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EDITORIAL COMMENTARY

Syndrome of inappropriate antidiuresis and cerebral salt wasting syndrome: are they different and does it matter?

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Abstract The syndrome of inappropriate antidiudresis (SIAD) and cerebral salt wasting (CSW) are similar conditions with the main difference being the absence or presence of volume depletion. The two conditions may be indistinguishable at presentation, as volume status is difficult to assess, which can lead to under-diagnosis of CSW in patients with central nervous system (CNS) disease. Carefully conducted studies in patients with CNS disease have indicated that CSW may be more common than SIAD. CSW may be differentiated from SIAD based on the persistence of hypouricemia and increased fractional excretion of urate following the correction of hyponatremia. Hyponatremia should be prevented if possible and treated promptly when discovered in patients with CNS disease as even mild hyponatremia could lead to neurological deterioration. Fluid restriction should not be used for the prevention or treatment of hyponatremia in hospitalized patients with CNS disease as it could lead to volume depletion especially if CSW is present. 0.9% sodium chloride may not be sufficiently hypertonic for the prevention of hyponatremia in hospitalized patients with CNS disease and a more hypertonic fluid may be required. The preferred therapy for the treatment of hyponatremia in patients with CNS disease is 3% sodium chloride.

Keywords Cerebral salt wasting syndrome · Syndrome of inappropriate antidiureris · Hyponatremia · Saline · Sodium · Fluid therapy · SIAD · SIADH

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Introduction

In this issue of *Pediatric Nephrology*, Bettinelli et al. take on the daunting task of explaining cerebral salt wasting syndrome (CSW). The literature on this topic is confusing as there are no consistent criteria established on how to distinguish CSW from the syndrome of inappropriate antidiuresis (SIAD) [1–3]. This commentary will try to clarify the differences between SIAD and CSW, discuss the most pertinent literature that distinguishes these two conditions, and explain some of the practical aspects of the evaluation and management of children with central nervous system (CNS) disease.

Syndrome of inappropriate antidiuresis

Hyponatremia (serum sodium <135 mEq/L) is one the most frequently encountered electrolyte abnormalities in children. A common cause of hyponatremia in hospitalized children is the syndrome of inappropriate antidiuresis (SIAD). SIAD is usually associated with central nervous system disorders, pulmonary disorders, malignancies, and medications, but there are numerous other medical conditions associated with it. SIAD is a euvolemic hyponatremia that is essentially a diagnosis of exclusion. Before a diagnosis of SIAD can be made, other causes of hyponatremia must be excluded, namely volume depletion, edematous states, such as congestive heart failure, cirrhosis and nephrosis, renal dysfunction, adrenal insufficiency, and hypothyroidism [4]. Hypovolemia can be particularly difficult to rule out in hyponatremic patients as it can be subclinical, with the majority of the volume depletion corrected by free water retention, such as is seen with thiazide diuretics or Addison's disease. A key means of distinguishing SIAD from other causes of hyponatremia has been the use of serum and urine

biochemistries. SIAD is usually associated with an elevated spot urine sodium (> 20 mEq/L), elevated fractional excretion of sodium (> 0.55%), low blood urea nitrogen (BUN) and plasma uric acid, and low plasma renin activity and aldosterone, whereas the converse of these biochemistries is noted in hypo- and hypervolemic causes of hyponatremia [5].

Cerebral salt-wasting syndrome

Another hyponatremic condition that is virtually indistinguishable from SIAD is cerebral salt-wasting syndrome (CSW). CSW is a less common condition that is primarily but not exclusively associated CNS disease. Maesaka et al. have suggested that renal salt-wasting syndrome (RSW) is a more appropriate term than CSW. For the purposes of discussion we will primarily use the more familiar term, CSW, with the understanding that the term RSW with or without cerebral disease may be a more correct designation [3]. CSW would be best described as a syndrome of inappropriate natriuresis that leads to volume depletion. The pathophysiology of SIAD and CSW is fundamentally different. In SIAD the primary disorder is the inappropriate release of arginine vasopressin (AVP). AVP excess increases water permeability in the collecting duct leading to water retention and subclinical volume expansion with an increase of approximately 7–10% in total body water [6]. This volume expansion triggers hemodynamic regulatory mechanisms to maintain plasma volume at the expense of sodium, which is in part due to a pressure-natriuresis and a secondary release of natriuretic peptides [7]. In CSW there is inappropriate and excessive release of natriuretic peptides, which leads to a primary natriuresis and volume depletion with a secondary neurohormonal response with an increase in the renin–angiotensin system and in AVP production. One might suspect that the two conditions could be easily distinguished on physical examination and by different serum and urinary biochemistries, but in fact the two conditions can be nearly indistinguishable at presentation. Signs of volume depletion are not always apparent, and there are no biochemistries that have consistently been used to distinguish these two disorders at the time of presentation [3]. Natriuretic peptides are known to inhibit the renin–angiotensin system and the secretion and action of AVP, and to increase glomerular filtration rate (GFR) [8]. This complex mechanism can lead to biochemical features that are indistinguishable from those of SIAD, with a normal BUN, low uric acid and normal plasma renin, aldosterone, and AVP levels in the setting of volume depletion. To make matters even more complicated, hyponatremia is not a necessary feature of CSW. In addition, urine sodium can be less than 20 mEq/L if fluid and sodium are restricted, fluid and sodium balance can be matched when a steady state is achieved, and mild forms of CSW exist [9]. For these reasons many authors have doubted the existence of CSW and have questioned reports of CSW as they felt that there was inconclusive evidence of volume depletion or that there was an alternative explanation for the hyponatremia [10, 11]. A closer appraisal of the literature reveals that CSW does exist and is a distinct entity from SIAD.

Evidence supporting the existence of CSW as a distinct entity from SIAD

Cerebral salt-wasting syndrome is primarily seen in neurosurgical patients and in particular those with subarachnoid hemorrhage (SAH). There have been four prospective studies in adult neurosurgical patients where extracellular volume (ECV) was assessed by the gold standard method of radioisotope dilution [12–15]. In these studies over 50% of the patients had decreased ECV, supporting a diagnosis of CSW rather than SIAD. In one study by Audibert et al., the development of hyponatremia was prevented in 19 patients with SAH by the prophylactic administration of 0.9% sodium chloride, yet 53% had decreased ECV, demonstrating that CSW can be common in neurosurgical patients and that hyponatremia is not a necessary feature [15]. Similar prospective studies with ECV measurements have not been conducted in children, but retrospective studies in children with CNS disease suggest that CSW may be as common as SIAD [16].

Maesaka et al. have carefully studied CSW and have noted that this condition can occur in patients without overt CNS disease. For this reason they favor the term RSW [17]. In particular, they have described RSW in a 76-year-old woman with a hip fracture, hyponatremia, decreased ECV as measured by radioisotope dilution, and overt evidence of volume depletion [9]. They also described an 80-year-old man with pneumonia and hyponatremia who had RSW based on different biochemical responses to a saline infusion and water loading test than those seen in patients with SIAD [18]. RSW without cerebral disease has been described in a 9-year-old girl following a lightning strike, so RSW without cerebral disease does also appear to occur in children [19]. These studies and numerous similar case reports describing hyponatremic patients with a natriuresis in the presence of clinical evidence of volume depletion establish CSW as a distinct clinical entity separate from SIAD [20]. What remains to be determined is how common CSW is and how often it may be misdiagnosed as SIAD.

Assessing the relative frequency of SIAD vs CSW

It is difficult to assess the relative frequency of CSW in hyponatremic patients as the clinical features are similar to

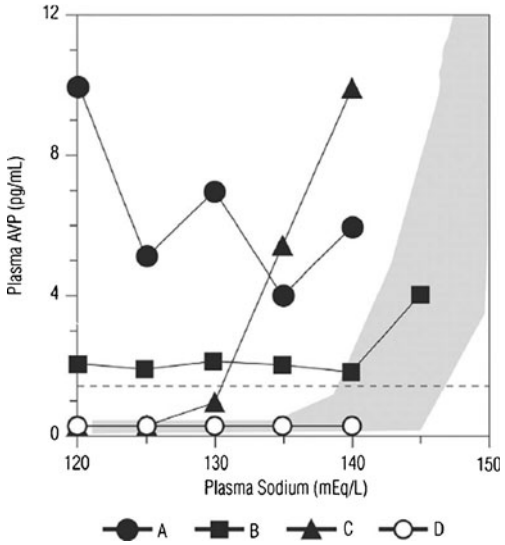

Fig. 1 Osmoregulation of plasma arginine vasopressin (AVP) in patients with the syndrome of inappropriate antidiuresis (SIAD). In type A, AVP production is erratic, constantly elevated, and not influenced by serum osmolality. In type B, AVP excretion increases in response to osmotic stimuli when serum osmolality is within the normal range, but AVP excretion cannot be maximally suppressed in the presence of hypo-osmolality. Type C is referred to as "reset osmostat". In type D AVP is undetectable. Modified from [21] and used with permission

those of SIAD and there are no readily available diagnostic tests at presentation to reliably distinguish these two conditions. SIAD is a heterogeneous condition. Robertson et al describe four distinct patterns of AVP production in SIAD (types A–D; Fig. 1), so it is possible that Robertson misclassified some cases of CSW as SIADH [21, 22]. In particular, in type B SIAD, AVP excretion increases in response to osmotic stimuli when serum osmolality is within the normal range, but AVP excretion cannot be maximally suppressed in the presence of hypo-osmolality. This pattern of AVP production is similar to what would be expected with CSW.

If CSW were to be confused with SIAD one would expect these patients to develop hypovolemia or orthostatic hypotension in response to treatment with vasopressin receptor antagonists. Vasopressin receptor antagonists are a new class of drugs for the treatment of euvolemic and hypervolemic hyponatremia and are referred to as vaptans. These drugs are contraindicated for the treatment of hypovolemic hyponatremia. The vaptans have been studied in hundreds of patients with euvolemic hyponatremia (i.e., SIAD), and they have not been associated with an increased risk of hypotension compared with placebo [23–26]. There have been three studies evaluating the use of vaptans for the treatment of hyponatremia in 69 patients in the neuro-intensive care unit, and four patients (6%) developed hypotension as a medication complication [27–29]. Therefore, it seems unlikely that stable patients with euvolemic hyponatremia are being misdiagnosed with SIAD, but a small percentage of neurocritical care patients may be.

Urate clearance to distinguish CSW from SIAD

While it is difficult to distinguish SIAD from CSW at presentation, Maesaka et al. have made the astute clinical observation that differences in urate clearance can differentiate CSW from SIAD [3, 9, 17, 18]. Beck originally noted that differences in urate clearance could distinguish SIAD from other forms of hyponatremia [30]. Patients with SIAD were noted to have hypouricemia with serum uric acids less than 4.0 mg/dL and increased urate clearance with fractional excretion of urate (FEUrate) greater than 12% (normal <10%) at the time of hyponatremia [30]. Beck further noted that following the correction of hyponatremia the hypouricemia resolved and FEUrate returned to normal at less than 10% [30]. Maesaka et al., building on this observation, noted that hypouricemia and an elevated FEUrate were also present in patients with CSW, but did not improve following the correction of hyponatremia. They therefore suggested that the normalization or failure thereof of plasma uric acid and FEUrate following the correction of hyponatremia could be used in an algorithm to distinguish SIAD from CSW respectively [17]. They applied this algorithm in two patients with RSW but with no cerebral disease, and the persistence of hypouricemia and elevated FEUrate following the correction of hyponatremia appeared to confirm the diagnosis of RSW [9, 18]. It is not fully understood why urate clearance is high in SIAD and CSW or why the clearances differ following correction of hyponatremia.

While change in urate clearance is a provocative and simple diagnostic test to distinguish SIAD from CSW, to date it has not been validated by investigators other than Maesaka et al., nor has it been applied in other case reports or series of CSW. Further studies to evaluate its usefulness in the evaluation of hyponatremia and in establishing the incidence of SIAD vs CSW would be welcomed. If validated, this test could prove to be useful, not only to distinguish SIAD from CSW, but also to make an early diagnosis of CSW in neurosurgical patients with normonatremia and hypouricemia with elevated FEUrate, as well as to assess the resolution of CSW as demonstrated by the normalization of plasma uric acid and decreasing FEUrate.

Therapeutic implications of CSW

The appreciation of CSW as a distinct clinical entity from SIAD has therapeutic implications for the fluid management of hospitalized patients with CNS disease and neurosurgical patients in particular. Hyponatremia is poorly tolerated in

patients with central nervous system (CNS) disorders, and prophylactic measures must be taken to prevent a fall in serum sodium [31, 32]. Even a small fall in serum sodium can aggravate vasogenic cerebral edema caused by a disruption in the blood–brain barrier and increase intracranial pressure (ICP) [33–35]. In children with La Crosse encephalitis, mild hyponatremia, sodium 132 mEq/L, was associated with neurological deterioration [33]. In children with brain tumors, perioperative hyponatremia, sodium <130 mEq/L, was associated with a 33% incidence of seizures and an odds ratio for seizures of 15 [35]. We have advocated the use of 0.9% sodium chloride (NaCl) to prevent the development of hospital-acquired hyponatremia, but we have been careful to point out that this may be an insufficient measure for the neurosurgical patient who may have CSW or SIAD [31, 36]. Children with CSW can have a urine sodium concentration in excess of 300 mEq/L [37], and 0.9% NaCl (154 mEq/L) would not prevent the development of hyponatremia in such a case. Patients with CNS disease are at a high risk of increased ICP and would probably be best off managed with an intravenous fluid containing a sodium concentration greater than 0.9% NaCl. In my experience, an intravenous fluid with a sodium concentration of approximately 250 mEq/L can be required to maintain a normal serum sodium in a severe case of CSW or SIAD. A fluid of this tonicity would not be expected to produce hypernatremia in a patient without SIAD or CSW in the absence of a renal concentrating defect or large extrarenal free water losses, as normally functioning kidneys can generate free water by excreting a hypertonic urine [38]. A 3% NaCl; (513 mEq/L) infusion can be titrated with a 0.9% NaCl infusion to obtain the desired sodium concentration in order to maintain serum sodium. Fluid restriction should not be attempted as a means of preventing hyponatremia as there is too great a risk of developing volume depletion [39]. CSW is a volume-depleted state and attention should be paid to the fluid balance to ensure that volume depletion does not develop.

The treatment of choice for hyponatremia in a hospitalized patient with CNS disease is 3% NaCl (513 mEq/L) [40]. This sodium concentration is sufficiently high that any patient will have an increase in serum sodium. A more hypotonic fluid such as 0.9% NaCl (154 mEq/L) or 1.5% NaCl (257 mEq/L) will not guarantee an increase in serum sodium in a patient with a severe natriuresis. Nor should fluid restriction be attempted to correct the hyponatremia as it could worsen neurological status. Wijdicks et al. [41] report a high incidence of cerebral infarction in hyponatremic adults with SAH treated with fluid restriction. Vasopressin receptor antagonists, vaptans, are a promising therapy for euvolemic hyponatremia. At this time they cannot be recommended for the routine treatment of hyponatremia in hospitalized patients with CNS disease as there is a chance that these patients could have unappreciated CSW, in which case the use of vaptans could lead to volume depletion. 3% NaCl is an extremely safe, effective and inexpensive means of correcting hyponatremia, and this should be considered the first line of therapy [42].

Vaptans may play a role, though, in the management of chronic euvolemic hyponatremia in patients with CNS disease who appear to have SIAD. To date, there have been few data on the use of vaptans in children; thus, recommendations for its use cannot be made. In a stable patient with CNS disease who appears to have CSW, oral salt supplementation with or without the addition of florinef may be effective.

Summary

The syndrome of inappropriate antidiuresis and cerebral salt-wasting syndrome are similar yet discrete clinical entities, the main distinction being the absence or presence of volume depletion. The two conditions may be indistinguishable at presentation, which can lead to under-diagnosis of CSW in patients with CNS disease. CSW has been reported in patients without cerebral disease; therefore, it may be more appropriately called RSW. A provocative way to distinguish CSW from SIAD is based on the persistence of hypouricemia and increased fractional excretion of urate following the correction of hyponatremia, but further validation studies are needed. Hyponatremia should be prevented if possible and treated promptly when discovered in a patient with CNS disease, as even mild hyponatremia can lead to neurological deterioration. Fluid restriction should not be used for the prevention or treatment of hyponatremia in hospitalized patients with CNS disease as it could lead to volume depletion if CSW is present. 0.9% sodium chloride may not be sufficiently hypertonic for the prevention of hyponatremia in hospitalized patients with CNS disease and a more hypertonic fluid may be required. The preferred therapy for the treatment of hyponatremia in patients with CNS disease is 3% sodium chloride.

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