How to Cite this article: Biff Palmer and Deborah Clegg, Cerebral salt wasting is a real cause of hyponatremia: Commentary, Kidney360, Publish Ahead of Print, 2022, 10.34067/KID.0001452022

Article Type: Moderator Commentary

Cerebral salt wasting is a real cause of hyponatremia: Commentary

DOI: 10.34067/KID.0001452022

Biff Palmer and Deborah Clegg

Key Points:

Abstract:

Disclosures: The authors have nothing to disclose.

Funding:

Author Contributions: Biff Palmer: Writing - review and editing Deborah Clegg: Writing - review and editing

Data Sharing Statement:

Clinical Trials Registration:

Registration Number:

Registration Date:

The information on this cover page is based on the most recent submission data from the authors. It may vary from the final published article. Any fields remaining blank are not applicable for this manuscript.
Cerebral salt wasting is a real cause of hyponatremia: Commentary

Biff F. Palmer\textsuperscript{1} and Deborah J. Clegg\textsuperscript{2}

\textsuperscript{1}Professor of Internal Medicine, Department of Medicine, Division of Nephrology, University of Texas Southwestern Medical Center
\textsuperscript{2}Professor of Internal Medicine, Vice President for Research, Texas Tech Health Sciences Center, El Paso, Texas

Address all correspondence to:
Biff F. Palmer, M.D.
Professor of Internal Medicine
Department of Internal Medicine
University of Texas Southwestern Medical Center
5323 Harry Hines Blvd.
Dallas, Texas 75390
214-648-7848 (w)
214-648-2071 (fax)
biff.palmer@utsouthwestern.edu
The syndrome of inappropriate antidiuretic hormone (SIADH) secretion and cerebral salt wasting (CSW) are causes of hyponatremia in patients with disorders of the central nervous system. The concept of a CSW syndrome was first introduced in a series of reports in the early 1950’s describing patients who presented with hyponatremia, clinical evidence of volume depletion, and kidney sodium wasting in the setting of various forms of cerebral disease (1-3). It was theorized the syndrome resulted from cerebral disease disrupting neural input into the kidney causing salt wastage and ultimately depletion of extracellular fluid volume. With the subsequent description of SIADH in 1957, CSW became viewed as either an extremely rare disorder or a misnomer for what was truly SIADH and the term largely disappeared from the literature for almost 20 years (4). The resurgence of CSW as a clinical entity began in the early 1980’s with reports of patients developing hyponatremia following neurosurgical procedures or in association with subarachnoid hemorrhage or stroke (5-7). Despite meeting the clinical criteria for SIADH, these patients were found to be in negative salt balance and had reductions in both plasma and blood volume, findings more consistent with CSW. This rediscovery of CSW as a distinct entity persists today as evidenced by a continuous stream of published case reports in diverse neurologic diseases such as carcinomatous or infectious meningitis, encephalitis, poliomyelitis, central nervous system tumors, and following CNS surgery. CSW is viewed as particularly common in patients with subarachnoid hemorrhage.

Distinguishing between these two entities can be challenging because there is considerable overlap in the clinical presentation. Both conditions present with hyponatremia with a low plasma osmolality, an inappropriately elevated urine osmolality
(>100 mOsm/Kg and usually >300 mOsm/Kg), a urine sodium concentration usually >40 mEq/L, and a low serum uric acid concentration due to urate wasting in the urine. The critical distinction lies in the assessment of the effective arterial blood volume (EABV) (8). SIADH is a volume-expanded state because of antidiuretic hormone-mediated kidney water retention. CSW is characterized by a contracted EABV resulting from kidney salt wasting. The overlap in clinical and laboratory findings along with the difficulty in accurately assessing effective arterial blood volume has contributed to the controversy as to whether CSW is a real cause of hyponatremia and is the subject of this debate.

Sterns and Rondon-Berrios set a high bar for proof of CSW. They require the rapid development of a maximally dilute urine following volume repletion with isotonic saline reflecting removal of the hypovolemic stimulus to vasopressin release. Discontinuation of fluids should then lead to redevelopment of hyponatremia accompanied by a urine that is concentrated with a high rate of sodium excretion and clinical evidence of volume depletion such as weight loss and hemoconcentration. They suggest a pseudo-CSW syndrome can occur in patients with intracranial pathology who are treated with salt containing intravenous fluids. Consider a patient with subarachnoid hemorrhage who is typically given large volumes of isotonic saline to prevent cerebral vasospasm. At the same time, sympathetically mediated vasoconstriction shifts fluid into the central circulation. A high rate of sodium excretion would be an appropriate physiologic response in this scenario and not an indicator of salt wasting. Combined with excretion of hypertonic urine due to inappropriate antidiuretic hormone secretion, CSW might be erroneously diagnosed based on development of hyponatremia, increased urine sodium excretion, and reduced plasma volume.
Maesaka and Imbriano argue CSW is a real cause of hyponatremia and acknowledge the critical importance of volume status in distinguishing this disorder from SIADH. They propose an algorithm based on fractional excretion of urate and response to isotonic saline to lessen the reliance on more traditional clinical and laboratory tools used to assess volume status. Infusion of isotonic saline results in urinary dilution and correction of hyponatremia in patients with CSW whereas no effect is seen in SIADH. The fractional excretion of urate is >11% in both groups when hyponatremic. However, following correction of the plasma sodium concentration, the fractional excretion decreases in SIADH while remaining elevated above 11% in patients with CSW. This rapid response to saline and persistence of increased fractional excretion of urate following correction of hyponatremia is described in a patient without neurologic disease leading the authors to suggest the terminology should be changed from CSW to renal salt wasting (9). The authors also comment on the identification of a protein in salt wasting patients possessing characteristics of a proximally acting diuretic called haptoglobin-related protein without signal peptide.

One criterion that can be used to favor the existence of a phenomenon is to ask whether there is teleological benefit. In this regard, it has been suggested development of kidney salt wasting and resultant volume depletion is protective in limiting extreme rises in intracranial pressure following central nervous system injury (8). Prior studies have suggested a role for natriuretic peptides (brain and atrial natriuretic peptide) in the development of CSW (10,11) (Figure 1). The vasodilatory properties of these compounds would provide additional protection by decreasing the tendency for vasospasm in disorders such as subarachnoid hemorrhage. In rodent models of traumatic
brain injury and intracerebral bleeding, brain natriuretic peptide improves cerebral blood flow and reduces brain inflammation manifested by reduced neurodegeneration and improved functional outcomes (12). The stimulatory effect of natriuretic peptides on lipolysis would provide the substrate for increased production of ketone bodies which have been shown to provide a wide range of neuroprotective effects (13). Natriuretic peptides activate existing depots of brown adipose tissue and promote beiging of white adipose tissue which in turn leads to increased insulin sensitivity. This effect would guard against development of hyperglycemia which exerts an adverse effect in models of brain injury (13,14). One can argue brain natriuretic peptide may actually attenuate the degree of hyponatremia that otherwise occurs in CSW through inhibitory effects on vasopressin secretion and water intake (15,16).

The reader will have to decide based on the arguments made and their own clinical experience whether CSW is a real cause of hyponatremia. The moderator has described a case of CSW and therefore would be hard pressed to deny its existence (17). It will take interested investigators who are willing in the fog of acute illness to document the stringent criteria proposed by Sterns and Rondon-Berrios in order to better define the frequency of CSW. The concept of non-cerebral renal salt wasting described is of interest. One would like to know the characteristics of these patients and whether they are prone to recurrent hyponatremia over time. Further characterization of the peptide described by Maesaka and Imbriano may ultimately add insight into this disorder. One area of agreement between the two camps based on prior publications is the preferential use of hypertonic saline in patients with intracranial disease who develop symptomatic hyponatremia (9,18). In this setting administration of saline can worsen the degree of hyponatremia in SIADH while fluid restriction alone is to slow considering the risk of further neurologic deterioration or herniation in such patients.
Disclosures: The authors have nothing to disclose.

Funding: None.

Acknowledgments: The content of this article reflects the personal experience and views of the author(s) and should not be considered medical advice or recommendation. The content does not reflect the views or opinions of the American Society of Nephrology (ASN) or Kidney360. Responsibility for the information and views expressed herein lies entirely with the author(s).

Author Contributions: Biff Palmer: Writing - review and editing. Deborah Clegg: Writing - review and editing.
References:


Figure legends:

Figure 1. **A model for the pathophysiology of cerebral salt wasting (CSW).** Increased urinary sodium excretion in the setting of volume contraction would be expected to cause kidney potassium wasting, a finding notably absent in CSW. The lack of kidney potassium wasting can be accounted for by the failure of aldosterone to increase in spite of reduced extracellular fluid volume. Brain natriuretic peptide (BNP) and atrial natriuretic peptide are attractive candidates to explain many of the features of CSW. While some studies have shown a correlation with increased levels of these peptides, this has not been a universal finding. However, even in the absence of increased levels, these peptides may still play a pathophysiologic role through changes in receptor number or affinity brought about by cerebral disease. Maesaka has described a proximal tubular natriuretic compound called haptoglobin-related protein without signal peptide (HPRWSP). They propose this protein exerts a direct inhibitory effect on sodium and urate transport.
Central Nervous System Disease

↓ Sympathetic nervous system outflow

↑ Brain and atrial natriuretic peptide

↓ Proximal Na\(^{+}\) reabsorption

↑ Distal Na\(^{+}\) delivery

↑ Renin

↑ Aldosterone

↑ Antidiuretic hormone

↓ Effective arterial blood volume (EABV)

↑ Urinary concentration

↓ Proximal urate reabsorption

↑ Fractional excretion of urate and hypouricemia

↑ Aldosterone

↓ Na\(^{+}\) reabsorption in inner medullary collecting duct

Teleologic benefits

• Natriuresis to decrease EABV contributing to ↓ intracranial pressure
• Vasodilation contributing to less vasospasm
• Lipolysis to provide substrate for ketogenesis
• Activation of BAT and beiging of WAT to improve insulin sensitivity to avoid hyperglycemia
• Direct favorable effects on injured brain tissue
• Inhibition of ADH and thirst mitigating degree of hyponatremia

Hyponatremia