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REVIEW ARTICLE

Hyponatremia and Brain Injury: Historical and Contemporary Perspectives

Matthew A. Kirkman · Angelique F. Albert · Ahmed Ibrahim · Doris Doberenz

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Abstract Hyponatremia is common in neurocritical care patients and is associated with significant morbidity and mortality. Despite decades of research into the syndrome of inappropriate antidiuretic hormone (SIADH) and cerebral salt wasting (CSW), their underlying pathophysiological mechanisms are still not fully understood. This paper reviews the history behind our understanding of hyponatremia in patients with neurologic injury, including the first reports of CSW and SIADH, and current and future challenges to diagnosis and management in this setting. Such challenges include distinguishing CSW, SIADH, and hypovolemic hyponatremia due to a normal pressure natriuresis from the administration of large volumes of fluids, and hyponatremia due to certain medications used in the neurocritical care population. Potential treatments for hyponatremia include mineralocorticoids and vasopressin 2 receptor antagonists, but further work is required to validate their usage. Ultimately, a greater understanding of the pathophysiological mechanisms underlining hyponatremia in neurocritical care patients remains our biggest obstacle to optimizing patient outcomes in this challenging population.

M. A. Kirkman (✉) · A. Ibrahim
Victor Horsley Department of Neurosurgery,
The National Hospital for Neurology and Neurosurgery,
Queen Square, London WC1N 3BG, UK
e-mail: matthew.kirkman@gmail.com

A. F. Albert
Neurointensive Care Unit, Greater Manchester Neurosciences Centre, Salford Royal NHS Foundation Trust, Salford, UK

D. Doberenz
Intensive Care Unit, Charing Cross Hospital,
Imperial College Healthcare NHS Trust, London, UK

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Introduction

Hyponatremia is the commonest electrolyte abnormality in hospital inpatients [1] and is the most important and frequently encountered electrolyte disturbance in the neurocritical care setting [2, 3]. Although definitions for hyponatremia vary between studies, it has been shown to affect up to 38 % of intensive care patients [4–6] and up to 50 % of neurosurgical patients [7–13]. Common pathologies resulting in hyponatremia in the neurointensive care setting include acute brain injuries (ABIs), especially subarachnoid hemorrhage (SAH) [9, 12] and traumatic brain injury (TBI) [3]. Hyponatremia is associated with significant morbidity and mortality, more so if corrected too fast or too slowly [14–16]. Many consider the two principal causes of hyponatremia in patients with ABI to be cerebral salt wasting (CSW) and the syndrome of inappropriate antidiuretic hormone secretion (SIADH). However, it is unclear whether CSW and SIADH represent two distinct clinical entities or form part of a spectrum, possibly prevailing at different times during the course of illness in the same patient. In addition, some other important factors may contribute to the hyponatremia so commonly encountered in patients with ABI.

This paper reviews the history behind our understanding of hyponatremia in patients with ABI, including the first reports of CSW and SIADH. Challenges in the assessment, management, and prevention of hyponatremia in patients with ABI are also discussed.

Historical Review

Early Beginnings

The French physiologist Claude Bernard first raised the possibility of a direct relationship between the central nervous system and renal excretion of osmotically active solutes in 1858 [17]. He found that a unilateral lesion in the reticular substance at the floor of the fourth ventricle produced a diuresis of chloride, but not glucose, and that this was intensified by bilateral lesioning. Bernard reproduced this syndrome through renal denervation. Over half a century later, Jungmann and Meyer in Germany induced polyuria and increased urinary salt excretion in animals through medullary lesioning [18]; restricting water intake did not stop the polyuria, and salt continued to be excreted in the urine despite restricting its intake.

A Salt Wasting Syndrome?

The development of the flame photometer soon after World War II facilitated the measurement of serum sodium concentration. Almost a century after the pioneering work of Bernard in animals, three patients with varying cerebral pathologies (encephalitis, hypertensive intracranial hemorrhage, and bulbar poliomyelitis) with severe dehydration and hyponatremia were described by Peters, Welt, and co-workers in 1950 [19]. All three patients were unable to prevent urinary sodium loss despite low serum sodium levels and no evidence of extrarenal sodium loss. Their hyponatremia responded to salt therapy. One patient, initially in stupor, became "alert and responsive" after the administration of a high dose of sodium chloride. The authors postulated that this provided evidence of an extra-pituitary cerebral structure mediating normal sodium metabolism, but were unsure of its location or mechanism of action.

Reflecting on a rather unorthodox experiment in the treatment for sodium balance disorders, in the discussion that followed the manuscript in the Transactions of the Association of American Physicians a Dr. Dock made the following remark:

> I would like to point out that recently Dr. Tinsley Harrison's co-workers in Dallas have shown that the salt retention usually associated with circulatory changes can be prevented by putting a rather tight cuff around the neck, which produces progressive edema of the brain and thus invokes the salt-losing phenomenon in a very short time [19].

Dr. Dock then postulated that salt-losing could represent a protective mechanism for cranial pathologies with brain swelling. Highlighting that normalizing the sodium returned the conscious level of his patient with encephalitis to normal, Dr. Peters asserted that salt-losing was unlikely a protective mechanism.

In 1952, Welt and colleagues described another six patients with cerebral lesions (including trauma, tumor, and infection) exhibiting severe clinical dehydration, hyponatremia, a negative sodium balance, but no potassium retention [20]. All responded to sodium chloride administration, but administering aldosterone precursor 11-deoxycorticosterone did not reverse renal sodium loss. The authors felt neither pituitary nor adrenal insufficiency was involved, but that direct neural control of renal proximal tubular reabsorption of sodium was disrupted. Animal studies at the same time suggested that renal denervation disrupts proximal tubular reabsorption resulting in osmotic diuresis in the distal tubule [21].

The term "Cerebral Salt Wasting" was coined in 1954, as the title of a paper by Cort describing a patient with a thalamic glioma resulting in hydrocephalus and raised intracranial pressure [22] (although it is prudent to note that the earlier-described work by Peters, Welt and colleagues in 1950 [19] was presented in a paper entitled "A salt-wasting syndrome associated with cerebral disease"). This patient was hyponatremic and clinically dehydrated with initial salt therapy not reversing this. Salt restriction resulted in ongoing natriuria. Recommencement of salt therapy subsequently increased serum sodium. Treatment with adrenocorticotropic hormone (ACTH) and deoxycortone acetate (having potent mineralocorticoid activity) had no effect.

The author postulated an external influence on renal function not adrenal or pituitary in origin. Unfortunately, the patient died three and a half weeks later in "circulatory failure with terminal shock" [22]. At autopsy, the pituitary and adrenal glands were normal. Given Bernard's ability to create a chloride diuresis without glycosuria though renal denervation (as discussed above), Cort postulated the existence of a neuronal connection between the hypothalamus and proximal tubule of the kidney influencing electrolyte reabsorption.

In all above-described cases, there was evidence of hyponatremia and dehydration. In the ensuing years, however, hyponatremia in cerebral pathology was described without clinical or laboratory evidence of dehydration.

A Syndrome of Inappropriate Antidiuretic Hormone Secretion

In 1957 and 1960, the first reports of hyponatremia and renal sodium loss corrected by fluid restriction in patients with bronchogenic carcinoma were published [23, 24]. With urine persistently more concentrated than plasma, the underlying disease process was thought to be due to inappropriate release of antidiuretic hormone (ADH) resulting in body fluid volume expansion although no direct vasopressin

measurements were taken. Vasopressin-ADH administration to normal humans was shown to result in water retention and urinary loss of electrolytes (primarily sodium) in other studies at the time [25]. Renal and adrenal function appeared intact, but, unlike in the earlier case of "cerebral salt wasting" described by Cort [22], an increase in renal absorption and plasma concentration of sodium occurred with administration of ACTH and deoxycortone acetate.

Inappropriate Antidiuretic Hormone Release in Cerebral Pathology

Some observations of hyponatremia in patients with cerebral disease [26, 27] identified symptoms predominantly of water intoxication as opposed to dehydration as in CSW; in these patients, changes in fluid intake and hydration were seen as pivotal to the development of hyponatremia and sodium loss. This led to the concept of SIADH in cerebral pathology. In 1961, Carter et al. [28] described a patient with a cerebral tumor and another with a basal skull fracture, both demonstrating hyponatremia, clinically normal or increased extracellular volume and low blood urea nitrogen levels. The authors proceeded to perform a series of experiments on the latter patient, in a manner that would be impossible with present standards in research ethics. The patient underwent sequential experimental treatments with the mineralocorticoid 9-alpha-fluorohydrocortisone, salt restriction and 2.5 L/day water intake, hypertonic saline (the first description of this treatment for hyponatremia, although details on the exact sodium chloride concentrations and mode of administration were not reported), and water restriction (250–750 mL/day).

Administration of sodium chloride hypertonic in relation to plasma led to not only an initial rise in plasma sodium but also a rise in urine volume and sodium excretion. Mineralocorticoid administration and fluid restriction corrected the hyponatremia. Interestingly, only fluid restriction has continued to be described and used as the standard treatment of SIADH. In the study by Carter et al., salt restriction and liberal water intake worsened hyponatremia. These measures were associated with urine becoming hypertonic to serum despite positive water balance, suggesting increased vasopressin-ADH secretion despite worsening hyponatremia. Thus, water retention, due a presumed inappropriately high vasopressin-ADH secretion, appeared to be the underlying cause of hyponatremia.

CSW or SIADH?

Following these publications, the term "cerebral salt wasting" vanished from the literature for over two decades with hyponatremia in patients with cerebral pathology assumed to result from SIADH. Then, in 1981, a study of twelve neurosurgical patients mainly with SAH found ten to have decreased red blood cell mass, plasma volume, and total blood volume despite "fulfilling laboratory criteria" for SIADH [29]. However, CSW should decrease plasma volume while leaving red blood cell mass intact [30].

Nevertheless, the authors concluded that these patients had findings better described as CSW than SIADH and that fluid restriction as standard treatment for SIADH could aggravate the underlying volume deficit. It might also worsen vasospasm after SAH.

Despite significant research efforts investigating hyponatraemia in brain injury, uncertainties as to the underlying pathophysiological mechanisms remain. Some believe that CSW [29, 31–34] predominates in this population, others SIADH [35–37]. However, studies in this field have often been criticized for the lack of significant differences between study populations, poor recruitment, and selection of control groups, if any. Although recent guidelines demonstrate rationalization of an approach to managing hyponatremia in this population [38], many challenges and controversies remain. These will now be discussed.

Current Perspective and Challenges

Assessment and Differential Diagnosis of Hyponatremia

Hyponatremia is often inadequately investigated, diagnosed, and treated; the recent development of clinical guidelines may remediate this [38]. A methodical workup is required (Fig. 1; Table 1). A multitude of acute and chronic extracranial pathologies may contribute to hyponatremia in the neurocritical care patient. The assessment and management of hyponatremia may be seriously confounded by some common treatments used in patients with brain injury or hemorrhage. Use of norepinephrine to maintain cerebral perfusion pressure or induce hypertension as part of treatment for vasospasm after SAH may lead to pressure-diuresis and natriuresis is a normal physiologic renal response to increased mean arterial pressure, resulting in decreased blood volume (hypovolemic hyponatremia) [39]. Nimodipine, commonly used in the prevention and treatment of vasospasm following SAH, can also cause or worsen hyponatremia by activation of atrial natriuretic peptide [40] and inhibition of aldosterone [41, 42].

Another important issue in causation, assessment, and treatment of hyponatremia in patients with ABI is potentially excessive administration of salt containing intravenous fluids, which manipulates blood and extracellular volumes, making the presentation of a "classic" SIADH or CSW

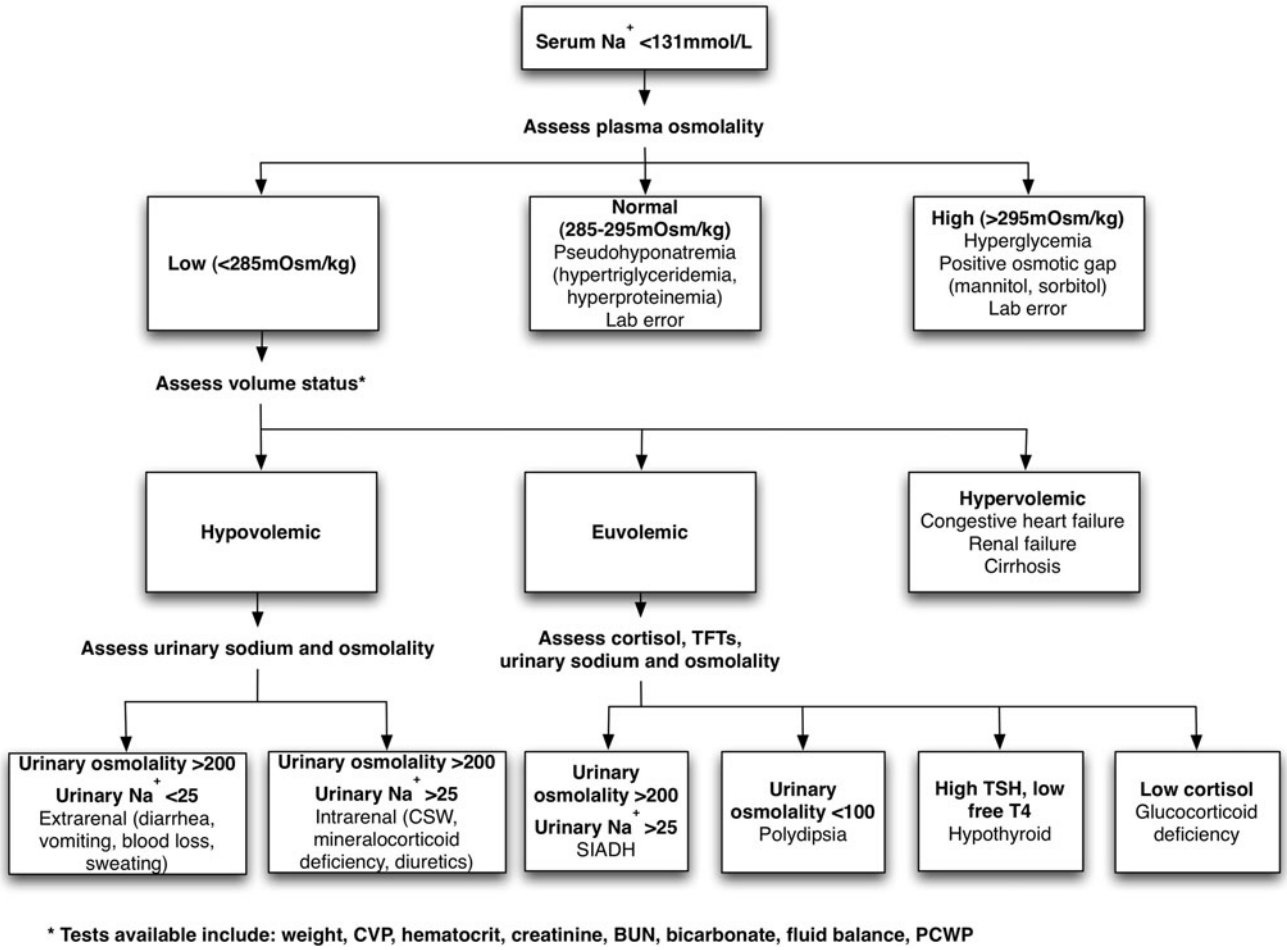

Fig. 1 Workup of a patient with hyponatremia. Based on data from [38, 98]. Na^+ sodium, *CVP* central venous pressure, *BUN* blood urea nitrogen, *CSW* cerebral salt wasting, *PCWP* pulmonary catheter wedge pressure, *SIADH* syndrome of inappropriate anti-diuretic hormone secretion, *TFTs* thyroid function tests

picture less likely than when they were first described in the 1950s and 1960s. It also leads to salt loss through activation of natriuretic peptides, suppression of aldosterone, and involution of renal tubular membrane sodium transporting receptors [39].

Thus, the assessment of volume and sodium balance for the whole hospital stay is an important part of the assessment of hyponatremia in these patients.

Despite significant research efforts, the underlying pathophysiology of hyponatremia in brain-injured patients is still not entirely understood (Figs. 2, 3). Some question whether a clinically significant difference between CSW and SIADH exists [43], and most clinical and laboratory criteria cannot distinguish between the two [44]. CSW and SIADH may actually represent different parts of a clinical spectrum.

Most authorities and textbooks state that the distinction between CSW and SIADH must be based on the clinical and laboratory assessment of extracellular fluid status (Table 2).

Establishing Fluid Status

If the two clinical entities of CSW and SIADH exist, determining extracellular fluid status is important [45] as a basis for correct treatment; fluid restriction in a patient with CSW could be fatal [46]. To diagnose CSW, evidence of inappropriate urinary salt loss and reduced "effective arterial blood volume" are required [43], excluding other causes of excess urinary salt loss. However, "effective arterial blood volume" is not a measurable variable but a concept, often defined clinically through analyzing urinary sodium excretion [47]—itself increased by CSW and influenced by administration of fluids, diuretics, and other drugs. Determining blood volume or extracellular fluid status is done in various ways, none of which are foolproof [30, 47–49]. What is a "normal" extracellular volume? A true assessment of fluid and sodium balance is rarely achieved, even on the intensive care unit. In fact, many reports of CSW relied solely on clinical impressions regarding volume depletion

Table 1 Some causes of hyponatremia

Cerebral salt wasting
Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
Pressure natriuresis (e.g. due to excessive fluid administration or norepinephrine)
Endocrinologic causes:
• Hypothyroidism
• Adrenal insufficiency
Renal failure
Sepsis
Diarrhea
Vomiting
Blood loss
Excessive sweating
Primary polydipsia
Nephrotic syndrome
Cirrhosis
Congestive cardiac failure
Iatrogenic/drugs[a]:
• Hypotonic fluids
• Norepinephrine
• Calcium channel blockers e.g. nimodipine used in SAH for prevention and treatment of vasospasm
• Carbamazepine
• Serotonin-specific reuptake inhibitors
• Steroids
• Tricyclic antidepressants
• Dopamine
• Diuretics
• Vasopressin
• Phenothiazines
• Vincristine
Ketonuria
Osmotic diuresis

[a] Some of the drugs cause hyponatremia through causing SIADH

[19]. In modern hospital medicine, true underlying fluid status may be influenced or masked by fluid administration, which is a routine part of the management of brain injuries and hemorrhage. Central venous pressure (CVP) measurements are widely used in the assessment of fluid status with a value below 5 mmHg deemed diagnostic of CSW [50]. However, significant evidence indicates the relationship between CVP and blood volume is poor [51]. A young patient with a normally functioning right heart should not demonstrate a lasting change in CVP following fluid administration until fluid overloaded, whereas an elderly patient with cor pulmonale may have a raised CVP irrespective of fluid status.

Radioisotope measurements of blood volume are more accurate but are only performed in a few centers. Pulse contour cardiac output monitoring (PiCCO) provides an estimate of intrathoracic blood and global end diastolic volume from its calibration injections of cold saline, and is superior to CVP as preload indicators [52, 53]. This may be helpful in determining fluid status and for a more accurate method of preload determination in SAH patients undergoing triple H therapy. It is, however, invasive, requiring a long arterial and a central venous catheter, and only available in intensive care units.

Subarachnoid Hemorrhage

SAH presents unique challenges in the treatment of hyponatremia. Thirty to forty percent of patients with SAH experience hyponatremia [48, 54–56], which increases the risk of cerebral edema, vasospasm, and cerebral infarction [57]. Studies have reported increased atrial [12, 58–63] and brain [64–66] natriuretic peptides (ANP and BNP, respectively) to be associated with hyponatremia in SAH and predict the development of cerebral vasospasm [66, 67]. However, cardiac dysfunction [68] and hypervolemia, hypertension, and hemodilution (HHH) therapy [69] may stimulate BNP release after aneurysmal SAH. Thus, whether the association between BNP, vasospasm, and hyponatremia is associative or causative is unclear. Brain natriuretic peptide release is usually cardiac in origin, confirmed by jugular venous sampling in suspected CSW [70]. BNP levels appear to be associated with reduced aldosterone synthesis [64], and peak before ANP [34], suggesting potentially different underlying mechanisms of action. Some SAH studies have found no increase in ANP [64, 71].

For three decades, HHH-therapy has been widely adopted for the prevention and treatment of cerebral vasospasm in SAH without evidence from randomised controlled trials of benefits on morbidity or mortality [72]. Administration of significant amounts of isotonic saline, common with HHH-therapy, increases extracellular fluid volume, thus activating natriuretic peptides and suppressing aldosterone. This could mimic the clinical presentation of CSW, more so if combined with significant adrenergic hormone release (elevated in patients with major brain pathology) [73] or administration, including norepinephrine or dopamine, also a diuretic and natriuretic in its own right (Fig. 3) [74, 75].

Most hyponatremic SAH patients are thought to have CSW as opposed to SIADH. Thus, the volume expansion with salt-containing fluids could treat their CSW and should also prevent or treat vasospasm. However, HHH therapy may not improve vasospasm [76]. Evidence suggests that induced hypertension improves cerebral blood flow (CBF) and cerebral oxygenation (as assessed by brain tissue oxygen tension [$PtiO_2$] monitoring), whereas hypervolemia and hemodilution have no or even a negative effect on CBF and $PtiO_2$ values [77]. While further work is required to elucidate

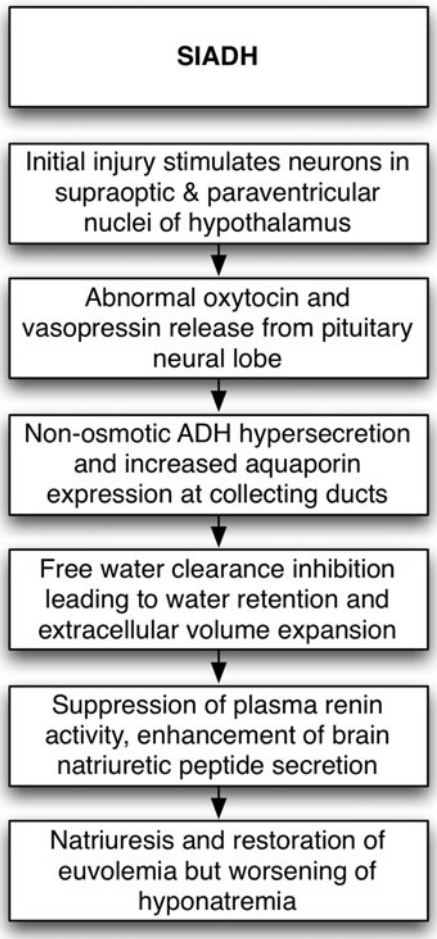

Fig. 2 Schematic illustration of the putative underlying pathophysiology of the syndrome of inappropriate antidiuretic hormone release (SIADH)

on this, the implication for SAH patients is that large fluid volumes (that can itself exacerbate hyponatremia) may not be necessary in those with SIADH at risk of vasospasm who require fluid restriction. However, class II evidence indicates that hyponatremia in SAH patients at risk of vasospasm should not be treated with fluid restriction [38]. Vasopressors represent an alternative therapeutic option for maintaining cerebral perfusion although they too can result in a pressure natriuresis.

Induced hypertension alone is now recommended above triple H therapy in treating delayed cerebral ischemia in the latest Neurocritical Care Society guidelines for management of aneurysmal SAH [78].

Management (Fig. 4)

The treatment of hyponatremia in neurocritical care patients is reviewed extensively elsewhere [38, 79]. However, in general terms, principles for correction of hyponatremia depend on whether the patient has acute symptomatic hyponatremia or chronic (i.e., present for over 48 h) hyponatremia. In the setting of acute symptomatic hyponatremia, it has been recommended that hypertonic saline (3 %) is used to raise plasma sodium by 1–2 mmol/h to a total of 4–6 mmol, which should be sufficient to alleviate severe acute signs and symptoms (such as seizures, coma, dilated pupils, and neurogenic pulmonary edema) [80]. Once this acute correction has occurred, ongoing correction for hyponatremia can follow the guidelines for chronic hyponatremia, whereby correction should be no faster than 0.5 mmol/h (to avoid the risk of osmotic demyelination syndrome). The use of potassium supplementation in fluids

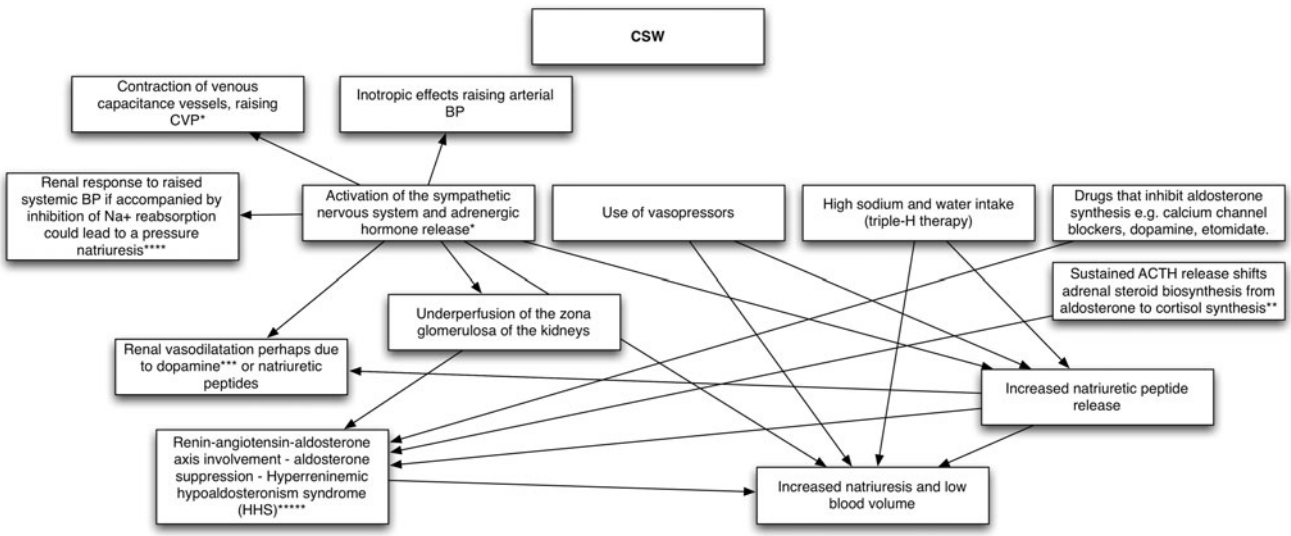

Fig. 3 Schematic illustration of the putative underlying pathophysiology of cerebral salt wasting (CSW). *BP* blood pressure, *CVP* central venous pressure, *Ref. [73], **Ref. [99], ***Ref. [75], ****Ref. [100], *****Ref. [34]

Table 2 Features of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and cerebral salt wasting (CSW)

	SIADH	CSW
Serum sodium (mmol/L)	<135	<135
Serum osmolality (mOsm/kg)	<285	<285
Urine osmolality (mOsm/kg)	>200	>200
Urinary sodium (mmol/L)	>25	>25
Extracellular fluid volume	Increased or no change	Reduced
Central venous pressure (cmH_2O)	≥6	<6
Pulmonary wedge pressure (mmHg)	>8	<8
Blood urea nitrogen	Reduced	Increased
Serum albumin concentration	Normal	Increased
Serum potassium concentration	Decreased or no change	Increased or no change
Hematocrit	Normal or reduced	Increased
Uric acid	Reduced	Reduced
Bicarbonate	Reduced	Increased
Creatinine	Reduced	Increased
Jugular venous distension	Yes	No
Fluid balance	Positive	Negative
Weight	Increased/higher	Reduced/lower

Based on data from [38, 79]

for management of hyponatremia can increase the rate of sodium correction and this must be borne in mind.

Treatment of the underlying illness causing CSW or SIADH is not always possible. While treatment with hypertonic saline or salt supplementation will raise serum sodium levels, in SIADH, these interventions will not address the physiologic effects or underlying pathophysiology of excess ADH. Implementing fluid restriction is also difficult, especially in patients on intravenous medications. In patients on renal replacement therapy, the use of large volumes of fluids during dialysis can result in too rapid shifts in sodium and osmotic myelinolysis. As opposed to imposing specific intakes or restrictions of fluid and sodium, there is evidence that quantifying volume and sodium losses and replacing them *quid pro quo* can prevent hyponatremia in patients with ABI [34, 44, 64]. As such, perhaps treatment of hyponatremia should be more individualized than it currently is.

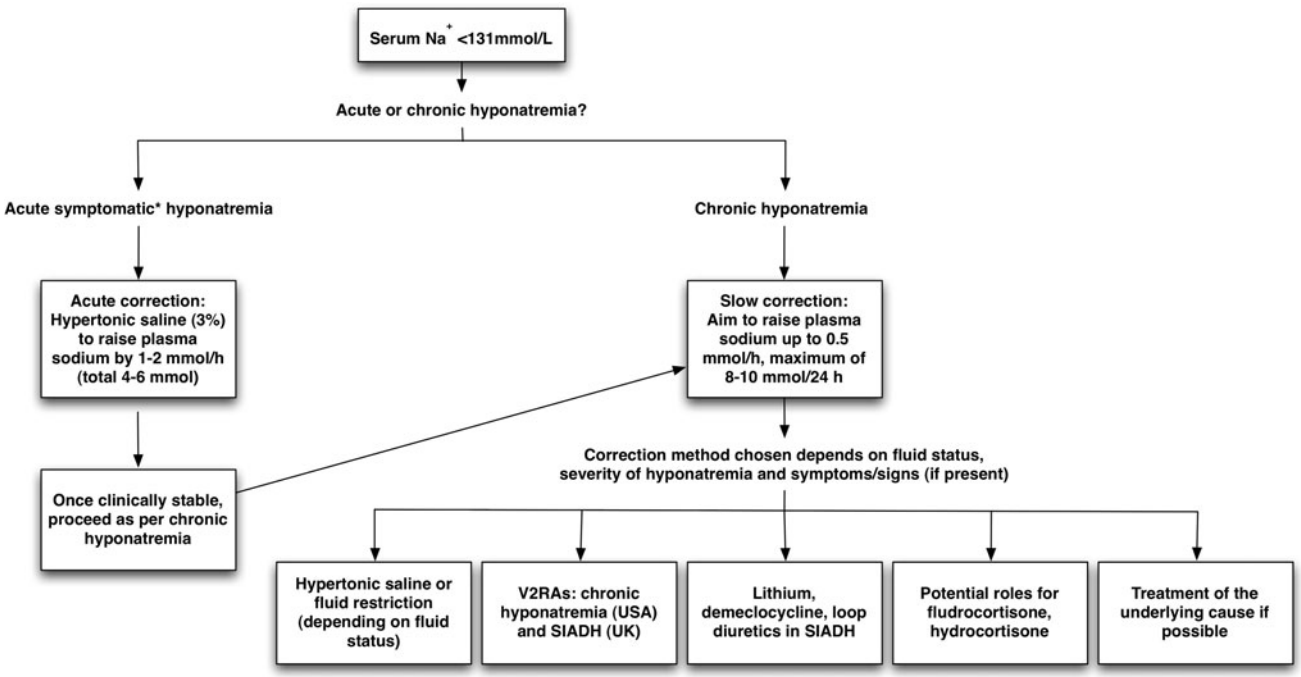

Fig. 4 Management of hyponatremia. *symptoms/signs include seizures, coma, dilated pupils, and neurogenic pulmonary edema. *V2RAs* vasopressin 2 receptor antagonists, *SIADH* syndrome of inappropriate antidiuretic hormone release

Treatments for SIADH, including lithium and demeclocycline, can be nephrotoxic. The use of loop diuretics such as furosemide is controversial, in part, because they alter the levels of other electrolytes in addition to sodium [81]. Fludrocortisone has been shown to reduce natriuresis [82] and the risk of vasospasm [83, 84], and hydrocortisone to prevent natriuresis [85, 86] in hyponatremic SAH patients. Further evaluation of the role of these hormones in natriuresis is necessary.

The use of hypertonic saline has become routine since isotonic saline does not prevent or treat hyponatremia [87] and can in fact worsen it [88]. Some advocate treating all neurocritical care patients with hyponatremia using hypertonic saline for this reason, and also since the risk of neurologic deterioration or death is too significant, and water restriction is slow as well as minimally effective [89]. Animal studies have suggested that mannitol could be an alternative to hypertonic saline for acute hyponatremia [90], but clinical evidence is lacking and severe caution should be excised since it can actually result in hypertonic hyponatremia [91]. Despite the prevalence of hyponatremia, no study has compared the different treatment modalities in a large prospective randomized controlled trial.

Vasopressin 2 receptor antagonists (V2RAs) are licensed in the USA for the management of chronic hyponatremia, and in the UK for hyponatremia secondary to SIADH. By reducing the aquaporin expression at the collecting ducts of the kidneys, they promote water excretion without electrolyte loss; however, the ensuing rise in plasma sodium increases thirst and plasma vasopressin concentration and thus may limit the utility of this class of drugs [89]. V2RAs may correct hyponatremia too rapidly (>1 mmol/L/h) [92, 93] and increase the risk of osmotic myelinolysis. Further, their effects on an individual level are variable and unpredictable [89]. In addition, they are not licensed for use in acute hyponatremia, and the trials validating their use incorporated patients with hyponatremia secondary to liver cirrhosis and chronic cardiac failure as well as SIADH, and the underlying cause of SIADH was not described; further, patients with severe hyponatremia (<120 mmol/L), head trauma, postoperative conditions, and cerebrovascular accident were excluded [94]. While preliminary data from small series and a case report supports their use in the ABI population outside of intensive care [95, 96], further data in patients with ABI are necessary, including evidence that they improve morbidity and mortality safely [97].

Recommendations

Given the above challenges in the management of hyponatremia in the brain-injured patient, the following recommendations offer practical advice to the clinician involved in the care of such a patient:

1. All patients with hyponatremia need a thorough workup using a protocol as illustrated in Fig. 1, being especially mindful of extracranial and iatrogenic causes of hyponatremia, especially osmotherapy and drugs.
2. Determining fluid status is key in differentiating between CSW and SIADH in the clinical setting (if they do indeed exist as two different clinical entities). However, one must bear in mind that the (often substantial) fluid administration given in the neurocritical care setting may impair the ability to make this distinction.
3. In patients with SAH, induced hypertension alone is now preferred above triple H therapy in preventing delayed cerebral ischemia as per guidelines from the Neurocritical Care Society [78].
4. The exact treatment of hyponatremia in the brain-injured patient depends on the type (acute vs chronic) and degree of hyponatremia. One should be mindful of the risk of osmotic demyelination syndrome that can accompany overzealous correction. If possible, treatment of the underlying cause should be prioritised to prevent relapse.
5. Several medications may offer an adjunct/alternative to fluid therapy in hyponatremia, including V2RAs (Fig. 4), but further evidence is required before they are used in widespread clinical practice.

Conclusions

Hyponatremia is common in brain-injured patients, and can have devastating consequences if not treated promptly and successfully. Since the first cases of CSW (and later SIADH) reported in the middle of the last century, progress in understanding the pathophysiology behind these conditions has been made, but many uncertainties remain. Indeed, a definite pathophysiological difference between CSW and SIADH may never be proven. The management of hyponatremia in neurocritical care patients presents many challenges for the foreseeable future. Especially in SAH, a normal physiologic pressure natriuresis with hyponatremia can result from administration of large volumes of saline. Many medications and non-neurologic/neurosurgical pathologies can mimic the clinical picture of CSW and SIADH. These and the other pitfalls discussed in this paper must be remembered when managing neurocritical care patients with hyponatremia.

Aside from hypertonic saline, treatments for hyponatremia including vasopressin 2 receptor antagonists, fludrocortisone, and hydrocortisone show promise, but need further validation before widespread use. A greater

understanding of the pathophysiological mechanisms underlining hyponatremia in neurocritical care patients is perhaps our biggest obstacle to optimizing patient outcomes in this challenging population.

Conflict of interest No authors have any conflicts of interest or financial disclosures.

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