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Key Points:

Abstract:

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Cerebral salt wasting is a real cause of hyponatremia: CON

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It has been suggested that cerebral salt wasting is an important cause of hyponatremia that must be distinguished from the syndrome of antidiuretic hormone secretion (SIADH) because failure to do so will lead to inappropriate therapy. We disagree.

Historical overview of the controversy

The term “cerebral salt wasting” (CSW) arose in the early 1950’s, before the physiology of SIADH was understood. Several patients with neurological disease were described who paradoxically (it seemed) excreted sodium in their urine despite hyponatremia. CSW nearly vanished from the literature after studies in normal volunteers showed that water retention induced by exogenous vasopressin causes a physiological natriuresis. These studies led to the seminal description of SIADH in patients with small cell lung cancer. Subsequently, meticulous balance studies in patients with neurological disease showed that inappropriate secretion of arginine vasopressin (AVP) was the cause of hyponatremia; sodium in the urine was a physiological response to water retention and not a pathological phenomenon. For the next two decades hyponatremia in patients with neurological disease was attributed to SIADH.

In 1981, Nelson and co-workers found low red blood cell (RBC) and plasma volumes in hyponatremic patients admitted to a neurosurgical service, a finding they considered inconsistent with a diagnosis of SIADH. Four years later, Wijdicks and co-workers found that treatment of hyponatremia due to subarachnoid hemorrhage with fluid restriction was associated with cerebral infarction. These observations led to a rebirth of the concept of cerebral salt wasting which was embraced by most neuro-intensivists. Maesaka and co-workers took the concept one step further, asserting that CSW is more common than SIADH even in the absence of cerebral disease
and can occur with normonatremia. By contrast, a prospective study failed to find a single case of CSW among 49 patients with hyponatremia due to subarachnoid hemorrhage.

**Appropriate and inappropriate arginine vasopressin secretion in hyponatremia**

Regardless of whether one attributes hyponatremia to CSW or to SIADH, the disturbance is caused by non-osmotic secretion of AVP. In CSW, AVP secretion is an appropriate physiologic response to volume depletion. In SIADH, AVP is secreted pathologically.

AVP secreting neurons receive two afferent inputs: a) signals from nearby osmoreceptor neurons that respond to plasma tonicity (and hence indirectly to SNa), i.e., osmotic secretion; b) signals from baroreceptors that respond to effective arterial blood volume (EAVB), i.e., non-osmotic secretion. AVP secretion is considered “appropriate” if it is inhibited by low SNa or stimulated by low EABV. In a patient with hyponatremia and decreased EABV, inhibitory signals from osmoreceptors are overridden by stimulatory signals from baroreceptors; AVP is secreted even when SNa is low. If reduced EABV is corrected, inhibitory signals from osmoreceptors prevail and AVP secretion ceases.

AVP levels cannot be used clinically because reliable measurements of the hormone are only possible in research laboratories. Clinicians must rely on urine osmolality (UOsm) which reflects AVP levels. If AVP is appropriately suppressed by hyponatremia and euvoelema, the urine should become maximally dilute, with a UOsm <100 mOsm/kg, and often as low as 50 mOsm/kg. In a patient with hyponatremia, a UOsm >100 mOsm/kg indicates that AVP is probably playing a role.
**Sodium excretion in hyponatremia**

Sodium excretion normally responds to EABV – a function of the extracellular fluid volume, cardiac output and vascular tone. An expanded EABV increases sodium excretion regardless of SNa; contracted EABV decreases sodium excretion.

In hyponatremia caused by SIADH, AVP secretion without a physiologically appropriate osmotic or hemodynamic stimulus is the primary defect and persists despite additional volume expansion; sodium losses are secondary and cease after correction of hyponatremia with water restriction. In hyponatremia caused by CSW, sodium losses are the primary defect; AVP secretion is caused by hypovolemia and should cease after volume expansion.

**What would constitute convincing evidence of hyponatremia due to CSW?**

Proof that hyponatremia is caused by appropriate secretion of AVP due to hypovolemia requires evidence that AVP can be suppressed by volume repletion. Patients with hypovolemic hyponatremia (due to salt losses outside the kidneys, previous use of diuretics, or true kidney salt wasting caused by cisplatin or Addison disease) respond within minutes to volume repletion (and cortisol replacement if needed) with excretion of maximally dilute urine (UOsm <100 mOsm/kg) and rapid correction of hyponatremia. However, excretion of dilute urine is also seen after transient SIADH (e.g., surgery, pneumonia, nausea, or medication) resolves. To distinguish between CSW and transient SIADH, evidence of persisting salt wasting is required: volume repletion should eliminate clinical signs of hypovolemia, lower the hematocrit, and provoke excretion of maximally dilute urine; then, when isotonic saline is stopped, hyponatremia should
recur, with concentrated urine, a high rate of sodium excretion, weight loss, a rising hematocrit, and clinical signs of hypovolemia.

The extensive growing literature on CSW does not provide such convincing evidence; rather it rests on several lines of evidence that we consider both flawed and unconvincing (Table 1).

**Unconvincing data supporting the diagnosis of CSW**

**Blood and Plasma Volume**

Low blood and plasma volumes have been called the “gold standard” for the diagnosis of CSW. However, the standard is tarnished. Contraction of plasma volume should raise the hematocrit. Low hematocrit values and reduced RBC mass, more consistent with bleeding, have been reported in patients said to have CSW. Decreased plasma volume should not be equated with low EABV. Plasma volume resides primarily in venous capacitance vessels; splanchnic veins have a large population of adrenergic receptors. An adrenergic surge after a cerebral insult will decrease plasma volume while increasing EABV (Figure 1). Even several days of bed rest will measurably decrease plasma volume.

**Central venous pressure**

A central venous pressure (CVP) \( \leq 5 \text{ cm H}_2\text{O} \) is often cited as a criterion for the diagnosis of CSW. CVP, the pressure of blood in the thoracic vena cava near the right atrium,
is used as a surrogate for intravascular volume. Normal CVP values range between 0 and 8 cmH$_2$O (or 0 to 6 mmHg).\textsuperscript{14} Thus a low value is not diagnostic of hypovolemia since it may be normal. A systematic review demonstrated a very poor relationship between CVP and blood volume and the reliability of CVP for predicting fluid responsiveness is no better than flipping a coin.\textsuperscript{15}

**Response to saline**

UOsm less than plasma osmolality or rising SNa during saline infusion are invalid diagnostic criteria for CSW. Either can be found in patients with unequivocal SIADH\textsuperscript{2,3,16} Hypertonic saline diminishes but does not completely suppress vasopressin secretion (as reflected by plasma copeptin) in some patients with SIADH.\textsuperscript{9} Definitive evidence of CSW requires a UOsm <100 mOsm/kg after volume repletion. Furthermore, continued isotonic saline infusion in patients with intracranial pathology with inappropriate AVP secretion can result in volume expansion and excretion of hypertonic urine leading to decrease in SNa\textsuperscript{12}, a pseudo-CSW pattern (Figure 1).

**Fractional excretion of uric acid**

Fractional excretion of uric acid (FEurate) >11% after correction of hyponatremia is said to reflect sodium wasting by the proximal tubule.\textsuperscript{6} The argument is based on two dubious assertions: a) FEurate is often > 11% in SIADH, but always falls below 11% once hyponatremia is corrected; b) volume expansion with saline does not provoke FEurate >11%.
In 1979, Beck reported that hypouricemia can help distinguish SIADH from other causes of hyponatremia.\textsuperscript{17} Measurements of FEurate in three patients with SIADH yielded values between 11.1 and 20.3\% before treatment and 4.7 to 7.7\% after treatment with water restriction. Data confirming the observation are sparse. FEurate often exceeds 12\% after treatment of SIADH with water restriction in elderly patients (whose FEurate is increased because of reduced glomerular filtration rates).\textsuperscript{18} More importantly, a fall in FEurate after water restriction does not mean FEurate will fall after treatment with saline. Patients with SIADH are total body sodium depleted (making them clinically euvoletic despite excess body water); with water restriction, urine sodium excretion falls to low levels reflecting a transient decrease in EABV until sodium deficits are replaced. Therefore, since uric acid clearance is volume-sensitive, a fall in FEurate would be expected after water restriction; the response to saline is unknown. It has been asserted that volume expansion with saline does not raise FEurate above 12.1\%.\textsuperscript{6} However, in the cited study, short-term administration of hypertonic saline to normal volunteers increased FEurate to a mean value of 12.1\%; FEurate was >18\% in several individual subjects. In another study, peak FEurate after short-term infusion of 2.5\% saline averaged 18.7\%.\textsuperscript{20} The response of FEurate to prolonged volume expansion is unknown.

Presence of natriuretic factors

A proximally acting natriuretic factor has been described in patients with cerebral disease.\textsuperscript{6} However, its presence is not proof of CSW because such a factor could be released in response to volume expansion.
Distinction between CSW and SIADH is unnecessary

If CSW exists, its treatment need not differ from the treatment of SIADH. All patients with intracranial pathology (e.g., tumor, recent ischemic or hemorrhagic stroke, trauma, and surgery) who develop symptomatic hyponatremia should be treated with hypertonic saline, the risk of herniation in such patients is too great to do otherwise. Because of adaptive urinary sodium losses, most patients with SIADH are sodium depleted, which is why they appear euvolemic; salt is needed during correction. SIADH can coexist with volume depletion due to gastrointestinal losses and must be treated with volume repletion.

Conclusion

Although rare cases may occur, assertions that CSW is a common cause of hyponatremia do not stand scrutiny. Because treatment of both conditions is similar, differentiation between SIADH and CSW is unnecessary.
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<th>Criteria</th>
<th>Limitations</th>
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<tr>
<td>1. Physical exam findings of hypovolemia</td>
<td>Poor sensitivity and specificity.</td>
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<tr>
<td>2. Reduced RBC mass</td>
<td>CSW should leave RBC mass constant and increase the hematocrit.</td>
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<tr>
<td>3. Reduced plasma volume</td>
<td>Sympathetically mediated vеноconstriction can reduce plasma volume without decreasing effective arterial blood volume.</td>
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<td>4. CVP ≤ 5 cmH₂O</td>
<td>Normal CVP values are between 0 and 8 cmH₂O and are an inaccurate measure of volume status.</td>
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<td>5. Negative sodium balance</td>
<td>Patients with SIADH also develop natriuresis and negative sodium balance to compensate for initial water retention.</td>
</tr>
<tr>
<td>6. SNa increases in response to saline</td>
<td>Isotonic saline may increase SNa in patients with SIADH whose UOsm is &lt;500 mOsm/kgH₂O.</td>
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<tr>
<td>7. UOsm falls below SOsm in response to saline</td>
<td>UOsm should fall to ≤ 100 mOsm/kgH₂O in response to saline if hypovolemia is the cause of hyponatremia.</td>
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<tr>
<td>8. FEurate &gt; 11% after correction of hyponatremia</td>
<td>Volume expansion with saline can provoke FEurate &gt;11%; FEurate is often &gt;11% in elderly patients because of decreased GFR.</td>
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<tr>
<td>9. Present of natriuretic factors</td>
<td>Natriuretic factors can be released in response to volume expansion.</td>
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RBC = red blood cell, CSW = cerebral salt wasting, CVP = central venous pressure, SIADH = syndrome of inappropriate antidiuretic hormone secretion, SNa = serum sodium, UOsm = urine osmolality, SOsm = serum osmolality, FEurate = fractional excretion of uric acid, GFR = glomerular filtration rate
Figure 1. Pseudo - Cerebral Salt Wasting

Subarachnoid hemorrhage results in sympathetically mediated vasoconstriction and inappropriate secretion of arginine vasopressin (AVP). A shift of blood from venous capacitance vessels reduces plasma volume (PV) while expanding effective arterial blood volume (EABV). Infusion of 0.9% saline further expands EABV. Inappropriately secreted AVP concentrates the urine while an expanded EABV promotes sodium excretion, which can be misinterpreted as cerebral salt wasting (CSW). Excretion of hypertonic urine desalinates infused isotonic saline, generating electrolyte-free water and lowering the serum sodium (SNa). ↓ = Decreased, ↑ = Increased
Figure 1

Inappropriate AVP Secretion
Venoconstriction

Baseline

Normal SNa
Normal PV
Normal EABV

NaCl 0.9%

Inappropriate AVP Secretion

Normal SNa
↓PV
↑EABV

Excretion of Hypertonic Urine

Inappropriate AVP Secretion

NaCl 0.9%

Electrolyte-Free Water

↓SNa
↓PV
Normal EABV

Pseudo-CSW