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Review article

Cerebral salt wasting syndrome: Review

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Abstract

Hyponatremia is the most frequent electrolyte disorder in critically neurological patients. Cerebral salt wasting syndrome (CSW) is defined as a renal loss of sodium during intracranial disease leading to hyponatremia and a decrease in extracellular fluid volume. The pathogenesis of this disorder is still not completely understood. Sympathetic responses as well as some natriuretic factors play a role in this syndrome. Distinction between SIADH and CSW might be difficult. The essential point is the volemic state. It is necessary to rule out other intermediate causes. Treatment requires volume replacement and maintenance of a positive salt balance. Mineral corticoids may be useful in complicated cases.

Keywords: Cerebral; Salt; Wasting; Hyponatremia; Inappropriate ADH syndrome

1. Introduction

Cerebral salt wasting syndrome (CSW) is defined as a renal loss of sodium during intracranial disorders leading to hyponatremia and a decrease in extracellular fluid volume. This disorder was first described by Peters et al. in 1950, but the identification seven years later of the Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH), which is also seen in disorders of the Central Nervous System (CNS), eventually eclipsed the interest of the researchers [1]. Indeed, some authors have doubted the existence of CSW [2,3], but afterwards reports supporting the existence of this phenomenon have been published. [1,4–6].

2. Epidemiology

Hyponatremia is the most common electrolyte finding in hospitalized patients; its frequency; however, depends on many factors including its own definition [7]. Hyponatremia is also the most frequent electrolyte disorder in critically neurological patients [8]. It is associated with numerous intracranial pathologies but one of the most studied has been subarachnoid haemorrhage (SAH).

In a recent observational study of 316 patients with SAH, 179 (56.6%) developed hyponatremia (plasma sodium <135 mmol/l), including 62 (19.6%) who developed severe hyponatremia (plasma sodium <130 mmol/l) [9]. The aetiology of hyponatremia below 130 mmol/l was SIADH in 39 cases (62.9%), CSW in 4 (6.5%), hypovolaemic hyponatremia in 13 (21%), and mixed CSW/SIADH in 3 (21%). In a follow-up of 102 consecutive patients, survivors of severe or moderate traumatic brain injury, 13 patients (12.9%) developed SIADH and 1 (0.98%) had CSW in the immediate postraumatic period [10].

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In a recent study carried out in our hospital from 129 consecutive patients attended in the neurology unit, we found hyponatremia in 14% of the patients. The main causes of hyponatremia were: inappropriate electrolytic therapy, use of diuretic, and SIADH in 78% of the patients. We found CSW as the cause of hyponatremia only in 2 patients (10.5% of hyponatremia patients). In our series, most hyponatremia were detected on the first day of hospitalization, whilst hypernatremia were more frequently found between the 3rd and 5th day [11].

In some observational studies CSW has been found even more frequently than SIADH [4,12]. Nevertheless, the number of patients included in those studies was low (21 and 23, respectively). Some authors believe, however, that CSW is not as frequent when restricted criteria are used [13]. Most of the reports we have found in the literature come from neuroanaesthesia and neurocritical care units, whilst we have not found studies about its prevalence in patients attended in non-critical neurology wards.

Apart from SAH other nervous system disorders can cause CSW, amongst CNS infections it has been observed in tuberculous meningitis [14,15] viral meningoencephalitis [16], and herpetic encephalitis [17]. CSW has also been described in carcinomatous meningitis, metastasic carcinoma, cranioencephalic trauma, transsphenoidal surgery for pituitary pathologies, gliomas, resection of acoustic neuroma [18], and after calvarial remodelling [19].

3. Pathogenesis

The mechanism by which intracranial disease leads to CSW is still not completely understood. CSW goes with primary natriuresis which leads to hypovolemia and sodium (Na+) depletion, without a known stimulus to excrete large amounts of sodium. It is believed that natriuretic factors such as atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP), and dendroaspis natriuretic peptide (DNP) may play a role in CSW. In recent years, several reports attempt to find a causal relationship between natriuretic peptides and CSW. Amongst the various natriuretic peptides, BNP might be the most probable candidate to mediate CSW [20]. It is believed that an increased plasma volume that could distend atrial walls, a sympathetic stimulus, or the increased angiontensine II or endoteline, would increase the release of these peptides. This would lead, therefore, to a diminished activity of the Renine–Angiotensine–Aldosterone system and an increased natriuresis for its action regarding the distal tubule.

In recent studies performed in patients with neurosurgical conditions and hyponatremia, 31 patients affected by SAH were observed. It was found that low plasma sodium was due to an increase of ANP rather than SIADH [21]. Another clinical series involving 9 patients with craniosynostosis, who underwent calvarial remodelling, observed that by postoperative day 1, the ANP and BNP increased by 3–6 fold compared with the preoperative levels [13] and returned to normal state by postoperative day 5. The ADH concentration was normal even after operation. The urinary Na+ level increased in all patients by postoperative days 1 and 3, although serum Na+, and serum and urine osmolality remained normal.

In a prospective observation of 49 patients suffering SAH the plasma concentration of ANP was not altered [22]. Nonetheless, BNP initially increased in patients with moribund aneurism and in those with ruptured anterior communicant aneurysm. Hyponatremia and symptomatic vasospasm tended to occur in patients who had a persistent increase of plasma BNP concentration during one week after SAH. The initial increase of BNP following SAH was attributed to direct damage by SAH on the hypothalamus.

Another prospective study carried out on 40 patients with SAH, a more than three-fold increase in admission serum BNP was associated with hyponatremia and predicted the Glasgow Coma Scale score 2 weeks after SAH [23]. Moreover, it was observed that BNP levels significantly increased during the first 24 hours after vasospasm.

Nevertheless, the mechanism by which the increase of BNP occurs in SAH is not completely understood. Some authors [24] have claimed that this increase of BNP can be associated with an increase in cardiac production triggered by noradrenalin release, which would be induced by stress. It is not known whether either brain or cardiac tissue, or both, contribute to the increased BNP concentrations.

BNP brain expression has been localized to the hypothalamus and its sympathetic projections and may be released when this part of the brain is damaged [25]. Moreover the adrenal medulla also synthesizes BNP [26]. The effect of circulating natriuretic peptides at the nephron is well documented, whereas their intrinsic function within the central nervous system and peripheral autonomic nervous system is less well understood but it has been suggested that disregulation of the sympathetic response may be a central aspect of CSW. A recent case of a patient with CSW in association with neuroleptic malignant syndrome supports the connexion between the sympathoadrenal system and natriuretic peptides [27].

Natriuretic peptides released in the CNS regulate the water and Na+ content of the brain and CSF production. A direct relation with ANP/BNP and intracranial pressure (ICP) has been reported [20] suggesting that the development of renal salt wasting is a protective measure, limiting extreme rises in ICP and tendency for vasospasm in disorders such as SAH.

Despite this evidence, some authors have not found a direct relationship between BNP and CSW. A recent study performed in a SAH model with 24 rats showed that urine volume and Na+ excretion in SAH rats increased compared with those without SAH or with subdural haemorrhage, although ANP significantly decreased BNP did not change [28].

In a paediatric series with 9 patients with features of CSW, both ANP and BNP were elevated only in 1 out of 6 in whom

Na+ turnover vanished in 2 weeks; and in 2 of 7 who underwent surgical procedure, respectively [29]. Plasma renin and aldosterone were either suppressed or in the low-normal range.

In other follow-up of 50 children with acute neurological deterioration [30], it was observed that plasma ANP levels were increased in those with brain injury in comparison to the control group, but not in those less than one year of age.

Apart from ANP/BNP other natriuretic peptides have been studied. In a clinical series with 8 patients after SAH and 9 healthy controls, DNP levels increased and were significantly associated with hyponatremia caused by a hypernatriuresis [31]. On additional observational study carried out in 14 severely brain injured adult patients and 8 healthy volunteers [32] showed that the plasma DNP levels were higher in the group of patients. Hyponatremia with negative fluid balance occurred in 7 patients. It was, therefore, concluded that the DNP level is related to the enhancement of natriuretic and diuretic responses in severely neurological-injured patients.

BNP has been shown to increase significantly in other pathologies such as congestive heart failure or acute ischemic stroke [33]. The increased sympathetic activity after an acute stroke is supposed to be responsible for the increase in BNP. This increase is at the maximum level on day 1 and declines on the following days; nevertheless, no relationship with hyponatremia has been reported. A compilation of the main studies is shown in Table 1.

As a consequence, the increase in natriuretic peptides cannot be the only cause of CSW. Two other mechanisms have been suggested: a severe degree of extracellular volume expansion could down-regulate transporters in renal Na+ absorption and an adrenergic surge that could lead to pressure natriuresis. Although hyperactivity of the sympathetic nervous system occurs after SAH it has been suggested that acute brain injury may ultimately lead to an interruption in sympathetic output [1]. The decrease in renal sympathetic activity would cause an increase in renal blood flow and glomerular filtration, a decrease in renin release with decrease in renal tubular sodium reabsorption [34].

Nevertheless, the research carried out is still controversial. Vasopressin levels can be only evaluated in relation to the tonicity of body fluids, and natriuresis is a common finding pathway for both CSW and SIADH syndromes. We found that there is a need for strict metabolic studies, and the main problem is the difficulty of carefully controlling Na+ and water balance in hospitalized patients.

4. Clinical picture

In neurologically injured patients it is important to distinguish between SIADH and CSW as they both share several diagnostic criteria. Both diagnosis approach and monitoring are based on the assessment of Na+, water loss, and extracellular fluid volume. The main difference between these disorders is found in plasma volume and urinary excretion of Na+ and Chloride (Cl−). CSW is characterized by a low plasma volume with symptoms of dehydration, low serum osmolality, and a large urinary excretion of Na+ and Cl−, whereas SIADH shows a high plasma volume with low plasma osmolality. Low central venous pressure confirming a volumic depletion indicates the diagnosis of CSW, and elevated plasma vasopressin levels may be appropriate for the degree of volume contraction [35–37].

Other laboratory findings that are useful include hemoconcentration and raised serum bicarbonate. Serum uric acid tends to be low in both disorders. A compilation of the main characteristics to distinguish CSW from SIADH is shown in Table 2.

The determination of the volemic state is essential for diagnosis, since patients with SIADH are either euvolemic or hypervolemic, while those with CSW are hypovolemic. It is usually difficult for the physician to confirm from a bedside observation whether a patient has a low extracellular volume. Electrolyte balance can be accurately estimated and is

Table 1

Article	Subjects	Population	Illness	ANP	BNP	CNP	DNP
Kurokawa [21]	31	Adults	SAH	↑	–	–	–
Byeon [19]	9	Adults	Calvarial remodeling	↑	↑	–	–
Tsubokawa [22]	49	Adults	SAH	=	↑	–	–
Mc Girt [23]	40	Adults	SAH	–	↑		
Berendes [20]	10	Adults	CNS Tumors	=	–	–	–
	10		SAH	=	↑	=	–
	40		Healthy	=	=	=	–
Tomida [24]	18	Adults	SAH	=	↑	–	–
Von Bismarck [29]	9	Children	Cerebral disease	↑	↑	–	–
Ibarra de la Rosa [30]	50	Children	Acute brain injury	↑	–	–	–
Khurana [31]	8 patients	Adults	SAH	–	–	–	↑
	9 controls						
Gao [32]	14 patients	Adults	Brain injured	–	–	–	↑
	8 volunteers						

SAH: Subarachnoid hemorrhage. CNS: Central nervous system. ANP: Atrial natriuretic peptide. BNP: Brain natriuretic peptide. CNP: C-type natriuretic peptide. DNP: Dendroaspis natriuretic peptide. (–) not investigated. (=) Without changes.

Table 2

	CSW	SIADH
Plasma volume	⇓	⇑ or normal
Salt balance	Negative	Variable
Water balance	Negative	⇑ or normal
Signs and symptoms of dehydration	Present	Absent
Central venous pressure	⇓	⇑ or normal
Serum Osmolality	⇓	⇓
Hematocrit [a]	⇑ or normal	Unchanged
Plasma BUN/creatinine	⇑ or normal	⇓
Urine sodium	⇑ ⇑	⇑
Urine volume	⇑ ⇑	⇓ or normal
Treatment	Normal saline	Fluid restriction
	Hypertonic saline	Hypertonic saline
	Fludrocortisone	Democycline
		Furosemide

[a] Hematocrit does not differentiate post-operatively.

essential in order to make a diagnosis [38]. Mass electrolyte balance should be evaluated daily during a period of time in order to avoid diagnostic mistakes that could lead to an inappropriate treatment.

The onset of this disorder is typically seen within the first ten days following a neurosurgical procedure or after a definable event, such as a subarachnoid haemorrhage (SAH) or stroke [39].

An exhaustive assessment of the patient must be done in order to rule out other causes that may interfere with the Na+ metabolism and renal resorption such as standard diuretics, inborn errors leading to a decreased resorption of Na+ (e.g. Bartter syndrome), renal tubular damage, adrenal insufficiency or hypothyroidism. However hypothyroidism would present with a hypoosmolar hyponatremia [40], renal sodium loss would be within the normal range and there would not be signs of dehydratation [41]. Adrenal insufficiency would present hypoosmolar hyponatremia with increased renal sodium loss, but there would be low plasma cortisol. [42]. Central diabetes insipidus which can be present in hypothalamic and pituitary disorders can be excluded only on the basis of proportional parallel increase of plasma osmolality and plasma vasopressin level [43].

According to some authors [13] hyponatremia is mostly due to the expansion of ECF which may cause natriuresis and salt wasting. There must be a deficit of Na+ exceeding 2 mmol/kg body weight to imply that ECF has been contracted.

Some diagnostic tests have been used to discriminate between SIADH and CSW. The furosemide test which consists of the infusion of 20 mg of furosemide normalises Na+ serum levels in SIADH patients, but not in CSW patients who remain hyponatremic [44]. Likewise aggravation of hyponatremia after infusion of 100 ml of 0.9% NaCl suggests SIADH and it has been proposed as another diagnostic test to differentiate CSW from SIADH when diagnosis is not clear. However, the safety and reproducibility of these tests have not been validated and should not be used. In the meanwhile, fluid restriction may be deleterious if there is an SAH or bacterial meningitis [5].

Sometimes the distinction between CSW and SIADH could be very difficult because both disorders may occur successively in the same patient [45]. Moreover critical patients are usually using multi-drug medications. In these complex cases natriuretic peptides can bring forward the diagnosis [46].

5. Treatment

Making a distinction between CSW and SIADH is of crucial importance given the divergent nature of therapy. The management of CSW begins with treatment of the underlying neurological process. CSW is characterized by the requirement of vigorous salt replacement in order to compensate renal salt wasting using either isotonic or hypertonic saline [6], while SIADH needs fluid restriction as vasopressin is the cause of a relative water excess. Both SIADH and CSW syndromes may require Na+ replacement, but most cases of hyponatremia can be managed without hypertonic saline administration [47]. When patients are capable of taking oral medications, salt tablets can be utilized.

Treatment for CSW should be performed in two parts: first, it is necessary to raise natremia to safe levels; second, it is necessary to replace the Na+ pool and volume status of the patient. Replacement should be done slowly in order to avoid further complications such as pontine myelinolysis [4,48]. A cautious approach is to raise serum sodium no faster than 0.7 mEq per litre per hour, for a maximum total daily change not to exceed 20 mEq per litre [1].

In SAH patients the neurological effects of hyponatremia mimic delayed ischemic neurological deficit from cerebral vasospasm and hyponatremic patients have three times the incidence of delayed cerebral infarction after SAH [49]. CSW often disturbs the effects of the triple-H therapy on prevention and treatment of vasospastic cerebral ischemia. A decrease in plasma volume could potentially worsen cerebral blood flow by increasing blood viscosity and decreasing cardiac output. It has been reported that attenuating CSW could prevent vasospastic cerebral ischemia after SAH [50,51]. Therefore in these patients intravenous fluids must continue to be given in accordance with the triple-H regimen which usually consists in a combination of crystalloids and colloids [52]. In patients with CSW due to other intracranial disorders a simple regimen of salt and water supplementation with crystalloids should be enough [5].

Other therapies to treat hyponatremia in neurological patients, for example vasopressin antagonists as aquaretic agents [53], have recently been suggested with promising results, although long-term studies will be needed. Fludrocortisone has been reported in isolated case reports in doses of 0.05 to 0.1 mg twice daily with effective results. It directly acts on the renal tubule to enhance sodium reabsorption. Secondary effects such as hypokalemia, pulmonary edema and hypertension may occur if prolonged use. Therefore it should be used only if salt and fluids replacement can't manage to counteract the excess of natriuresis [54].

Studies of the use of hypertonic saline in hypovolemia and brain injury are promising, but additional research is needed to determine dose and relative risks associated with these treatments.

6. Conclusions

Hyponatremia may complicate the clinical course of neurological and neurosurgical patients. Physicians working with patients with intracranial disease of any aetiology should include CSW in the differential diagnosis of hyponatremia.

7. Learning points

- In some prospective studies CSW has been found even more frequently than SIADH.
- CSW is characterized by a low plasma volume with symptoms of dehydration, decreased serum osmolality, and a large urinary excretion of Na+ and Cl−.
- Making a distinction between CSW and SIADH is of crucial importance given the divergent nature of therapy.

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