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Cerebral salt wasting is a real cause of hyponatremia: PRO

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Introduction

The first documentation of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) epitomized the power of deductive reasoning in unraveling the intricate clinical manifestations of a hyponatremic patient that were identical to the studies on the metabolic effects of daily injections of pitressin to normal healthy subjects. (1, 2) They concluded that ADH levels were inappropriately high because ADH did not respond to the usual volume or osmolar stimuli at a time when ADH levels could not be determined. They eliminated hypovolemia as a cause of increased levels of ADH by demonstrating an increase in extracellular sulfate space. (1) As a result, SIADH rightfully captured the admiration of clinicians and basic scientists and SIADH is perceived to be the most common cause of hyponatremia.

The first reports of cerebral salt wasting (CSW) did not receive the same enthusiastic response because they unconvincingly utilized changes in non-protein nitrogen or BUN, undocumented low blood pressure measurements and correction of hyponatremia by large intake of sodium. (3) We hope to evaluate the data that have been utilized to create the controversy over the existence and relative prevalences of SIADH and CSW by assessing the credibility of the data that led to divergent conclusions.

Volume approach to hyponatremia

The longstanding volume approach of being euvolemic, hypervolemic or hypovolemic has been the format to identify the different causes of hyponatremia despite the universal agreement that we cannot determine the volume status of patients by usual clinical criteria. Why are we continuing to utilize this approach with low credibility?

Important clinical parameters that are identical for SIADH and CSW

SIADH has been defined by the following criteria: hypo-osmolality of plasma (hyponatremia), clinical euvoolemia, normal renal and thyroid function with absence of hypocorticism, inappropriate urine concentration with urine osmolality (Uosm) > 100 mOsm/kg for the level of hypo-osmolality and elevated sodium excretion on usual sodium and water intake, with the supplemental addition of an abnormal water loading test, plasma ADH inappropriately increased relative to plasma osmolality and no significant correction of serum sodium with volume expansion but improvement after fluid restriction. (4) Unfortunately, patients with CSW present with identical clinical characteristics except for being hypovolemic and having appropriately increased ADH levels. Determining blood volume is the most credible means to diagnose SIADH and CSW. Because blood volumes are not quantified with any regularity, it is imperative to develop reliable methods to differentiate SIADH from CSW because of divergent therapeutic goals, to water-restrict waterlogged patients with SIADH or administer salt and water to dehydrated patients with CSW.

CSW considered rare despite credible evidence of being common

Why are we concerned about deciding whether to water-restrict or administer saline to hyponatremic patients when CSW is considered to be rare in textbooks and review articles in medicine? However, 3 studies in neurosurgical patients revealed blood volume to be reduced in 67-94 % as in CSW and increased in 6 - 33 % as in SIADH as determined by the highly credible gold standard radioisotope dilution methods, Table 1. (5-7) We have cited these studies for many years and appreciated the need to differentiate SIADH from a commonly occurring CSW.

A new and superior physiological approach – Fractional excretion (FE) of urate

There are sufficient credible data to utilize FEurate to identify many important causes of hyponatremia, especially to differentiate SIADH from CSW and simplify identification of patients with a reset osmostat, psychogenic polydipsia, pre-renal azotemia and Addison's disease. (8) FEurate will not differentiate SIADH from CSW on first encounter with the patient because it is increased to $> 11\%$ in both conditions when they are hyponatremic.

Differentiation can only occur when FEurate normalizes to $< 11\%$ in SIADH or is persistently increased at $> 11\%$ after correction of hyponatremia by water-restriction, isotonic or hypertonic saline, figure 1a. (8)

Response to isotonic saline infusions

We determined blood volume by radioisotope dilution methods to prove unequivocally the diagnosis in 1 CSW and 2 SIADH patients and investigated their response to isotonic saline infusions. (9, 10) We utilized the physiologic precept that the volume stimulus to ADH secretion is more potent than the osmolar stimulus. (11) Therefore, a volume-depleted patient will continue to have appropriately increased levels of ADH and hyponatremia as long as they are volume depleted. The infusion of isotonic saline in a hip fracture patient without evidence of cerebral disease, low blood volume and increased baseline renin, aldosterone and ADH levels diluted her urine with undetectable plasma ADH 13 hours after infusion of isotonic saline and correction of hyponatremia within 48 hours, figure 1b. (10) Isotonic saline eliminated the more potent volume stimulus for ADH secretion to allow the coexisting hypo-osmolar plasma to inhibit ADH secretion, induced excretion of dilute urines and corrected the hyponatremia. (10)

We infused isotonic saline to two patients with increased blood volumes, decreased renin, and aldosterone levels at baseline to prove unequivocally the diagnosis of SIADH. Both failed to dilute their urines or correct their hyponatremia, figure 1c. (9) These data in SIADH are consistent with a comment made by Bartter et al in 1967 "A striking and consistent finding in patients with SIADH is the persistence of hyponatremia even when large quantities of sodium are administered". (12) All 3 patients had increased FEurate when hyponatremic and the patient with CSW had persistently increased FEurate after correction of hyponatremia. (9, 10) The inclusion of blood volume in these patients eliminated any question about the credibility of our conclusions.

High prevalence of CSW on general medical wards

We utilized FEurate and response to isotonic saline infusion in 62 hyponatremic patients from the general medical wards of the hospital. (13) Seventeen patients (27%) had SIADH as determined by normalization of FEurate after correction of hyponatremia in 8 while 11 of them failed to dilute their urines with isotonic saline infusions. Twenty-four patients (38%) had CSW with 11 patients having persistently elevated FEurate after correction of hyponatremia. Isotonic saline infusion induced excretion of dilute urines in 19 of them. Ten patients required infusions of 5% dextrose in water to prevent rapid correction of hyponatremia and osmotic demyelination. Twenty-one did not have evidence of cerebral disease to support our proposal to change cerebral to renal salt wasting. Nineteen patients (31%) had a reset osmostat with normal FEurate. (13) One patient had Addison's disease and another was on hydrochlorothiazide. These studies provide physiologically credible data to demonstrate the unexpectedly high prevalence of CSW. Although these studies were extremely difficult to

perform, they served to expose the high prevalence of CSW and the need to differentiate SIADH from CSW because of divergent therapeutic goals.

Identification of natriuretic protein that causes CSW

We demonstrated natriuretic activity in the plasma of 21 neurosurgical and 18 Alzheimer's disease (AD) patients in 1993. (14, 15) Technological advancements in protein analysis facilitated recent identification of the natriuretic protein as haptoglobin related protein without signal peptide (HPRWSP) in a salt wasting patient with a subarachnoid hemorrhage (SAH) and another with AD. (16) This peptide increased fractional excretion of lithium from a control of 24.4 % to 46.1 % as compared to the fractional excretion of sodium, which increased from 0.02% to only 1.7%, respectively. Since lithium is transported on a one to one basis with sodium almost exclusively in the proximal tubule, it appears that the proximal tubule is most affected in CSW. (17) This protein has satisfied our long search for a potent proximal diuretic. (14-16) Future studies intend to develop the protein as a biomarker for CSW to resolve the diagnostic and therapeutic dilemma in addition to introducing a new syndrome of salt wasting in AD among other clinical applications.

Controversy over existence/prevalence of CSW

There may be a general acceptance of the existence of CSW, but its prevalence has not been addressed by many and questioned in the literature by only one investigator. (18, 19) Among the many disagreements with both publications, we will address the most pertinent flaws that weakened the conclusion that CSW is a rare disease. (18,19) As noted in Table 1 from reference 18, the proposed rarity of CSW in the retrospective and flawed prospective studies by the same

group was favored over the 3 neurosurgical studies where blood volume studies showed CSW to be very common, table 1. (5-7) The credibility of the retrospective study was diminished by concluding that 4.8% of patients had the incongruous combination of CSW and SIADH in the same patient without explaining how they arrived at such an unlikely diagnosis. (20) The prospective study by the same group studied 49 hyponatremic patients with SAH. (20) The diagnosis of SIADH was made by satisfying the definition of SIADH without going through the rigors of differentiating SIADH from CSW. (20) Moreover, they infused isotonic saline at rates of 125-250 ml/hour without being water-restricted, receiving hypertonic saline or the V2 ADH receptor inhibitor, tolvaptan. Isotonic saline corrected the hyponatremia in all 49 patients at a median of 3 days, which as noted above, does not correct in SIADH but does correct in CSW, figures 1b and 1c. (12, 13, 21) The correct conclusion is that all 49 hyponatremic SAH patients had CSW because isotonic saline corrected their hyponatremia. (9,11,13,21) Thus, it is incorrect to agree that the hyponatremia in SIADH can be corrected by isotonic saline infusions alone while claiming in their definition of SIADH that volume expansion does not correct the hyponatremia and presenting an SIADH patient who was misdiagnosed as having CSW when the hyponatremia corrected with water restriction but not by isotonic saline. (4, 18, 19) The status of the prevalence of CSW appears to have credible physiologically derived data to suggest it is a common disorder but needs to be tested further in the future. (13) It would be interesting to utilize HPRWSP as a reliable biomarker of CSW on first encounter with the patient and improve clinical outcomes by administering the proper therapy to patients with SIADH or CSW.

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Table 1: Modified table 1 from reference 18 showing differences in prevalence of CSW in neurosurgical patients with blood volume determinations as compared to retrospective and prospective studies in SAH

	Blood volume	
	CSW/Total	CSW %
Nelson	10/12	81
Wijdicks	6/9	67
Sivakumar	17/18	94
	Retrospective studies	
Sherlock	4/62	6.5
Gao	11/49	22.9
	Prospective study	
Hannon	0/49	0

Figure Legends

Figure 1a. Figure showing relationship between serum sodium and fractional excretion (FE) of urate in SIADH and CSW. Shaded areas represent normal values. Note increased FEurate with hyponatremia in both SIADH and CSW, normalization of FEurate after correction of hyponatremia in SIADH and persistently increased FEurate after correction of hyponatremia in CSW.

Figure 1b. Figure showing excretion of dilute urines 13 hours after initiation of isotonic saline infusions at a time when increased levels of ADH at baseline were now undetectable. Also, note correction of hyponatremia within 48 hours after initiation of isotonic saline infusion whose diagnosis of CSW was confirmed by a decreased blood volume Reference 10.

Figure 1c. Figure showing response of serum sodium and urine osmolality during isotonic saline infusions over time. Note failure of urine osmolality to be in dilute ranges and failure of hyponatremia to correct in a patient who had an increase in blood volume, which is a common observation in SIADH, suggesting that it is incorrect to state that SIADH patients are euvolemic. Identical results were found in a second SIADH patient with increased blood volume determinations. Reference 9.

Figure

Figure 1a: Relationship between FEurate and serum Na (SNa) in SIADH and CSW

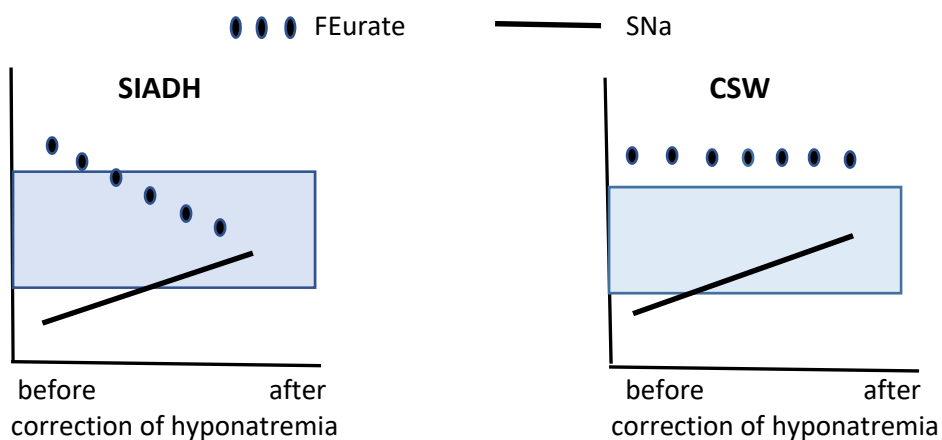
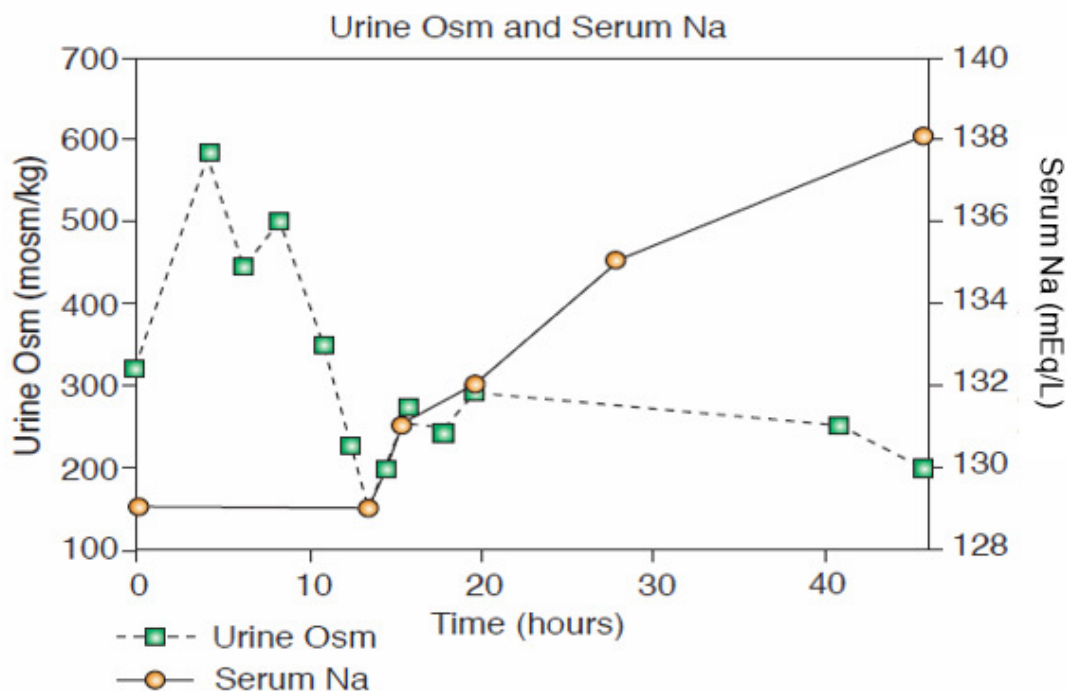


Figure 1b: Effect of isotonic saline infusion in hyponatremic patient with hip fracture with low blood volume



Figure

Figure 1c: Effect of isotonic saline infusions in SIADH patient with increased blood volume

