocytoma tissue¹¹¹ and later revealed in human brain matter,^{112,113} AM is a potent vasodilator with natriuretic and diuretic properties. Elevation in plasma levels of this peptide has been shown to be high immediately after SAH and may reflect the severity of hemorrhage; however, its levels do not seem to correlate with the presence angiographic vasospasm.²⁵ Conversely, cerebrospinal fluid concentrations of AM do seem to parallel the development of hyponatremia and delayed ischemic neurologic injury for at least 8 days after the onset of hemorrhage.²⁷ The release of this hormone in the setting of aneurysmal SAH might serve a protective role against the development or worsening of cerebral vasospasm through its vasoactive properties. The site of CNS production of AM within the hypothalamus extends neuronal

projections to regions within the brainstem and spinal cord, which can ultimately effect sympathetic tone.¹¹³ Interestingly, a decrease in renal sympathetic activity with subsequent natriuresis and diuresis has been demonstrated in an animal model after AM was introduced into the cerebral ventricular system.¹¹⁴ Although new molecules and mechanisms have been described, BNP and ANP continue to be implicated as the main offenders toward the development of CSW, of which the former continues to be of primary suspect.²¹

DIAGNOSIS OF CSW

Differentiating CSW from most other common causes of hyponatremia (diuretic use, adrenal insufficiency, extrarenal-induced volume-deplete states, hypothyroidism, congestive heart failure)¹¹⁵ is typically not difficult. Obtaining a meticulous history and inventory of recent medications and laboratory studies often reveals the correct diagnosis. The challenge lies in the differentiation of CSW from SIADH, because both disorders cause similar serum and urine laboratory abnormalities and occur in the same neurologic and neurosurgical diseases.^{116,117} Accurately distinguishing between these two disorders is crucial, because misdiagnosis can lead to inappropriate therapy, often with serious consequences. Volume

restriction instituted for a presumptive diagnosis of SIADH in patients with aneurysmal SAH and CSW, for example, has been shown to increase the risk of delayed ischemic deficits and mortality.¹¹ Treatment based on an inaccurate diagnosis can also lead to progressive worsening of hyponatremia and its direct neurologic complications.¹¹⁵ Despite the availability and general ease in obtaining tests for the determination of electrolyte concentrations and osmolality in the serum and urine, only the careful determination of volume status in the hyponatremic patient accurately differentiates CSW from SIADH (Table 1).

SIADH is a syndrome of euvolemic hyponatremia. It is characterized by (1) euvolemia and an even fluid balance; (2) hyponatremia (serum sodium <135 mmol/L^{115,117}) and hypo-osmolality (serum osmolality <275 mOsm/kg H₂O in an adult); (3) a urine osmolality that is greater than that of maximally dilute urine (>100 mOsm/kg H₂O in an adult); and (4) the presence of an elevated urinary sodium concentration (>40 mmol/L) in an individual with normal salt and water intake.¹¹⁷ This constellation of findings is a result of excessive ADH-induced water reabsorption from the glomerular filtrate at the distal nephron, which produces inappropriately concentrated urine despite serum hypo-osmolality. CSW, however, is a syndrome of hypovolemic hyponatremia. Its major clinical features are (1) hypovolemia, often with a net

Table 1 Differential diagnosis of CSW and SIADH		
Variable	CSW	SIADH
Urine osmolality	↑ (>100 mOsm/kg)	↑ (>100 mOsm/kg)
Urine sodium concentration	↑ (>40 mmol/L)	↑ (>40 mmol/L)
Extracellular fluid volume	↓	↑
Body weight	↓	↔ or ↑
Fluid balance	Negative	Neutral to slightly +
Urine volume	↔ or ↑	↔ or ↓
Heart rate	↔ or ↑	↔
Hematocrit	↑	↔
Albumin	↑	↔
Serum bicarbonate	↑	↔ or ↓
Blood urea nitrogen	↑	↔ or ↓
Serum uric acid	↔ or ↓	↓
Sodium balance	Negative	Neutral or +
Central venous pressure	↓ (< 6 cm H ₂ O)	↔ or slightly + (6–10 cm H ₂ O)
Wedge pressure	↓	↔ or slightly ↑

Abbreviations: CSW, cerebral salt wasting; SIADH, syndrome of inappropriate antidiuretic hormone secretion.
Adapted from Rabinstein AA, Wijdicks EF. Hyponatremia in critically ill neurologic patients. *Neurologist* 2003;9: 290–300; with permission.

negative fluid balance; (2) hyponatremia and serum hypo-osmolality; (3) an elevated urine osmolality (>100 mOsm/kg); and (4) elevated urinary sodium (>40 mEq/L). In contrast to SIADH, the findings in CSW are caused by excessive renal sodium and water excretion. Because sodium excretion is disproportionately higher than that of water, the urine is inappropriately concentrated for the degree of serum hypo-osmolality. Salt wasting typically occurs early following acute cerebral injury and can persist beyond 5 days. Hyponatremia often follows and develops by the first week following the insult.^{8,9,11,17}

It is not possible to distinguish CSW from SIADH based on serum and urine laboratory findings alone, because their associated abnormalities are identical. For this reason, accurate determination of the patient's volume status is the key to differentiating these syndromes. Unfortunately, determination of volume status is notoriously difficult to perform accurately in routine clinical practice. Despite the use of complex, labor intensive, and elegant methods of determining intravascular volume status in experimental studies of CSW, no universally accepted standard exists for this purpose.¹¹⁸ Precisely because of this difficulty in conclusively and consistently differentiating hypovolemic hyponatremia from euvolemic and hypervolemic hyponatremia, Sterns and Silver¹¹⁸ have recently suggested that differentiating between CSW and SIADH is not currently possible. Rather, they suggest that because hyponatremia from any cause in a brain-injured patient is best treated with hypertonic saline, the two conditions should be considered a single entity called the "cerebral salt wanting syndrome." This idea is intriguing, but needs to be tested to determine its value in clinical practice.

Classical signs and symptoms of hypovolemia including hypotension, orthostatism, lassitude, increased thirst, and muscle cramps all lack specificity, particularly in critically ill patients; however, in the appropriate clinical context (eg, vomiting, diarrhea, diaphoresis, diuretic use, and polyuria), these symptoms can provide clues that the patient is hypovolemic. Weight loss, the absence of jugular venous distention, prolonged capillary refill time or diminished skin turgor, or the presence of dry mucous membranes can be suggestive of diminished extracellular fluid volume. Unfortunately, physical examination provides limited sensitivity in the assessment of hypovolemia.^{119,120} Similarly, measurement of serum concentrations of the conventional biochemical markers that normally reflect hypovolemia (renin and aldosterone) is unreliable because these substances are abnormally suppressed in

CSW.^{22,62,121} Other more common laboratory data used to support a volume-contracted state are the presence of an elevation in serum bicarbonate, blood urea nitrogen concentration, or hematocrit, but none of these is independently diagnostic and all lack specificity. Elevated serum uric acid levels can be seen in the hypovolemic state, but uric acid levels have surprisingly been found to be low in both CSW and SIADH.^{122,123}

Measurement of CVP can be useful for estimating intravascular volume status when clinical and laboratory data are nondiagnostic and accurate intravascular volume evaluation is critical. Damaraju and colleagues¹²⁴ assessed the intravascular volume status in 25 neurosurgical patients who fulfilled the diagnostic criteria for SIADH by monitoring CVP. Hypovolemia was defined as a CVP less than 5 cm H₂O. Patients with a CVP less than 5 cm H₂O received 50 mL/kg/d of volume replacement and an initial sodium intake of 12 g per day. The main outcome measured was an improvement in serum sodium concentration from two consecutive measurements 12 hours apart or within 72 hours of initiation of therapy. Nineteen of their 25 patients were found to be both hypovolemic and able to achieve normal serum sodium values (defined as >130 mEq/L) within this time frame after therapy. The authors concluded that neurosurgical hyponatremic patients with natriuresis were more likely to be affected by CSW rather than SIADH and that CVP-directed treatment of hyponatremia and volume status in such patients is effective. Although the CVP is a very useful estimate of intravascular volume status, key limitations to its use exist.¹²⁵ Placement of a CVP catheter is an invasive procedure associated with rare but important complications.¹²⁶ Also, CVP measurements can be inaccurate in the setting of abnormal cardiac function, which is not uncommon in acute cerebral injuries. For example, despite high pulmonary wedge pressures, the CVP can be falsely low-normal in patients with isolated left or right-sided heart failure. Conversely, patients with cor pulmonale can have a falsely elevated CVP.

An accurate and timely diagnosis of CSW relies on several clinical and laboratory features when considered in the appropriate context (eg, SAH). The disorder is characterized by hyponatremia with increased urinary sodium concentration and hypovolemia in the setting of acute intracranial disease. Because other features of CSW are identical to SIADH, the key in distinguishing the two disorders lies in determining the patient's volume status. An estimation of volume status can often be made on the basis of simultaneous consideration of the symptoms, signs, and laboratory

parameters discussed previously. Of these, meticulously recorded fluid balance values are probably most informative. In rare patients with hyponatremia in whom precise management of intravascular volume is essential, placement of a central venous catheter for measurement of CVP can be useful.

TREATMENT

The mainstay of therapy for CSW is replacement of the sodium and water that is lost as a result of pathologic natriuresis and diuresis. This is in direct contrast to the treatment of SIADH, the crux of which is free water restriction. Patients with CSW typically have significant extracellular volume depletion and a total-body sodium deficit of at least 2 mmol of sodium/kg body weight.⁶⁶ In patients who are hypovolemic, a reasonable initial management strategy is administration of normal saline with the intent of restoring intravascular volume. This is particularly important in patients with aneurysmal SAH, because the risk of vasospasm and its downstream complications is increased in the setting of hypovolemia.^{11,17–20,127} Cautiously aggressive administration of intravenous fluids has become the mainstay of initial therapy in patients with SAH and has been shown to prevent volume contraction but not the development of hyponatremia.¹²⁸

Once euolemia is achieved, attention should be directed to the correction of hyponatremia. One method for augmenting both serum sodium concentration and intravascular volume is the use of mineralocorticoids. One should be mindful that although correction of hyponatremia and hypovolemia can often be achieved,^{65,129–132} these medications have not been shown to be beneficial in preventing additional secondary complications of SAH, such as cerebral vasospasm.¹³¹ The authors typically use fludrocortisone, 0.1 to 0.2 mg orally twice a day, starting once the diagnosis of CSW is made and continuing until serum sodium concentrations and intravascular volume remain stably normal, typically 3 to 5 days later. Especially when the serum sodium approaches dangerously low levels (<125 mEq/L) or when large volumes of intravenous fluid are required to maintain euolemia, intravenous hypertonic saline can also be a useful adjunctive therapy in CSW. A dose of 1.5% sodium chloride can be administered through peripheral veins, and can safely and effectively restore and maintain intravascular volume and serum sodium concentration when administered at rates that are titrated to achieve a normal to slightly positive fluid balance. The authors routinely use 1.5% sodium chloride in patients with CSW at rates between 50 and 150

mL per hour. The use of 3% saline in CSW should be reserved for uncommon patients with CSW who have severe hyponatremia (<120 mEq/L) because it must be administered through a central vein and cannot be given at rates high enough to effectively restore or maintain intravascular volume.

Treatment with hypertonic saline and mineralocorticoids has important side effects. To gauge the efficacy of treatment and to avoid osmotic myelinolysis as a consequence of overly rapid correction of hyponatremia, the serum sodium concentration should be carefully and frequently monitored during treatment. In general, the serum sodium concentration should not be increased by more than an average of 0.5 mEq/L/h.¹¹⁵ Similarly, it is useful to use a serum sodium concentration of 130 mEq/L or greater rather than restoration of a normal concentration of 135 to 145 mEq/L as an end point for treatment. In most patients, this strategy effectively treats the negative consequences of hyponatremia while minimizing the likelihood of causing osmotic myelinolysis. Aggressive fluid and sodium administration and the use of mineralocorticoids can also cause volume overload, hypertension, pulmonary edema, and renal medullary washout,⁶⁵ warranting vigilance for these important complications during treatment. Finally, mineralocorticoid-like drugs also frequently cause hypokalemia and, because of their steroid properties, can promote hyperglycemia. Serum glucose and potassium concentration should be carefully monitored during such therapy.^{65,129,131,132}

A novel treatment strategy for hyponatremia that has only recently become available highlights the need to differentiate CSW from SIADH. Conivaptan is a nonselective antagonist at the V1a and V2 vasopressin receptor subtypes. By antagonizing the action of vasopressin in the renal collecting duct, it promotes electrolyte-free water excretion (a process termed “aquaresis”), thereby raising serum sodium levels. As its mechanism of action indicates, conivaptan is a highly specific and effective treatment for SIADH caused by a number of conditions.¹³³ It has recently been approved by the US Food and Drug Administration for the treatment of euolemic and hypervolemic hyponatremia^{133,134} for which it has demonstrated a satisfactory safety profile.¹³⁵ Conversely, this medication should not be used to treat hypovolemic hyponatremia, of which CSW is an important cause, because of its tendency to induce a negative fluid balance. The use of this medication in patients with neurologic injury has been examined in only small, uncontrolled retrospective studies.¹³⁴ Murphy and colleagues¹³⁴ assessed

the efficacy of intermittent bolus doses of 20 or 40 mg of intravenous conivaptan to correct acute euvolemic or hypervolemic hyponatremia that developed within 48 hours of admission to the neurologic intensive care unit. The studied patients had a variety of primary neurologic diagnoses, but patients with SAH who were suspected of having CSW were excluded. Patients who received the drug were those who had symptomatic hyponatremia, were at high risk of developing cerebral edema, or had low serum sodium levels refractory to traditional therapy. A 4 to 6 mEq/L rise in serum sodium concentration by 12 hours after a single dose was seen in 59% of patients and there were no adverse effects, including intravenous site reactions or hypotension. Conivaptan clearly shows promise in treating refractory hyponatremia in critically ill neurologic patients. A careful determination of the likely cause of hyponatremia must take place, however, before administering this drug to such patients. Patients with CSW are volume depleted in addition to being hyponatremic, and conivaptan causes volume loss by aquaresis. Because poor outcome has been associated with volume depletion in SAH patients with hypovolemic hyponatremia, conivaptan should not be administered to patients in whom CSW or a high likelihood for cerebral vasospasm is suspected.¹¹

SUMMARY

CSW is a syndrome of hypovolemic hyponatremia caused by natriuresis and diuresis. Once thought of as a rare novelty, recent clinical and basic science research has shown that CSW exists, is not uncommon in patients with certain types of brain injury, and can have significant negative consequences if not properly diagnosed and treated. The mechanisms underlying this syndrome have yet to be precisely delineated, although existing evidence strongly implicates abnormal elevations in circulating natriuretic peptides as the key pathophysiologic event. Nonetheless, several fundamental questions have yet to be answered, the most important of which are how cerebral injury leads to the release of excessive amounts of natriuretic peptides and why this occurs in only a small subset of cerebral injury types. The key in diagnosis of CSW lies in distinguishing it from the more common SIADH, although the value of this often imprecise process has recently been called into question.¹¹⁸ Volume status, but not serum and urine electrolytes and osmolality, is crucial for making this distinction. Volume and sodium repletion are the goals of treatment of patients with CSW, and this can be

performed using some combination of isotonic saline, hypertonic saline, and mineralocorticoids.

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