Witness Statement Ref. No. 156/3

NAME OF CHILD: Claire Roberts

Name: James Patrick McKaigue

Title: Dr.

Present position and institution:

Consultant Paediatric Anaesthetist- Royal Belfast Hospital for Sick Children

Previous position and institution:
[As at the time of the child's death]
Consultant Paediatric Anaesthetist- Royal Belfast Hospital for Sick Children ("RBHSC").

Membership of Advisory Panels and Committees:
[Identify by date and title all of those between October 1996-August 2012]

Association Paediatric Anaesthetists Executive Committee 2002-2006

Previous Statements, Depositions and Reports:
[Identify by date and title all those made in relation to the child's death]

WS-156/1	30th January 2012
WS-156/2	6th September 2012

OFFICIAL USE:
List of previous statements, depositions and reports attached:

Ref:	Date:	
WS-129/1	17th May 2012	Witness Statement to the Inquiry (Adam Strain)
WS-156/1	30th January 2012	Witness Statement to the Inquiry (Claire Roberts)

With reference to WS-156/2 Question 39(b)

Doc 090-006-008 was created for the benefit of the Paediatric Intensive Care Unit, the purpose being to profile admissions into the Intensive Care Unit. I believe the document was prepared by the secretary [redacted] *and compiled from the body of information contained in Doc 090-009-011. The document would have been filed in a ring binder.*

Doc 090-006-008 contributed to the record of admissions to the Paediatric Intensive Care Unit, and among other information contained therein identified the reason for the patient's admission. The information could be analysed for example to distinguish between emergency and elective admissions, or to get a breakdown by specialty.

I wish to amend my answer to 39(b) from Yes ***to*** *No and this is the explanation.*

THIS STATEMENT IS TRUE TO THE BEST OF MY KNOWLEDGE AND BELIEF

Signed: JPMcVaigue **Dated:** 6/11/12

Review Article

Cerebral salt wasting: Truths, fallacies, theories, and challenges

Sheila Singh, MD; Desmond Bohn, MB; Ana P. C. P. Carlotti; Michael Cusimano, MD; James T. Rutka; Mitchell L. Halperin, MD

Background: **The reported prevalence of cerebral salt wasting has increased in the past three decades. A cerebral lesion and a large natriuresis without a known stimulus to excrete so much sodium (Na^+) constitute its essential two elements.**

Objectives: **To review the topic of cerebral salt wasting. There is a diagnostic problem because it is difficult to confirm that a stimulus for the renal excretion of Na^+ is absent.**

Design: **Review article.**

Intervention: **None.**

Main Results: **Three fallacies concerning cerebral salt wasting are stressed: first, cerebral salt wasting is a common disorder; second, hyponatremia should be one of its diagnostic features; and third, most patients have a negative balance for Na^+ when the diagnosis of cerebral salt wasting is made. Three causes for the large natriuresis were considered: first, a severe degree of extracellular fluid volume expansion could down-regulate transporters involved in renal Na^+ resorption; second, an adrenergic surge could cause a pressure natriuresis; and third, natriuretic agents might become more potent when the effective extracellular fluid volume is high.**

Conclusions: **Cerebral salt wasting is probably much less common than the literature suggests. With optimal treatment in the intensive care unit, hyponatremia should not develop. (Crit Care Med 2002; 30:2575–2579)**

Key Words: antidiuretic hormone; adrenaline; hyponatremia; natriuretic hormones; syndrome of inappropriate secretion of antidiuretic hormone

Disorders of salt and water homeostasis are common in patients who have traumatic brain injury, subarachnoid hemorrhage, or a, brain tumor (1). Depending on the decade and the emphasis placed on individual factors such as hyponatremia, the preferred diagnosis was cerebral salt wasting (CSW) or the syndrome of inappropriate secretion of antidiuretic hormone (1–3). Before discussing CSW, however, it is important to define its essential diagnostic elements—we stress that hyponatremia is not one of them.

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DIAGNOSTIC CHALLENGE

The reported prevalence of CSW has increased steadily over the past three decades, whereas the types of intracerebral lesions in this population have probably not changed appreciably in this period (Fig. 1). Therefore it is reasonable to ask whether a change in therapy or a reporting bias was responsible for the recent resurgence of the diagnosis of CSW.

Clinical Diagnosis of CSW

CSW is a diagnosis of exclusion based on clinical criteria. Its essential features are a cerebral lesion and renal sodium (Na^+) and chloride (Cl^-) wasting. The latter feature implies that Na^+ and Cl^- were excreted without a physiologic stimulus. This means that one cannot make a diagnosis of CSW if there is an expanded extracellular fluid (ECF) volume or, more accurately, an expanded effective arterial blood volume. In addition, the patient must not have a condition causing a deficiency of a physiologic stimulator of renal Na^+ resorption such as aldosterone or the presence of a natriuretic agent that is not directly related to the cerebral lesion (Table 1). In this category, we include the standard diuretics, inborn errors leading to a decreased resorption of Na^+ (e.g., Bartter syndrome), and renal tubular damage. Molecular advances imply that ligands that occupy the calcium receptor in the thick ascending limb of the loop of Henle should be excluded because they induce a loop diuretic-like effect (4). Examples of these ligands include hypercalcemia (e.g., with metastatic cancers) or cationic drugs such as aminoglycosides.

Two diagnostic elements will be emphasized. First, although some investigators include hyponatremia as a diagnostic criterion for CSW because it is commonly observed in this setting (1–3, 5), we consider it a nonspecific clue. Second, to determine whether there is a true deficit of Na^+, mass balances rather than excretion rates for Na^+ must be known (6). To imply that the ECF volume is contracted, there must be a deficit of Na^+ that exceeds 2 mmol/kg body weight because this is the quantity of Na^+ excreted when normal subjects diminish their salt intake (7).

Hyponatremia Is not a Reliable Diagnostic Criterion for CSW. The plasma Na^+ concentration will be low in any patient who has an input of electrolyte-free H_2O and vasopressin to minimize its renal excretion (8). An electrolyte-free H_2O load can be given by oral or intravenous route, or it can be generated by the kidney by a process we called "desalination" of intravenous saline or body fluids

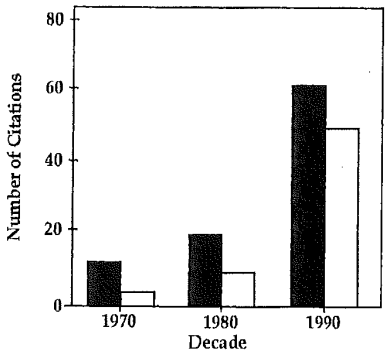

Figure 1. Prevalence of cerebral salt wasting in the past three decades. The data were obtained by a literature search using "cerebral salt wasting" and triple-H ("hypertension, hypervolemia, and hemodilution") as key words. The number of reports with cerebral salt wasting for each decade are shown in the *black rectangles*, and the number of reports with triple-H therapy for each decade is shown in the *clear rectangles*.

Table 1. Diagnosis of salt-wasting in a patient who has a cerebral lesion

The diagnosis of CSW is one of exclusion. One must have an intracerebral lesion and the excretion of Na^+ and Cl^- without another obvious cause.
1. The following must be ruled out
A physiologic cause for the excretion of Na^+ and Cl^- (e.g., an expanded ECF volume)
A noncerebral cause for the natriuresis
Exogenous diuretic administration
Pseudo-diuretic-like states
States with low aldosterone action (39)
Bartter syndrome; Gitelman syndrome
Ligands for the calcium receptor in the Henle loop, such as hypercalcemia, cationic drugs (e.g., gentamicin), and possibly, cationic proteins, such as in multiple myeloma
Obligation of Na^+ excretion by the excretion of anions other than Cl^-
High output renal failure
2. Possible explanations for salt wasting in patients with a CNS lesion
Natriuretic agents of cerebral origin
Down-regulation of renal Na^+ transport by chronic ECF volume expansion
Pressure natriuresis (e.g., adrenergic hormone overload)
Suppression of the release of aldosterone

CSW, cerebral salt wasting; ECF, extracellular fluid; CNS, central nervous system.

(9). The renal elements required to generate electrolyte-free H_2O include an intact concentrating process and a high rate of excretion of Na^+ (due to ECF volume expansion); both are often present in patients undergoing surgery (9). Patients with CSW have multiple stimuli for the release of vasopressin such as the central nervous system lesion, pain, stress, high intracranial pressure, and medications (10). Notwithstanding, hyponatremia could be prevented if the volume and the concentration of Na^+ in the intravenous solution matched that of the urine (11). Therefore, because hyponatremia is a secondary event, inappropriate secretion of antidiuretic hormone should not be confused with CSW.

Definition of a Normal ECF Volume. Na^+ ions are located primarily in the ECF compartment and Na^+, along with its attendant anions Cl^- and bicarbonate (HCO_3^-), exert the osmotic force that retains water outside cells. Therefore the ECF volume is determined primarily by the content of Na^+ in this compartment. If a patient had a low plasma Na^+ concentration, this will raise both the ECF and intracellular fluid volumes for any given ECF Na^+ content. Nevertheless, without knowing the content of Na^+ in the ECF compartment, the plasma Na^+ concentration does not provide insights about their ECF volume. For example, the ECF volume could be expanded (e.g., congestive heart failure) or contracted (e.g., adrenal insufficiency) in a patient with hyponatremia.

A decreased ECF volume can be due to a deficit of Na^+ or water. Only with the former will hyponatremia be present. There are two major subdivisions of the ECF compartment, the larger interstitial fluid volume and the physiologically more important intravascular volume. Focusing on the vascular compartment, its largest component (75%) is in the venous system. It is not really the venous volume that is the critical issue; rather, central venous pressure is the important factor because this variable is directly related to diastolic filling of the heart. Pressure in the central venous system is directly related to two factors, the venous volume and the size of venous capacitance vessels. If venous capacitance vessels were to constrict under the influence of adrenergic hormones, for example, there could be an increase in central venous pressure and thereby a tendency for a higher cardiac output and an expanded effective arterial blood volume even if the total ECF volume is contracted. Therefore, it is not clear how a normal ECF volume should be defined.

Control mechanisms for Na^+ homeostasis were designed in Paleolithic times when the diet contained very little Na^+ (12, 13); moreover, modern evolutionary pressures have not been strong enough to induce major modifications in this control system (14). This primitive set of controls is reflected by the fact that diuretics readily cause an initial large excretion of Na^+ in subjects who consume a typical Western diet. Nevertheless, once a 2 mmol/kg Na^+ deficit is induced, the natriuretic response to the same dose of a diuretic is much smaller (15). A conclusion that could be drawn from these data is that healthy subjects with their usual Western intake have a diet-induced expansion of their ECF volume in steady state (i.e., an expanded ECF volume is needed for the daily excretion of 150 mmol of Na^+ (2 mmol/kg)).

There are recent experiments in human subjects given a large oral NaCl load (16). These data suggest that there is another mechanism to deal with an extraordinarily large NaCl input akin to that seen in patients in the neurosurgical intensive care unit. In more detail, when close to 600 mmol of NaCl were ingested per day, a positive balance for NaCl was created. Nevertheless, there were unexpected findings—the plasma volume was expanded by 10–15%, but there was no change in either the total ECF volume, the plasma Na^+ concentration, or in body weight. This led to the impression that Na^+ could be sequestered in the body (presumably in the interstitial compartment). These observations add to the clinical problem of defining a normal and an expanded ECF volume, even when using measured values for Na^+ balance.

The difficulty in recognizing a NaCl deficit at the bedside was illustrated by the landmark experiment performed by McCance (17) in healthy subjects consuming a NaCl-free diet. When the negative balance for Na^+ exceeded 30% (close to 900 mmol in a normal man), the subjects felt unwell, but there were no objective physical findings, including a fall in blood pressure or a rise in pulse rate on assuming the upright posture. More recent studies confirmed that physicians are not able to ascertain that the ECF volume is contracted on physical examination (18). On the other hand, when a

smaller deficit of Na^+ occurred in conjunction with another lesion such as adrenal insufficiency, physical findings of a contracted ECF volume (e.g., postural hypotension) were evident (17). Therefore, our ability to detect a given deficit of NaCl on clinical grounds may more closely reflect the underlying cause rather than the specific NaCl deficit itself.

Laboratory data are often used to confirm that the ECF volume is contracted. Although elevated plasma renin activity and vasopressin or catecholamines levels could be helpful (19), these results are not usually available at the bedside in a timely manner. Urine electrolyte data can also be misleading (20). For example, excretion of a Na^+- or Cl^--poor urine is the expected observation in populations who eat a low quantity of NaCl (21). In contrast, finding a high rate of excretion of Na^+ and Cl^- does not define a normal ECF volume in a patient with salt wasting because these are the expected urinary results in a patient with this condition. Other indirect indexes to suggest that the ECF volume is contracted include a low fractional excretion of urea or total urates (22)—it remains to be seen how helpful these indirect indices will be to diagnose CSW. In summary, because CSW is a diagnosis of exclusion, it should not be made in a patient who lacks a sufficiently negative balance for $Na^+ + K^+$ (23).

CEREBRAL SALT WASTING

Factors other than an intracerebral lesion could be responsible for an excessive natriuresis, and these should be ruled out (Table 1). In this section, we shall discuss factors related to a central nervous system disturbance that could be responsible for an excessive natriuresis.

CSW Caused by Natriuretic Agents of Central Nervous System Origin. The simplest model for CSW is to have the brain release a natriuretic hormone. Although it is possible to have a large natriuresis in a patient with an intracerebral lesion if natriuretic agents were released from the brain, there are two issues to consider in this regard. First, the prototype of agents in this category, atrial natriuretic peptides, do not lead to a large natriuresis if there is a contracted ECF volume (24). Second, even more potent diuretics such as loop diuretics do not cause enough ECF volume contraction to produce clinically obvious hypotension in subjects with an input of NaCl (15). They primarily cause the elimination of Na^+ and Cl^-

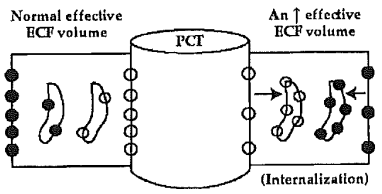

Figure 2. Development of a salt-wasting state by previous chronic expansion of the extracellular fluid (*ECF*) volume. For details, see text. The left portion of the figure represents the normal state with its luminal Na^+ transport system (*open symbols*) and basolateral Na-K-adenosine triphosphatase (*solid symbols*) that are the components of the system to resorb Na^+ in the proximal convoluted tubules (*PCT*). Most of these elements are in the luminal and basolateral membranes. The response to chronic expansion of the effective arterial blood volume is depicted in the right portion of this figure. Elements for Na^+ resorption are transferred intracellularly to vesicles inside PCT cells (internalization) (see Zhang et al. (31)).

retained in response to prior NaCl intake and become much less potent when the deficit of Na^+ approaches 2 mmol/kg (12, 13). Therefore it is unlikely that any of these agents could cause clinically obvious CSW with hypotension. Moreover, elevated levels of atrial or brain-derived natriuretic peptides are not a universal finding in patients who are said to have CSW (24–26).There is a second category of agents of central nervous system origin that could, in theory contribute to a severe salt-wasting state, the digitalis-like peptides (27, 28). Their role to explain the true cases of CSW is yet to be established.

Large Infusion of Saline May Cause a Significant Negative Balance for Na^+ and Cl^-. On the surface, it seems paradoxic that the physiologic natriuresis in response to a considerably expanded ECF volume might lead to renal salt wasting; however, this is a distinct possibility once NaCl intake is reduced (Figs. 1 and 2). In patients undergoing aneurysmal repair, four- to five-fold more Na^+ is given daily as intravenous isotonic saline than is present in a typical Western diet—moreover, this high intake of NaCl is given for up to a week or two after the surgery. Expansion of the ECF volume is designed to minimize intracerebral vasospasm (29, 30). A salt load may cause the arterial blood pressure to rise and induce a physiologic pressure natriuresis. In the rat, a NaCl load caused a natriuresis accompanied by down-regulation of renal Na^+ absorption along with internalization of the components of Na^+ resorption

Cerebral salt wasting is a diagnosis of exclusion that requires a natriuresis in a patient with a contracted effective arterial blood volume and the absence of another cause for this excretion of Na^+.

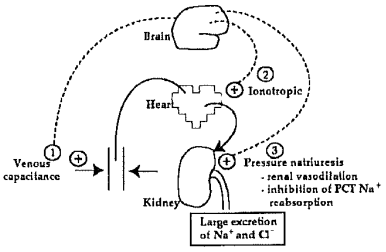

Figure 3. Possible role of an adrenergic surge in cerebral salt wasting. Three major actions of catecholamines (*dashed lines*) could lead to a natriuresis that is caused by a high effective arterial volume. *1*, contraction of the large venous capacitance vessels can lead to a rise in central venous pressure and, thereby, diastolic filling of the heart; *2*, there is the inotropic action of these compounds on the heart; *3*, if there were a renal vasodilator present such as dopamine, a pressure natriuresis could result. *PCT*, proximal convoluted tubules.

that were located in the luminal and basolateral membranes of their proximal convoluted tubules (Fig. 2) (31). If the same changes occurred in human subjects, this natriuresis could become more profound and eventually lead to a contracted ECF volume. Indeed, some of these patients eventually do develop signs consistent with chronic ECF volume contraction when the rate of infusion of saline is decreased. There is a second factor that can cause an excessive natriuresis in this setting. If expansion of the ECF volume is combined with a very high rate of release of adrenergic (32) hormones and inhibitors of Na^+ resorption in the kidney such as dopamine (33, 34) or natriuretic agents (24–26), the full-blown picture of CSW might become evident (Table 1).

In our institutes, when CSW was diag-

Table 2. An example of cerebral salt-wasting

Day	Na^+, mmol	K^+, mmol	Blood Pressure, mm Hg
1	−100	−70	145/80
2	−84	−55	138/78
3	−62	−28	130/65
4	−61	−34	128/74
5	−68	−29	126/72
6	−67	−46	124/68
7	−66	−57	132/68
8	−58	−38	128/69
9	−60	−32	138/74
Total	−626	−389	

Several days before the balance study, the patient was given a high salt intake (15 g or 250 mmol NaCl). She was placed on very low salt intake (9 mmol/day) for the 9-day balance study (36). The P_{Na} fell from 128 to 109 mmol/L, and the plasma K^+ concentration fell from 4.8 to 3.4 mmol/L over the 9-day period.

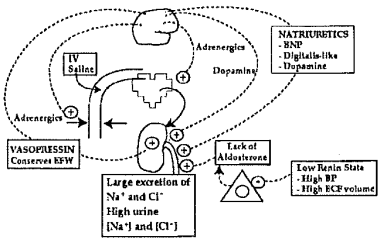

Figure 4. Cerebral salt wasting, an overview. For details, see text and Figures 2 and 3. *EFW*, electrolyte-free H_2O; *BNP*, brain natriuretic peptide; *BP*, blood pressure; *ECF*, extracellular fluid.

nosed using unreliable criteria such as a very large Na^+ excretion rate, a high urine Na^+ concentration, or hyponatremia, >90% of patients in our neurosurgical intensive care unit had an overall positive balance for Na^+ and Cl^- when calculations included all infusions from the time of first contact with medical or paramedical personnel. This suggests that their ECF volumes were not actually contracted. We have stressed that a diagnosis of CSW must not be based on a negative balance for $Na^+ + K^+$ or Cl^- on a few days in the intensive care unit (23)—overall balances must be evaluated.

There is another factor to consider with respect to renal Na^+ wasting in response to a chronically expanded ECF volume. Should a stimulator of Na^+ and Cl^- resorption such as a mineralocorticoid (fludrocortisone) be administered, the rate of NaCl excretion might fall (35). Nevertheless, one should not conclude that the prior natriuresis was due to a mineralocorticoid deficiency state without other evidence (36). For example, one should document that there were low levels of aldosterone before expansion of the ECF volume and that aldosterone levels failed to rise appropriately when the effective arterial blood volume became contracted.

Very large Adrenergic Surge May Cause a Natriuresis. The levels of adrenergic hormones are elevated in patients with major injuries to the brain (32). There are four possible elements in this response. First, adrenergic hormones could contract venous capacitance vessels, raising central venous pressure (32) (Fig. 3). Second, inotropic actions of catecholamines could raise the arterial blood pressure. Third, a very important element in this response would be renal vasodilation, perhaps due to actions of dopamine (34) or natriuretic peptides. Fourth, the renal response to a rise in systemic blood pressure, if accompanied by inhibited renal resorption of Na^+ by dopamine (34), for example, could lead to a pressure natriuresis (31). Nevertheless, even though a pressure natriuresis could cause a negative balance for Na^+ and a contracted ECF volume, the effective arterial blood volume and pressure could still be increased. Therefore, there are additional difficulties with the diagnostic criteria for CSW because one must detect a contracted effective arterial blood volume to make this diagnosis.

EXAMPLE OF CSW

In their classic description of CSW, Cort and Yale (36) described a young woman with a large thalamic tumor who was treated with a high intake of NaCl (250 mmol/day) (Table 2). A balance study was performed when this patient was switched acutely to a very low daily NaCl intake (9 mmol/day). During part of this balance study, the patient was given mineralocorticoids without discernible effects. The patient had consistently negative daily balances for Na^+ and for K^+. Her total deficit of Na^+ was 626 mmol, which is close to 40% of the estimated content of Na^+ in the ECF compartment of a normal 50 kg woman (50 kg × 60% water = 30 L, one third of which [10 L] is the ECF volume; 10 L × 140 mmol Na^+/L ECF = 1400 mmol total Na^+). Of special importance, there was little decline in her blood pressure and rise in her plasma creatinine concentration over this period.

Our interpretation of these data is shown in Figure 4. It involves a combination of factors thought to be important to explain the large natriuresis in CSW (Table 1). First, this patient began with a high salt diet that may have led to down-regulation of renal Na^+ resorption owing to chronic expansion of her ECF volume. Perhaps this ECF volume expansion and the absence of hyperkalemia could have led to a temporary state of hypoaldosteronism (37, 38). Second, the large tumor may have led to a high release of adrenergic hormones and thereby a pressure natriuresis. Third, natriuretic peptides of cerebral origin could have led to a significant inhibition of the renal resorption of Na^+ if her effective arterial blood volume was expanded (venous capacitance vessel contraction and myocardial inotropic actions of adrenergic hormones). Although vasopressin might be present, the urine volume might still be large because of the large natriuresis (see the equation below). Because the urinary concentrations of Na^+ and Cl^- should be very high, this could lead to the generation of electrolyte-free H_2O (9) and helps explain why hyponatremia might develop or become more severe. If more isotonic saline were given to avoid a daily negative balance for Na^+, the natriuresis could become even more marked.

$$\text{Urine volume} = \text{No. of solutes excreted}/(\text{solutes})_{\text{urine}}$$

CONCLUSIONS

CSW is a diagnosis of exclusion that requires a natriuresis in a patient with a contracted effective arterial blood volume and the absence of another cause for this excretion of Na^+ (Table 1). To establish a

diagnosis of CSW, the negative balance for $Na^+ + K^+$ or Cl^- should exceed 2 mmol Na^+/kg body weight. Although a low effective arterial blood volume should be present to imply that CSW is present, the pressure natriuresis due to high adrenergic hormones makes this distinction less clear. We suggest that CSW may actually be far less common than the literature indicates (Fig. 1). Hyponatremia is not a diagnostic feature of CSW, but it often provides an impetus for more detailed investigations.

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ENDOCRINE AND METABOLIC DYSFUNCTION SYNDROMES IN THE CRITICALLY ILL

Cerebral Salt Wasting Syndrome

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Hyponatremia is a common complication of intracranial disease and is associated with a number of disorders, including head injury, tumors, intracranial infections, and stroke. Hyponatremia occurs in as many as 30% of patients with subarachnoid hemorrhage (SAH) [18] and is associated with extracellular volume depletion and cerebral ischemia.[63] Neurologic dysfunction, which is thought to result from cerebral edema, is the principal manifestation of hyponatremia and can exacerbate underlying intracranial disorders. Severe hyponatremia, or a rapidly falling serum sodium level, can lead to confusion, lethargy, seizures, and coma. When severe hyponatremia is overcorrected or corrected too rapidly, pontine myelinolysis and death can result. Therefore, early diagnosis and effective treatment of hyponatremia are critical for hyponatremic patients with intracranial disease.

The term cerebral salt wasting (CSW) was introduced by Peters and colleagues in 1950.[45] They hypothesized that cerebral disorders can cause the kidneys to be unable to conserve salt, leading to salt depletion and concomitant extracellular fluid loss. Although this phenomenon was supported by other reports,[7] [62] it was eclipsed by identification of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) in 1957. In SIADH, physiologically inappropriate secretion of antidiuretic hormone (ADH) or increased renal sensitivity to ADH leads to renal conservation of water and dilutional hyponatremia. This syndrome has been well documented in association with a number of neurologic disorders. The primary treatment for SIADH is water restriction. Evidence has accumulated to indicate that many patients with intracranial disease actually experience CSW as it was originally described. This occurrence has important clinical implications, because the appropriate treatment of hyponatremia caused by CSW, salt and water supplementation, is the opposite of the accepted treatment for SIADH. The objectives of this article are to examine the evidence in favor of the CSW syndrome, explore the possible mechanisms behind CSW, and discuss the diagnosis and management of the patient with CSW.

DEFINITION OF CEREBRAL SALT WASTING

Cerebral salt wasting is defined as the renal loss of sodium during intracranial disease leading to hyponatremia and a decrease in extracellular fluid volume.

EVIDENCE IN FAVOR OF CEREBRAL SALT WASTING

In the original report of CSW in 1950, Peters and coworkers [15] described three patients with intracranial disease (encephalitis, intracranial hemorrhage, and bulbar poliomyelitis). Each patient had hyponatremia (serum sodium <120 mEq/L) and an inability to prevent loss of sodium in the urine. The patients demonstrated salt depletion and responded well to salt replacement. The authors speculated that renal salt wasting may occur in brain disease when adrenocorticotropic hormone secretion is disrupted, leading to a decrease in adrenal mineralocorticoid secretion, or may occur by way of an alteration of direct neuronal control over the kidneys. Two years later, Welt and colleagues[16] reported that the pituitary-adrenal axis was intact in two patients with intracranial disease, hyponatremia, and renal salt wasting. Cort[17] also found no evidence of pituitary or adrenal deficiency in a case report of a patient with a thalamic tumor, dehydration, severe hyponatremia, and renal salt wasting. These authors hypothesized that CSW was caused by a defect in the direct neural regulation of renal tubular activity.

After the identification of SIADH in 1957,[18] hyponatremia in patients with central nervous system disease was almost exclusively ascribed to SIADH. The concept of hyponatremia caused by renal salt wasting fell from favor, and many authors even equated the term CSW with SIADH.[6][19][20] The finding that 14% of patients with SIADH have no detectable abnormalities in ADH secretion[21] suggested that a mechanism other than excessive levels of ADH can lead to a clinical picture somewhat similar to SIADH. Subsequently, some patients who met the traditional laboratory criteria for SIADH were noted to be volume depleted rather than euvolemic or hypervolemic. In 1981, Nelson and colleagues[22] reported a study of 12 patients with intracranial disease (SAH, head injury, or craniotomy for unruptured aneurysm) who met the traditional laboratory criteria for SIADH. Blood volume analyses demonstrated significant decreases in red blood cell mass, plasma volume, and total blood volume in 10 of the 12 patients. These findings were consistent with the original concept of CSW, whereby an inability of the kidneys to conserve sodium leads to progressive salt wasting and volume depletion. The authors theorized that volume depletion stimulates ADH release, leading to water retention and, along with concomitant salt loss, hyponatremia.

Additional evidence in favor of CSW was gathered in a monkey model of SAH.[23] Seven of nine monkeys became natriuretic and hyponatremic after experimental SAH. The natriuretic period lasted an average of 4.4 days, and the average lowest serum sodium level was 125.7 mEq/L. Although the sodium balance was negative after SAH, the plasma volume was not significantly decreased. Plasma ADH levels were usually elevated for a day after surgery but were comparable to preoperative values during the period of natriuresis. In this model, hyponatremia seemed more likely to result from natriuresis and a negative salt balance than an excess of ADH.

Further support for CSW came in a study of sodium balance and volume status in 21 patients after aneurysmal SAH.[24] Plasma volume decreased by more than 10% in 11 of the 21 patients. Ten of the 11 patients with decreased volumes had negative sodium balances: six also had hyponatremia. Decreased plasma volume was accompanied by an increase in blood urea nitrogen and a decrease in body weight. This demonstration of hyponatremia, natriuresis, and volume depletion was incompatible with true SIADH.

In a study of 256 patients with severe brain injury, six patients met the criteria for SIADH: three in the first 3 days after injury and three after more than a week.[25] Plasma ADH levels were measured and found to be elevated only in the group with early hyponatremia. In the patients with late hyponatremia, plasma ADH levels were appropriate for serum osmolality. Moreover, two of the patients with late hyponatremia did not respond to fluid restriction. The authors theorized that elevated levels of ADH can occur after brain injury because of a number of factors that promote ADH release, such as hypovolemia caused by fluid or blood loss, stress, pain, medications and increased intracranial pressure. This hypersecretion of ADH, although not physiologically inappropriate, may lead to hyponatremia. Hyponatremia in the second week after brain injury, however, is more likely to be caused by CSW than SIADH.

More evidence in favor of CSW was provided by a series of 21 neurosurgical patients with hyponatremia who met the criteria for SIADH.[19] The patients had a variety of intracranial disorders. Volume status was assessed by measuring central venous pressure (CVP) and total blood volume; hematocrit was observed. All 21 patients were hypovolemic, with or without anemia. Hyponatremia was corrected in all patients after administration of isotonic saline and oral salt (and whole blood if anemic). The presence of volume depletion and the response to volume supplementation rather than restriction are more compatible with CSW than SIADH.

A succession of case reports has provided additional evidence for the existence of CSW and a demonstration of the variety of intracranial disorders that are associated with CSW. CSW, as diagnosed by hyponatremia, volume depletion, and clinical response to volume and salt replacement, has been described in patients with tuberculous meningitis,[11] [16] [28] metastatic adenocarcinoma of the lung and carcinomatous meningitis,[44] pituitary exploration and biopsy,[1] pilocytic astrocytoma involving the third ventricle and pituitary region,[39] parietal glioma[13] and transsphenoidal surgery for pituitary adenoma,[22] in elderly patients after head injury,[25] and in two pediatric patients with central nervous system disease (closed head trauma in one and seizure disorder, spastic diplegia, mental retardation, and hydrocephalus in the other).[12]

To investigate the possibility that fluid restriction may actually harm patients with hyponatremia, Wijdicks and coworkers[63] performed a retrospective study of 134 patients after aneurysmal SAH. Forty-four patients were hyponatremic, and 25 of these met the criteria for SIADH. Twenty-six patients were treated with fluid restriction, and cerebral infarctions developed in 21 (81%). The rate of cerebral infarction was significantly higher among the patients with hyponatremia versus the patients with normal serum sodium levels. These findings provided indirect evidence that hyponatremia in patients with SAH is more likely to be the result of CSW, in which case fluid restriction exacerbates underlying volume depletion, leading to an increased risk of cerebral infarction.

In summary, the evidence in favor of CSW converges on the three following points: (1) a negative salt balance precedes or accompanies the development of hyponatremia in many patients with intracranial disease; (2) these patients are volume contracted, a state that is incompatible with SIADH; and (3) these patients respond to salt and volume replacement rather than fluid restriction. The available studies indicate that CSW occurs as frequently as[54] or more frequently [34] [63] [39] [9] than SIADH in neurosurgical patients.

POSSIBLE MECHANISMS

The mechanism by which intracranial disease leads to renal salt wasting is not understood. The brain can influence renal sodium reabsorption by both humoral and neural mechanisms, and a derangement of either system, or both, may lead to CSW.

Natriuretic Factors

Infusion of hypertonic saline into the cerebral ventricles of the rat causes a natriuresis that persists after renal denervation,[64] [65] suggesting the existence of a blood-borne natriuretic factor capable of mediating CSW. Smith[56] first proposed the existence of a blood-borne natriuretic hormone; several natriuretic peptides have been identified since, the best known of which is atrial natriuretic peptide (ANP). ANP, a 28-amino acid polypeptide, was first identified in rat atrial muscle when infusions of extracts of atrial muscle were found to cause more than a 30-fold increase in urinary sodium and chloride excretion and a 10-fold increase in urinary volume.[66] The biologic effects of ANP include natriuresis and diuresis, vasodilation, and suppression of renin and aldosterone secretion.[67] ANP is released from the heart in response to atrial stretch, circulates in the plasma with a half-life of about 3 minutes, and is cleared by receptor and enzymatic mechanisms. ANP-containing neurons have been identified in the rat hypothalamus and lamina terminalis[68] [69]; however, the concentration of ANP in the brain is 10,000 times less than in the heart,[70] making it unlikely that brain secretion of ANP is responsible for CSW. Although atrial stretch is thought to

be the principal mechanism for cardiac ANP release, there is evidence that the central nervous system modulates cardiac ANP secretion. Adrenergic and cholinergic agents cause ANP release, and lesions of specific areas in the hypothalamus, intracerebroventricular injections of ANP immune serum, and deafferentation of baroreceptor input to the hypothalamus all reduce cardiac secretion of ANP in response to acute volume expansion. Thus, intracranial disease may lead to a disturbance of the brain's control over ANP secretion and, under certain conditions, excessive ANP secretion.

Measurement of ANP levels during intracranial disease implies a role for ANP in hyponatremia, although the picture is complex. Serum ANP levels were elevated above the normal range in six of eight neurosurgical patients with a variety of neurologic disorders, and a near-linear relationship was observed between serum ANP levels and urine sodium.[6] In a study of plasma ANP levels in 25 patients with intracranial aneurysms, ANP levels were significantly elevated in 21 patients with SAH, compared with 4 patients with unruptured aneurysms, and returned to normal over 2 weeks.[11] There was no correlation between ANP levels and serum sodium levels, and the ANP levels in two patients with SAH who had hyponatremia were not significantly different from those in the other patients with SAH. Thus, elevated levels of ANP alone do not account for hyponatremia observed after SAH.

In a report of a patient with hyponatremia after SAH, both plasma ADH and ANP levels were elevated above the normal range for 5 days after hemorrhage, but only ANP remained elevated at 13 and 28 days, associated with a prolonged period of hyponatremia.[28] These results suggest that SIADH may immediately occur after an acute intracranial insult, but prolonged hyponatremia is associated with persistent elevation of plasma ANP. This conclusion was supported by a study of 11 patients with hyponatremic SAH.[28] Both ADH and ANP concentrations were significantly elevated on days 0 to 2 after onset of SAH. ANP levels remained high in patients with hyponatremia on days 6 to 14 after SAH, whereas ADH levels became significantly lower during the second week.

Several observations oppose the idea that ANP is the primary natriuretic factor hypothesized to exist in CSW. Plasma ANP levels actually were found to decrease during experimental natriuresis induced by intracerebroventricular administration of hypertonic saline.[23] In the same model, the dopamine antagonist haloperidol, which attenuates the natriuretic effect of exogenous ANP, failed to impair brain-induced natriuresis.[24] [25] Two clinical series have failed to find an increase in plasma ANP levels after SAH, although one study did not consider serum sodium status[15] and the other included only one patient with hyponatremia.[29] Normal levels of ANP have been found in patients with CSW associated with parietal glioma[15] and intracerebral hemorrhage [6] and after surgery for pituitary adenoma.[27] In a case of SIADH associated with carcinoma of the lung, plasma ANP levels were elevated above the normal range, suggesting that high plasma levels of ANP may actually be a feature of SIADH rather than CSW.[5]

A regression analysis of 15 patients with CSW secondary to tuberculous meningitis found that alterations in plasma ANP levels accounted for only 65% of the variation in plasma sodium levels, implying that other factors are involved in CSW.[30] Two other natriuretic factors may have a role. Brain natriuretic peptide (BNP), originally found in porcine brain, is largely of cardiac ventricular origin and shares considerable sequence identity with ANP. It is secreted by the cardiac ventricles in response to increased pressure or stretch of the ventricles and has biologic effects similar to those of ANP. Plasma BNP levels are elevated in patients with SAH and are associated with hyponatremia.[11] [31] [32] Elevated plasma BNP levels also are associated with cerebral vasospasm.[33] Circulating BNP may be involved in CSW in several ways. Sympathetic stimulation during acute intracranial disease may cause release of cardiac BNP, which may suppress aldosterone secretion and act directly on renal function.[11] [34] Brain natriuretic peptide also has been localized to the hypothalamus[35] and may be released when this part of the brain is damaged.[34] Another protein, termed plasma natriuretic factor, was identified when rats treated with intraperitoneal infusion of plasma from neurosurgical patients developed natriuresis.[36] This factor awaits further characterization.

In summary, circulating natriuretic factors probably are involved in CSW. However, the presence of multiple natriuretic factors, possibly in combination with other factors or direct neural effects on the kidneys, are likely to be necessary for the development of CSW.

Ouabain-like Compound

The natriuretic response of the rat brain to intracerebroventricular infusion of hypertonic saline is blocked by the infusion of digoxin-specific antibodies into the cerebral ventricles.[28] This finding suggests that an ouabain-like compound (OLC) in the brain is involved in CSW. OLC immunoreactivity has been found in the hypothalamus and medulla of rat.[29] Plasma OLC immunoreactivity was identified in 18 of 25 patients with aneurysmal SAH.[28] The presence of OLC correlated with the amount of subarachnoid bleeding, and the data implied that a negative sodium balance and volume depletion occurred more often in patients who were positive for OLC, a trend that did not reach statistical significance. Thus, OLC appears to be released into the plasma in response to SAH, possibly as a result of hypothalamic damage. However, the potential for crossreactivity of antiglycoside antibodies with nonglycoside substances makes these results less certain.[27] In addition, ouabain, an inhibitor of Na^+ /K^+ -adenosinetriphosphatase, does not cause significant diuresis, except in toxic doses.[30] In the model of CSW induced by intraventricular administration of hypertonic saline, intravenous administration of large doses of digoxin-specific antibodies do not block central nervous system-induced natriuresis.[28] Taken together, these results suggest that brain OLC has a role in CSW but that it is unlikely that circulating OLC alone is the blood-borne natriuretic factor that is hypothesized to mediate CSW.

Direct Neural Effects

Generalized hyperactivity of the sympathetic nervous system occurs after SAH,[31] and sustained sympathetic stimulation leads to a decrease in plasma volume and total blood volume.[32] This occurrence may account for some of the volume loss seen in SAH and other acute intracranial disorders; however, decreases in renal sympathetic nerve activity lead to natriuresis and diuresis because of an increase in renal blood flow and glomerular filtration, a decrease in renin release, and a decrease in renal tubular sodium reabsorption.[33] [34] It is possible that acute brain injury ultimately leads to an interruption in sympathetic output to the kidneys that is analogous to spinal shock, whereby an acute spinal cord injury results in a transient inhibition of sympathetic activity. A combination of circulating natriuretic factors and direct neural involvement may be required for the development of CSW.[14]

Anatomic Correlations

A comparison of the anatomy of intracranial lesions with the occurrence of CSW might be useful in identifying parts of the central nervous system involved in CSW. CSW has been documented in patients with tumors in the right posterior thalamus[17] and the right parietal lobe.[19] Specific brain lesions are associated with natriuresis. An experimentally induced lesion in the medulla leads to natriuresis and polyuria.[35] Most reports of CSW concern patients with aneurysmal SAH, especially involving the anterior cerebral artery complex, which is frequently associated with damage to the hypothalamus.[8] Several reports of CSW associated with tuberculous meningitis also implicate the hypothalamus.[10] [36] [37] Tuberculous meningitis is typically localized to the basal cisterns, with associated endarteritis affecting the perforating vessels to the hypothalamus and basal ganglia, and potential ischemia or infarction of those regions.[37]

DIFFERENTIAL DIAGNOSIS

Causes of hyponatremia to consider in patients with intracranial disease include iatrogenic fluid overloading or diuresis, congestive heart failure, renal or liver disease, hypothyroidism, and adrenal insufficiency. Artifactual hyponatremia can be seen with hyperglycemia and hypertriglyceridemia. A less well-established cause of hyponatremia is sodium-potassium shift, in which sodium is shifted from the extra- to the intracellular compartment.[38] [39] This phenomenon has not been investigated in the setting of intracranial disease.[5] Because most patients with CSW seem to meet the general criteria for SIADH, a thorough examination and laboratory evaluation are necessary to distinguish between the two (Table 1) (Table Not Available) . Attention to volume status is critical. A decrease in extracellular fluid volume and a negative salt balance are

the most important features of CSW that set it apart from SIADH. Symptoms of diminished fluid volume include anorexia, nausea, vomiting, apathy, weakness, orthostatic light-headedness, and syncope. Physical findings include orthostatic hypotension, poor skin turgor, sunken eyes, dry mucous membranes, absence of axillary perspiration, and tachycardia. Weight loss is a signal of volume loss. A water input:output ratio <1 shows a negative water balance. For patients with invasive hemodynamic monitoring, a low pulmonary capillary wedge pressure (<8 mm Hg) or a low CVP (<6 mm Hg) implies volume contraction. A negative water balance,[64] clinical dehydration,[25] weight loss,[11 27 64 68] orthostatic hypotension,[11] and a CVP <6 mm Hg[11 64] are documented features of CSW.

TABLE 1 -- DIFFERENTIAL DIAGNOSIS OF CEREBRAL SALT WASTING VERSUS THE SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION*

(Not Available)

*CSW, cerebral salt wasting; SIADH, syndrome of inappropriate antidiuretic hormone secretion; ↓, decrease; ↑, increase; ↑ ↑, significant increase. *(From Harrigan MR: Cerebral salt wasting syndrome: A review. Neurosurgery 38:152-160, 1996; with permission)*

Several laboratory tests are useful in evaluating volume status and salt balance. Elevations in the hematocrit, the blood urea nitrogen:creatinine ratio, and the serum protein concentration suggest dehydration and argue against the presence of SIADH. Urine sodium concentration should be markedly elevated in CSW, whereas it is variable in SIADH. An elevated serum potassium level during hyponatremia is incompatible with SIADH and suggests CSW.[25] Serum uric acid is decreased in SIADH but is usually normal in CSW.[64] Derived parameters of sodium and water homeostasis, obtained from timed urinary collections and matching plasma samples, can help distinguish CSW from SIADH.[42] Creatinine, osmotic and free-water clearances, reabsorbed tubular water, and fractional water and sodium excretions, considered in the context of spot plasma and urinary electrolyte measurements, provide additional evidence for diagnosis when the clinical picture is unclear.

Studies of volume status, using isotope-dilution techniques, can be performed at the bedside. Diminished plasma volume (<35 mL/kg) is a central feature of CSW. Hyponatremic patients with intracranial disease were found to have an average plasma volume of 30.3 mL per kilogram, which is 26% less than that for normonatremic control patients.[43] A decrease in total blood volume (<60 mL/kg) is also associated with CSW.[68]

Serum ADH and ANP levels are not helpful in distinguishing between CSW and SIADH. Although elevated ADH levels can be diagnostic of SIADH and ADH is usually depressed in CSW, ADH levels can be misleading. Stress, pain, and increased intracranial pressure, common features of acute intracranial disease, can promote secretion of ADH. SIADH and CSW have been reported to occur successively in the same patient, particularly after SAH.[62] Cerebral salt wasting may occur after SIADH; the reverse situation may also occur: ADH secretion may appropriately increase, despite the presence of hyponatremia, in response to volume depletion.[43 68] ANP levels have been observed to be elevated [43 64 67 68] or normal[43 66 68] in CSW.

MANAGEMENT

The management of CSW begins with treatment of the underlying neurologic process. In particular, CSW related to acute hydrocephalus or elevated intracranial pressure may respond promptly to cerebrospinal fluid drainage.[64]

The cornerstones of the treatment of CSW are volume replacement and maintenance of a positive salt balance. Water and salt supplementation is the most common method. Intravenous hydration

with normal saline (0.9% sodium chloride [NaCl]),[11][13][15][18][19] hypertonic saline (3% NaCl),[13][15] or oral salt[11][13][18][19][20] may be used alone or in combination, depending on the severity of hyponatremia and the ability of the patient to tolerate enteral administration. Enteral administration of salt may be preferable, because intravenous administration of hypertonic saline may cause volume expansion and successive loss in the urine.[20] Blood products are useful for volume expansion if anemia is also present.[19] Colloids are effective as volume expanders by absorbing interstitial and third-space fluid.[13] The goal of water replacement is to match urine losses; the amount of sodium required may be estimated by multiplying the deficit in serum sodium concentration by total body water (50% ~ 60% of body weight).[13] Rapid correction of hyponatremia has been associated with pontine myelinolysis, but the optimal rate of correction is unclear. A cautious approach is to raise serum sodium no faster than 0.7 mEq per liter per hour, for a maximum total daily change not to exceed 20 mEq per liter. Overcorrection should be avoided.

A decrease in plasma volume of >10% occurs in some 50% of patients with aneurysmal SAH.[14] An added benefit of volume expansion for these patients is an improvement in cerebral perfusion and a reduction in risk of cerebral ischemia and infarction.[16][17][12][14]

In CSW, sodium administration corrects both volume contraction and hyponatremia, whereas in SIADH, it tends to be of only temporary and limited benefit. This response to saline infusion can help distinguish SIADH from sodium depletion.[14] An increase in salt intake during CSW may only further enhance sodium excretion.[16] Prevention of volume depletion by reducing renal sodium excretion is an alternative to volume replacement. The mineralocorticoid fludrocortisone acetate directly acts on the renal tubule to enhance sodium reabsorption. Adverse effects of fludrocortisone can include hypokalemia, pulmonary edema and hypertension. Prompt resolution of hyponatremia was reported after administration of fludrocortisone in three elderly patients with CSW after head injury.[15] A randomized, controlled trial in patients with aneurysmal SAH found that 0.1 mg of fludrocortisone, given orally three times a day for 8 days, significantly reduced water and sodium excretion and the frequency of hyponatremia.[19] Hyponatremia occurred in 6.6% of patients receiving fludrocortisone, compared with 33.3% of control patients. Transient hypokalemia, but not pulmonary edema, was observed in patients treated with fludrocortisone. All patients received therapeutic hypertension to maximize cerebral perfusion; fludrocortisone tended to reduce the need for dobutamine.

Serum sodium levels and volume status should be monitored closely during treatment of CSW. Fluid intake and output data and daily weights are easy to obtain and provide important information about volume status. Central venous pressure closely correlates with changes in total blood volume in patients with normal cardiac and pulmonary function and also can help guide management of hyponatremia in patients meeting these criteria.[14]

SUMMARY

There is significant evidence to show that many patients with hyponatremia and intracranial disease who were previously diagnosed with SIADH actually have CSW. The critical difference between SIADH and CSW is that CSW involves renal salt loss leading to hyponatremia and volume loss, whereas SIADH is a euvolemic or hypervolemic condition. Attention to volume status in patients with hyponatremia is essential. The primary treatment for CSW is water and salt replacement. The mechanisms underlying CSW are not understood but may involve ANP or other natriuretic factors and direct neural influence on renal function. Future investigation is needed to better define the incidence of CSW in patients with intracranial disease, identify other disorders that can lead to CSW, and elucidate the mechanisms underlying this syndrome.

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Is it cerebral or renal salt wasting?

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Cerebral salt-wasting (CSW), or renal salt-wasting (RSW), has evolved from a misrepresentation of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) to acceptance as a distinct entity. Challenges still confront us as we attempt to differentiate RSW from SIADH, ascertain the prevalence of RSW, and address reports of RSW occurring without cerebral disease. RSW is redefined as 'extracellular volume depletion due to a renal sodium transport abnormality with or without high urinary sodium concentration, presence of hyponatremia or cerebral disease with normal adrenal and thyroid function.' Our inability to differentiate RSW from SIADH lies in the clinical and laboratory similarities between the two syndromes and the difficulty of accurate assessment of extracellular volume. Radioisotopic determinations of extracellular volume in neurosurgical patients reveal renal that RSW is more common than SIADH. We review the persistence of hypouricemia and increased fractional excretion of urate in RSW as compared to correction of both in SIADH, the appropriateness of ADH secretion in RSW, and the importance of differentiating renal RSW from SIADH because of disparate treatment goals: fluid repletion in RSW and fluid restriction in SIADH. Patients with RSW are being incorrectly treated by fluid restriction, with clinical consequences. We conclude that RSW is common and occurs without cerebral disease, and propose changing CSW to RSW.

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OBJECTIVES

Cerebral salt wasting (CSW) or, more appropriately, renal salt wasting (RSW), is a syndrome with a controversial history that evolved from a misrepresentation of inappropriate secretion of antidiuretic hormone (SIADH) to acceptance as a distinct entity. Challenges confront us as we attempt to find clues to differentiate RSW from SIADH, ascertain the prevalence of RSW, and address reports of RSW occurring without cerebral disease.[1,2] The objectives of this mini review are to redefine RSW, explain how this controversy evolved, emphasize the appropriateness of antidiuretic hormone (ADH) secretion in RSW, differentiate RSW from SIADH by the persistence of hypouricemia and increased fractional excretion (FE) of the urate after correction of hyponatremia in RSW, stress the clinical importance of differentiating RSW from SIADH because of divergent therapeutic goals of fluid repletion in RSW or fluid restriction in SIADH, and advocate changing CSW to RSW.

DEFINITION OF RSW: EVOLUTION OF CONTROVERSY

RSW is defined as, 'extracellular volume (ECV) depletion due to a renal sodium transport abnormality with or without high urinary sodium concentration (UNa), presence of hyponatremia, or cerebral disease with normal adrenal and thyroid function'. Although this definition delineates the salient features of RSW, its existence has been an enduring controversy since the seminal description of SIADH.[3] The previous report of CSW was based on an inappropriately high urine chloride of 61.6 mmol/l in a clinically 'dehydrated' patient with cerebral disease.[4] As volume-depleted patients with normal kidneys avidly conserve salt, the urine chloride of 61.6 mmol/l was best explained by RSW.[5] When Schwartz *et al.*[3] encountered patients who mimicked normal individuals receiving exogenous ADH, it became apparent that an euvolemic hyponatremic patient can present with high UNa without implicating RSW. As the diagnosis of 'dehydration' was made by inaccurate clinical criteria, CSW was regarded as a misnomer of SIADH and considered nonexistent or rare.

The overlapping clinical and laboratory characteristics have largely perpetuated the diagnostic and therapeutic dilemma of restricting water in SIADH, or administering salt and water in RSW. Both present with normal adrenal and thyroid function, hyponatremia, hypouricemia, concentrated urine with UNa usually >20 mmol/l, and FEurate $>10\%$.

Euvolemia in SIADH and ECV depletion in RSW are the only variables that differentiate SIADH from RSW on first encounter, but clinical assessment of ECV is inaccurate.[6] Treatment for RSW, however, can be initiated if FEphosphate is >20% on first encounter.[2] Moreover, exceptions and misconceptions have fueled this controversy, although it can be concluded that RSW is a clinical entity that is more common than is perceived and must now be considered in those without cerebral disease.[1,2]

VOLUME STUDIES

The difficulty to assess ECV accurately and adherence to the notion that RSW is a misnomer of SIADH are major reasons for this longstanding diagnostic dilemma. Accurate determinations of ECV should, therefore, resolve this dilemma. Determination of ECV by radioisotope dilution is the gold standard, which correlates poorly with concomitant central venous pressure (CVP) measurements, suggesting that CVP is an unreliable determinant of ECV.[7] Nelson *et al.* measured blood volume by ^{51}Cr-tagged red cells and ^{131}I-tagged albumin in 12 hyponatremic neurosurgical patients as compared with that in 6 control patients. Of the 10 patients with decreased blood volume, 8 had subarachnoid hemorrhage (SAH) and 2 had increased blood volume, suggesting that 10 had RSW and 2 SIADH.[8] The UNa ranged from 41 to 203 mmol/l.[8] Wijdicks *et al.* measured plasma volume by ^{131}I-tagged albumin in 21 patients on the first day of admission within 48 h after SAH and on the sixth day after SAH. They compared differences between both the measurements to determine ECV while receiving at least 1500 ml of fluid daily and comparable sodium intake. Of the nine hyponatremic patients, plasma volume decreased by 10–20% in six, <10% in two, and increased by 4% in one.[9] Interestingly, in 12 normonatremic patients, plasma volume decreased by >10% in 5, <10% in 3, and increased by >5% in 4. Moreover, all 8 hyponatremic patients and 10 of 12 normonatremic patients with decreased plasma volume were in negative sodium balance.[9] This study concurs with Nelson's study and shows that RSW can occur without hyponatremia.[9] In a study of hyponatremic patients with diverse neurosurgical diseases meeting criteria for SIADH, Sivakumar *et al.* found hypovolemia in 17 of 18 hyponatremic patients using ^{51}Cr-tagged red cells. All 18 patients had decreased CVPs.[10] UNa ranged from 43 to 210 mmol/l and all 18 patients corrected their hyponatremia within 72 h after initiating saline therapy, which was consistent with RSW and not SIADH.[1,2,10] In a retrospective study of 319 patients with SAH, Sherlock *et al.* found 179 hyponatremic patients meeting the criteria for SIADH and CSW. They found that 69.2% had SIADH, 6.5% CSW, and 4.8% had combined SIADH and CSW. ECV was determined by CVP measurements, presence of hypotension, and undefined parameters.[11] This report suffers by its retrospective design, paucity of data to support their diagnoses, and reliance on CVP measurements that are poor determinants of ECV.[7] Moreover, the combination of SIADH and CSW in 4.8% of patients lacked supportive data to justify such a mutually exclusive diagnostic combination. In total, 10 patients with AIDS with saline-responsive postural hypotension were selectively studied. All the patients had CVP of 0 cm water, increased renin and aldosterone, hyponatremia, hypouricemia, elevated FEurate, and UNa >40 mmol/l, which collectively support the diagnosis of RSW.[6] Overall, these volume studies support the notion that RSW not only exists but is more common than SIADH in neurosurgical patients.

PATHOPHYSIOLOGY OF RSW AND SIADH

In RSW, the initiating defect in renal sodium transport leads to ECV depletion and multiple compensatory changes. At the onset, sodium excretion exceeds sodium input to decrease ECV, but as compensatory hemodynamic and neurohumoral factors come into play, the patient enters an equilibrated state where sodium input matches output. As in our well-documented case of RSW, UNa can thus be as low as 6 mmol/l when sodium intake is low.[1] The final ECV depends on the extent of the renal sodium transport defect and sodium input. The reduced effective arteriolar volume activates baroreceptors that increase ADH secretion and increase water conservation. As insensible fluid losses are hypotonic, the tendency to develop hypernatremia must be overcome by adequate free water intake for hyponatremia to develop. In those with defective thirst as seen in the aged or demented, such as Alzheimer's disease (AD), RSW can occur without hyponatremia or even hypernatremia.[12] As will be discussed later, the presence of increased FEurate and lower serum urate in the absence of hyponatremia and demonstration of natriuretic activity in AD plasma suggest that RSW is common in those with moderate-to-severe AD.[12] In RSW the volume stimulus for ADH secretion overrides the usual inhibition by the coexisting plasma hypoosmolality. The ECV depletion stimulates aldosterone production, but the proximal sodium transport defect in RSW will maintain salt supply to the distal nephron when salt intake is adequate to yield normal cyclo-oxygenase 2 activity and renin production.[13]

The primary defect in SIADH is the euvolemic, inappropriate increase in plasma ADH levels. With adequate free water intake, the increase in water reabsorption induces hyponatremia, plasma hypoosmolality, and a small degree of volume expansion, which along with increased atrial natriuretic peptide levels, decrease plasma renin and aldosterone.[6] There is an initial salt wasting and water retention, often leading to an equilibrated state of vasopressin escape where sodium and water input matches output, possibly due to a reduction in V2 receptor and urea transporter 2.[2,6] The hypouricemia and increased FEurate occurring only during the period of hyponatremia have not been adequately explained but cannot be ascribed to V1 activity of ADH because ADH levels are increased even after correction of hyponatremia when FEurate returns to normal (Figure 1b).[6,14] Moreover, the induction of SIADH by desmopressin acetate, which lacks V1 activity, was associated

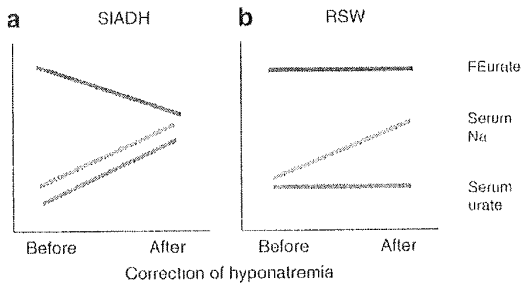

Figure 1 | Relationship between serum sodium, serum urate, and FEurate in SIADH and RSW. Relationship between serum sodium, serum urate, and FEurate in (**a**) inappropriate secretion of antidiuretic hormone (SIADH) and (**b**) renal salt wasting (RSW). Shaded areas represent normal values for each laboratory test. Hypouricemia and increased FEurate coexist with hyponatremia in both SIADH and RSW, but return to normal values with correction of hyponatremia in SIADH. In contrast, hypouricemia and increased FEurate persist after correction of hyponatremia in RSW. Serum sodium (orange), serum urate (green) and FEurate (red).

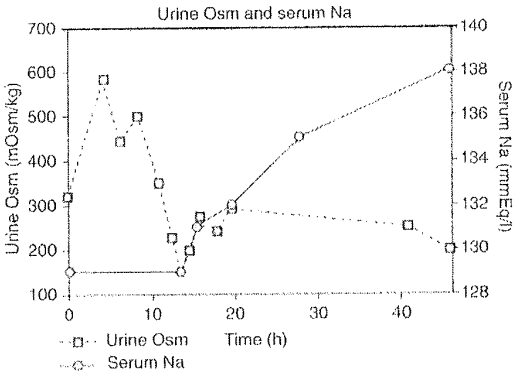

Figure 2 | Response of urine Osm and serum sodium concentration to saline infusion at 125 ml/h in hyponatremic patient with hip fracture without cerebral disease. Plasma antidiuretic hormone (ADH) was undetectable when urine Osm was 178 mOsm/kg water. Patient had 7.1% reduction in blood volume, increased plasma renin and aldosterone, and persistent hypouricemia and increased FEurate after correction of hyponatremia. Note prompt correction of hyponatremia after inhibition of ADH secretion and generation of dilute urine to increase free-water excretion.[1]

with an increase in FEurate.[15] ECV expansion as with saline is known to have a meager effect on FEurate but not to the extent seen in SIADH.[14]

VALUE OF FEurate OVER HYPOURICEMIA

Beck[16] proposed that the coexistence of hyponatremia and hypouricemia, defined as serum urate ≤ 4 mg per 100 ml, differentiated SIADH from most other causes of hyponatremia. The hypouricemia was largely due to increased FEurate. Interestingly, the hypouricemia and increased FEurate corrected after correction of the hyponatremia.[16] This relationship between sodium and urate has been observed by others in SIADH (Figure 1a).[14,16,17] We used this relationship between serum sodium, and serum urate and FEurate to differentiate SIADH from a group of patients whose hypouricemia and increased FEurate persisted after correction of their hyponatremia (Figure 1b).[6,14] One hyponatremic patient with bronchogenic carcinoma, normal CT scan of brain, and normal neurological examination, became profoundly volume-depleted during water restriction for an erroneous diagnosis of SIADH with postural hypotension, postural tachycardia, dry mucous membranes, flat neck veins, tenting of skin, and staggered gait, drooping of eyes, somnolence, and slurred speech on standing.[18] After his serum sodium increased to 138 mmol/l, his hypouricemia and increased FEurate persisted.[18] This and two other patients without cerebral disease prompted our concern that cerebral disease was not an invariable association in RSW.[18]

Increased FEurate with or without hyponatremia or hypouricemia was also noted in AIDS, as noted above, and all but two hyponatremic patients with diverse neurosurgical diseases and AD.[6,14] The persistence of hypouricemia and increased FEurate after correction of hyponatremia or in association with a normal serum sodium was inconsistent with SIADH and in our view represented a group with RSW (Figure 1b).[1,2,6,14] The persistent hypouricemia and increased FEurate that we reported in two patients with indisputable evidence of RSW supported our earlier proposal that this combination was a feature of RSW and that RSW can occur in patients without cerebral disease.[1,2] One had a hip fracture and the other pneumonia. Both were treated for an erroneous diagnosis of SIADH with fluid restriction, which induced anorexia and low sodium intake to account for the UNa of 6 mmol/l in the patient with a hip fracture.[1] She was initially thought to be a hypovolemic patient with normal kidneys, but the serum urate of 3.4 mg per 100 ml and FEurate of 29.6% were more consistent with either SIADH or RSW.[1,5] The 7.1% reduction in blood volume, increased plasma renin and aldosterone levels, and persistence of hypouricemia and increased FEurate after correction of hyponatremia were collectively diagnostic of RSW.[1] This case illustrates how a low sodium intake can result in low UNa in RSW, as sodium output reflects input when in an equilibrated state. In both cases without cerebral disease, saline removed the volume stimulus for ADH secretion and permitted the coexisting plasma hypoosmolality to inhibit ADH secretion, generate free water excretion, and correct the hyponatremia within 48 h (Figure 2).[1,2] Plasma ADH was undetectable when the urine was dilute in the patient with the hip fracture, a finding that illustrates the 'appropriateness' of ADH secretion in RSW.[1] The two cases of RSW strengthened our previous proposal that an increased FEurate in the absence of hyponatremia is a marker for RSW and support the applicability of our rat infusion studies to RSW (Figure 1b).[6,14] Finally, the baseline FEphosphate of 23% (normal < 20%) in one patient is consistent with RSW, as FEphosphate was not present in the two patients with SIADH or reported in SIADH, and is a

clue to infuse saline when present at baseline.[2] The increase in FEurate, occasional increase in FEphosphate, and increased FElithium in our rat infusion studies all favor the proximal tubule as the major site of defective solute transport in RSW.[1,2,14]

ABSENCE OF PRERENAL AZOTEMIA IN RSW

The BUN to creatinine ratio normally expected in prerenal azotemia is often absent and does not differentiate RSW from SIADH. In our well-documented cases of RSW and SIADH, we were unable to show an increase in BUN to creatinine ratio in RSW as compared with SIADH, being 14 and 20 to 1 in RSW and 15.7 and 23.3 to 1 in SIADH.[8,9] This is an important issue to clarify with actual data because it focuses on a fundamental physiological abnormality in RSW that differs from those with ECV depletion and normal kidney function. The intact proximal tubule responds to ECV depletion by increasing reabsorption of urea and other solutes over a nonreabsorbable creatinine to increase the BUN to creatinine ratio in prerenal azotemia. The increases in FEurate, occasional FEphosphate and in our rat studies, FElithium, support our assertion that the proximal tubule is the major site of defective solute transport in RSW. The reduction in sodium and water reabsorption in the proximal tubule reduces the transtubular urea gradient to decrease passive urea reabsorption to prevent the disproportionate increase in BUN over creatinine. The renal response to ECV depletion in RSW, therefore, cannot be equated to those with ECV depletion and normal kidney function.

DIFFERENTIATING RSW FROM SIADH

Determination of ECV by radioisotopic techniques in neurosurgical patients suggests that RSW, especially those with SAH, is more common than SIADH in this population, but its overall prevalence is yet to be determined. This can be ascribed to several factors: consideration of RSW enters the differential only in hyponatremic patients or those with cerebral disease; patients who are normonatremic and without cerebral disease are being overlooked; and hyponatremia occurs less frequently in neurosurgical units because isotonic saline is the fluid of choice.[19] Saline is the treatment of choice because fluid restriction in neurosurgical units, especially those with SAH, increases morbidity and mortality.[19] We and others have encountered instances where fluid restriction for an erroneous diagnosis of SIADH led to clinical deterioration of the patient with RSW.[1,15] The combination of the difficulty to differentiate RSW from SIADH, and occurrence of RSW with and without cerebral disease or hyponatremia contribute to the diagnostic and therapeutic dilemma.

Although differentiating RSW from SIADH on first encounter can be made only by differences in ECV and by an occasional increase in FEphosphate $>20\%$, there are differences that can contribute to making the proper diagnosis and treatment plan. An increase in FEphosphate has been reported in RSW but not in SIADH.[2] FEphosphate should be determined before administering saline. We have shown by clearance and micropuncture studies that saline or mannitol can promptly increase FEphosphate by acutely decreasing serum calcium and magnesium to stimulate parathyroid hormone secretion.[20] We are uncertain what the FEphosphate should be during variable degrees of volume depletion and normal kidney function. The increase in baseline plasma renin and aldosterone levels in RSW can differentiate RSW from the usually depressed levels found in SIADH,[1,2] Plasma renin, however, can be normal in RSW if the patient is ingesting sufficient amounts of salt (Table 1).[2] The defect in proximal salt transport maintains an adequate distal salt load to blunt cyclo-oxygenase 2 and renin production.[19]

Table 1 | Differentiation of SIADH from RSW

	RSW	SIADH
ECV	↓	N-↑
UNa	N-↑	N-↑
Renin	± ↑	± ↓
Aldosterone	↑	± ↓
Serum urate	↓-↓	↓-N
FEurate	↑ ↑	↑-N
FEphosphate	± ↑	N

ECV, extracellular volume; RSW, renal salt wasting; SIADH, secretion of antidiuretic hormone; UNa, urinary sodium concentration.
Table comparing laboratory expectations for RSW and SIADH. UNa can be normal or often >20 mmol/l; serum urate and FEurate are increased during hyponatremia in both RSW and SIADH but differ when serum is normal. Serum urate and FEurate remain abnormal in RSW and normalize in SIADH when serum sodium is normal.

NATRIURETIC FACTOR IN RSW

The persistence of hypouricemia and increased FEurate in the absence of hyponatremia in RSW affords greater credibility to our earlier rat clearance studies in which we infused the plasma of largely nonhyponatremic neurosurgical and AD patients with increased FEurates.[6,12,14] When compared with plasma from age- and gender-matched controls, there were significant increases in both FElithium and FENa.[6,12,14] As lithium is reabsorbed on a one-to-one basis with sodium predominantly in the proximal tubule, the increase in FElithium from 24 to 36.6% and from 27.2 to 41.7% in rats exposed to neurosurgical and AD plasma, respectively, reflects the reduction in proximal tubule sodium transport and large distal load of sodium.[6,12,14] The relatively modest increase in FENa from 0.29 to 0.59% and 0.33 to 0.63% in rats exposed to neurosurgical and AD plasma, respectively, suggests significant compensatory increase in distal sodium reabsorption, although a mild inhibition of distal sodium transport by the natriuretic factor might also be present.[6,12,14] These results support our clinical impression that the proximal tubule is the major site of abnormal solute transport in RSW. As urate and phosphate, like lithium, are exclusively or predominantly transported in the proximal tubule, the increased FEurate and occasional FEphosphate in our patients supports the findings in our rat studies, that the proximal tubule is the major site of solute transport abnormality in RSW. Future studies must test whether the natriuretic factor in RSW affects one or more of the transporters for sodium, urate, phosphate, and urea.

Atrial/brain natriuretic peptides, including urodilatin, have been implicated as possible causes of RSW, but their contribution to RSW is not supported by their modest effect on sodium and other solute transport. These peptides are vasodilators that increase sodium excretion by increasing glomerular filtration rates and a meager effect on distal sodium transport.[21] The administration of atrial natriuretic peptide in normal humans had no effect on lithium excretion rates. The plasma from our neurosurgical and AD patients failed to decrease blood pressure or increase GFR, and the low-normal atrial natriuretic peptide of 35 pg/ml in our hip fracture patient makes it highly unlikely that atrial/brain natriuretic peptides or urodilatin contribute to the salt wasting in RSW.[6,12,14]

CHANGE CSW TO RSW

As discussed above, RSW is more common than SIADH in neurosurgical patients and with the recent reports of RSW occurring in patients without clinical cerebral disease, we must expand our differential to include RSW in patients without cerebral disease.[1,2] Both cases of RSW without cerebral disease were treated by water restriction for an erroneous diagnosis of SIADH.[1,2] Fluid restriction in RSW can lead to variable clinical manifestations depending on the severity of the sodium transport defect and ECV depletion.[1,6] In our present state of understanding these two disorders, it would be interesting to query how many patients with RSW with or without cerebral disease are being fluid restricted for an erroneous diagnosis of SIADH. The extent of their clinical deterioration may depend on the severity of their underlying sodium transport defect and reduced fluid intake, and not on deterioration of their underlying disease. It is time to discard the outmoded, misleading, and inappropriate term, CSW, in favor of a more inclusive RSW. This change in designation, however, will have limited utility unless we can identify those who are likely to have RSW and improve our ability to differentiate RSW from SIADH on first encounter. The combination of diametrically opposing treatment goals and awareness that RSW is a common disorder occurring without hyponatremia or cerebral disease should hasten our pursuit to resolve the diagnostic and therapeutic dilemma, and improve clinical outcomes.

DISCLOSURE

All the authors declared no competing interests.

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