

Cerebral Salt Wasting Versus SIADH: What Difference?

Richard H. Sterns and Stephen M. Silver

Rochester General Hospital, Rochester, University of Rochester School of Medicine and Dentistry, Rochester, New York

ABSTRACT

The term *cerebral salt wasting* (CSW) was introduced before the syndrome of inappropriate antidiuretic hormone secretion was described in 1957. Subsequently, CSW virtually vanished, only to reappear a quarter century later in the neurosurgical literature. A valid diagnosis of CSW requires evidence of inappropriate urinary salt losses and reduced "effective arterial blood volume." With no gold standard, the reported measures of volume depletion do not stand scrutiny. We cannot tell the difference between CSW and the syndrome of inappropriate antidiuretic hormone secretion. Furthermore, the distinction does not make a difference; regardless of volume status, hyponatremia complicating intracranial disease should be treated with hypertonic saline.

J Am Soc Nephrol 19: 194–196, 2008. doi: 10.1681/ASN.2007101118

Last year, a visitor from Addis Ababa, Ethiopia, was admitted to our hospital with tuberculous meningitis, hyponatremia, atrial flutter, hypotension, and a hematocrit of 64%. Hemoconcentration and a urine sodium of 196 mmol/L, obtained after saline, suggested renal salt wasting. Once Addison disease was excluded, we wondered whether the patient had cerebral salt wasting (CSW). After cardioversion, and without additional saline, his weight stabilized and blood pressure (BP) normalized without orthostatic change. Blood urea nitrogen (BUN) and uric acid remained low, urine sodium fell to 71 mmol/L, and urine osmolality was 473 mOsm/kg despite persistent hyponatremia. His hematocrit settled in the mid-50s. A medical student of Ethiopian heritage reminded us that residents of Addis Ababa have high hematocrits because of the altitude. While wondering what to call his disease, we turned our attention to therapy. Because of neurologic symptoms with refractory hyponatremia and a persis-

tently high urine osmolality, we gave him hypertonic saline.

We had trouble telling the difference between CSW and the syndrome of inappropriate antidiuretic hormone secretion (SIADH), and the distinction did not alter our approach to his management. Was our experience typical? Is there a difference between CSW and SIADH? And if so, what difference does it make? The ambiguity of our case is rather typical of most of the literature on the subject of CSW. A historical overview may help us better understand why we ask, is this CSW or SIADH?

Shortly after World War II, the availability of the flame photometer made clinical determinations of the serum sodium concentration possible. Yale was one of the first medical centers to have the new device, and some of the first published observations about hyponatremia came from Yale. The role that salt depletion played in the etiology of hyponatremia was well known to clinicians of

that era (Donald Seldin, personal telephone communication, October 2007). In 1936, McCance defined the consequences of salt depletion in normal man.¹ Patients with extrarenal salt losses complicated by hyponatremia were found to be commonplace, and consistent with McCance's description, they excreted urine virtually free of sodium.

In 1950, Peters *et al.*² reported three patients seen at Yale New Haven Hospital with hyponatremia and diseases of the central nervous system. In each patient, urine sodium losses persisted despite hyponatremia and a high-salt diet. Although two of the patients were severely hypertensive, they were described as exhibiting "clinical signs of dehydration." Two years later, Cort³ described another similar patient seen at Yale, and he named the syndrome CSW. On a severely sodium-restricted diet, his patient continued to excrete sodium in her urine; however, despite negative sodium balance, she remained normotensive.^{3,4}

In 1953, Leaf *et al.*⁵ demonstrated that exogenous administration of the antidiuretic hormone vasopressin resulted in hyponatremia and a natriuresis dependent on water retention and weight gain. This was not "salt wasting"; it was a physiologic response to an expanded intra-

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Richard H. Sterns, 1425 Portland Avenue, Rochester, NY 14621. Phone: 585-922-4242; Fax: 585-922-4440; E-mail: Richard.Sterns@viahealth.org

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vascular volume. Four years later, Schwartz *et al.*⁶ published their landmark paper on SIADH. A subsequent paper from the group at Yale attributed hyponatremia in neurologic disease to SIADH.⁷ For over 20 yr, the term CSW virtually vanished from the literature.

In 1981, Nelson *et al.*⁸ studied hyponatremia in neurosurgical patients, primarily subarachnoid hemorrhage, and found that isotopically measured blood volumes were contracted; he attributed this finding to CSW. Other authors associated hyponatremia in subarachnoid hemorrhage with increased levels of natriuretic peptides, negative sodium balance,^{9,10} and low central venous pressure.¹¹ A MEDLINE search between 1981 and the present, using the keyword CSW, yielded 119 articles, with only 3 articles before that. CSW is back in fashion.

A valid diagnosis of “salt wasting” requires evidence of inappropriate urinary salt losses and a reduced “effective arterial blood volume.” Unfortunately, there is no gold standard to define inappropriate urinary sodium excretion. “Effective arterial blood volume” is a concept, not a measurable variable; in fact, we often define it clinically by looking at urine sodium excretion.¹²

The literature on CSW relies on several criteria for volume depletion: direct determinations of blood and plasma volume, negative sodium balance, clinical impressions, plasma levels of arginine vasopressin and natriuretic peptides, and responses to therapy.^{4,13–15} None of these measures is up to the task.

Some reports of CSW have used a low red cell mass to define hypovolemia. However, salt wasting should leave red cell mass constant, lowering plasma volume and raising the hematocrit. Plasma volume measurements are at least directed at the correct variable, but they cannot answer the question either. Most of the plasma volume resides in venous capacitance vessels. Sympathetically mediated venoconstriction can reduce plasma volume without causing true hypovolemia.⁴ Negative fluid balance should cause hemoconcentration. Surprisingly, the hematocrit is rarely reported in cases of purported CSW.¹⁴

The diagnosis of CSW is often based on negative sodium balance. However, patients with SIADH also develop negative sodium balance.^{5,6,16–18} Sodium lost in response to water retention or to catecholamine-induced vasoconstriction and hypertension is a physiologic natriuresis rather than “salt wasting.”⁴ Balance studies should include data from the first contact with medical or paramedical personnel; one such analysis showed that over 90% of patients with subarachnoid hemorrhage were in positive sodium balance on their arrival to the intensive care unit and subsequent “negative sodium balance,” therefore an appropriate physiologic response to a surfeit of sodium.⁴ Patients with subarachnoid hemorrhage are treated with extremely large volumes of isotonic saline to maintain cerebral perfusion. Decreasing the infusion rate could lead to a brief “overshoot” natriuresis because of adaptive internalization of the components of sodium reabsorption in the proximal tubule in response to sustained volume expansion.^{4,19}

Like the Peters *et al.*² first report of the syndrome, many articles on CSW rely on clinical impressions of volume depletion. Nephrologists know what a difficult determination this can be. Few published reports detail the clinical findings supporting a diagnosis of hypovolemia. BP values are rarely included. Central venous pressure measurements have become the gold standard in the neurosurgical literature; a central venous pressure less than 5 cm H₂O is said to be inconsistent with SIADH and diagnostic of CSW.¹¹ However, the central venous pressure is rarely measured in SIADH without neurologic disease, and the central venous pressure has been shown to be a poor marker of cardiac filling pressure.²⁰

Plasma levels of arginine vasopressin and natriuretic peptides offer little help. Both CSW and SIADH are associated with the nonosmotic release of vasopressin. In SIADH, natriuretic peptide levels increase in response to overfilling of the arterial circulation with water,²¹ a response indistinguishable from secretion provoked by cere-

bral injury. So-called brain natriuretic peptide is usually of cardiac origin; jugular venous sampling in suspected CSW did not support cerebral release of the peptide.²²

In many reports of CSW, correction of hyponatremia with salt is cited as evidence of sodium depletion. However, any maneuver increasing the ratio of body electrolyte to body water corrects hyponatremia, regardless of the cause. What is missing is the demonstration that volume expansion provoked a water diuresis (reflecting the loss of a volume stimulus for vasopressin). On the contrary, patients with purported CSW continue to excrete concentrated urine despite large volumes of isotonic saline. A prospective study of patients with subarachnoid hemorrhage showed that isotonic saline prevented volume contraction but did not prevent hyponatremia.²³

Traditional markers of volume depletion are not helpful. Renin and aldosterone levels are typically suppressed, but these findings have been ascribed to a reduction in sympathetic tone and/or suppressed secretion by natriuretic peptides.²⁴ Therefore, low levels of these hormones are said to be the cause of salt wasting rather than the response to volume expansion. Uric acid levels are low in both SIADH and CSW.¹⁵ In SIADH, a low serum uric acid level is ascribed to volume expansion. In CSW, the same finding is ascribed to impaired sodium reabsorption by the proximal tubule. One group has proposed that the response of uric acid clearance to correction of hyponatremia be used as a diagnostic test,^{15,25} but without a gold standard to define volume depletion, we have difficulty accepting this surrogate marker.

Our neurosurgical colleagues are likely to continue to ascribe hyponatremia to CSW. Neurointensivists routinely infuse large volumes of saline to their patients, and for good reason. Vasospasm and cerebral infarction are serious concerns in subarachnoid hemorrhage; hyponatremia, with its attendant cerebral edema, increases the risk of this complication.²⁶ Because isotonic saline neither prevents

nor cures hyponatremia, infusion of hypertonic saline has become routine.²⁷

Nephrologists may be more comfortable with a diagnosis of SIADH. But how should we treat SIADH associated with intracerebral pathology? We believe that any degree of hyponatremia in a patient with an intracranial mass lesion or hemorrhage, head trauma, recent stroke, or brain surgery should mandate treatment with hypertonic saline. The risk of neurologic deterioration or herniation in such patients is too great, water restriction is too slow, and isotonic saline can worsen hyponatremia in SIADH.²⁸

Is there a difference between CSW and SIADH? We doubt that one can be proven. And if they are different, what difference does it make? Probably none; the treatment is the same: salt. Because both neurosurgeons and nephrologists agree with this approach, perhaps “cerebral salt wanting syndrome” is the name that fits best.

DISCLOSURES

None.

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