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REVIEW ARTICLE

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

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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^+ .

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.

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

Introduction

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] [2] [3]). Before discussing CSW, however, it is important to define its essential diagnostic elements—we stress that hyponatremia is not one of them.

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.

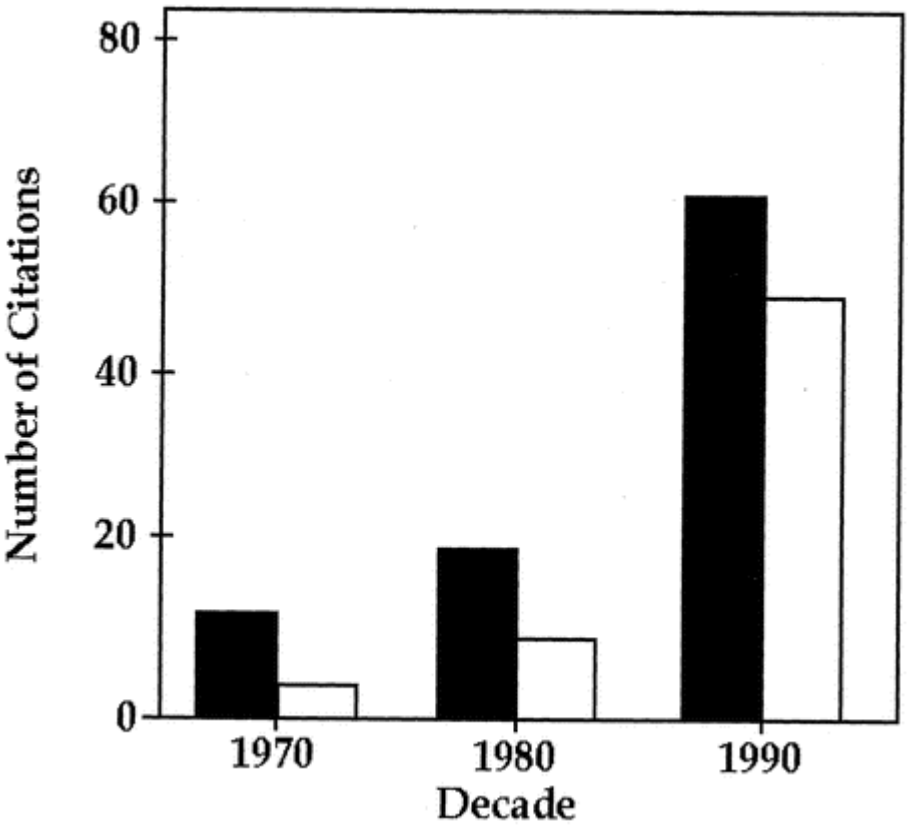

Figure 1. Prevalence of cerebral salt wasting in the past three decades. The data were obtained by a literature search using "cerebral salt wasting" and triple-H ("hypertension, hypervolemia, and hemodilution") as key words. The number of reports with cerebral salt wasting for each decade are shown in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

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.

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.

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] [2] [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 ([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^- 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] [25] [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 (figure 1, figure 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 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] [25] [26]), the full-blown picture of CSW might become evident (Table 1).

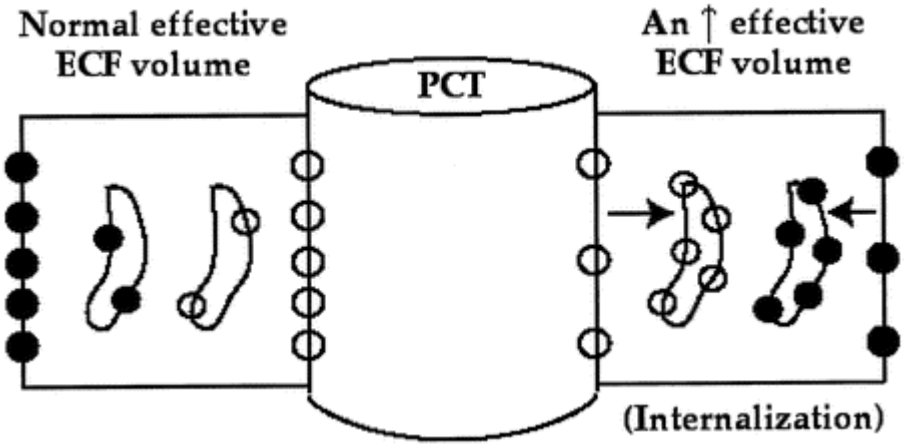

Figure 2. Development of a salt-wasting state by previous chronic expansion of the extracellular fluid (*ECF*) volume. For details, see text. The left portion of the figure represents the normal state with its luminal Na^+ transport system (*open symbols*) and basolateral Na-K–adenosine triphosphatase (*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])).

In our institutes, when CSW was diagnosed 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.

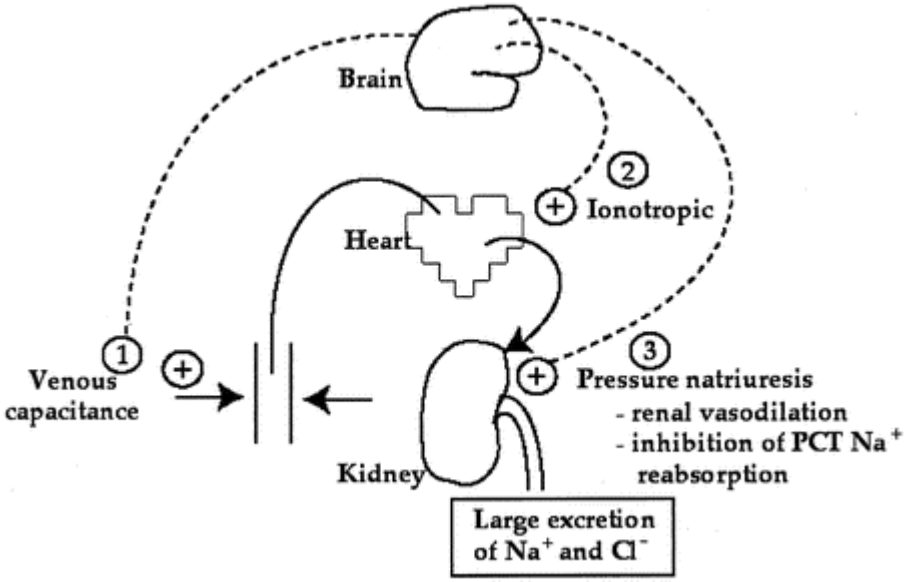

Figure 3. Possible role of an adrenergic surge in cerebral salt wasting. Three major actions of catecholamines (*dashed lines*) could lead to a natriuresis that is caused by a high effective arterial volume. *1*, contraction of the large venous capacitance vessels can lead to a rise in central venous 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.

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.

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.

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.

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

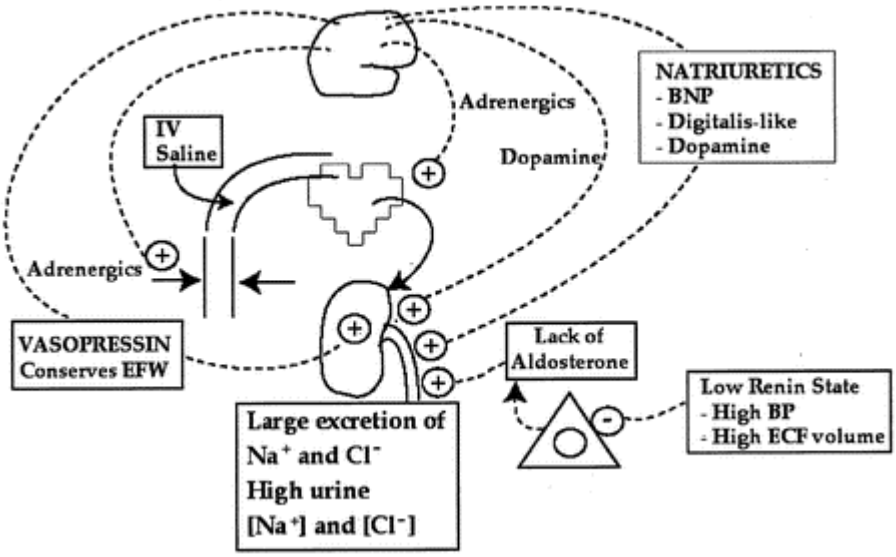

Figure 4. Cerebral salt wasting, an overview. For details, see text and figure 2, figure 3. *EFW*, electrolyte-free H_2O; *BNP*, brain natriuretic peptide; *BP*, blood pressure; *ECF*, extracellular fluid.

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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REFERENCES

1. Harrigan MR : Cerebral salt wasting : A review . Neurosurgery 1996 ; 38 : 152–160 Abstract

2. Nelson PB , Seif SM , Maroon JC , et al: Hyponatremia in intracranial disease : Perhaps not the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) . J Neurosurg 1981 ; 55 : 938–941 Abstract

3. Maesaka JK , Gupta S , Fishbane S : Cerebral salt-wasting syndrome : Does it exist? Nephron 1999 ; 82 : 100–109 Abstract

4. Hebert SC : Extracellular calcium-sensing receptor : Implications for calcium and magnesium handling in the kidney . Kidney Int 1996 ; 50 : 2129–2139 Citation

5. Ganong CA , Kappy MS : Cerebral salt wasting in children : The need for recognition and treatment . Am J Dis Children 1993 ; 147 : 167–169

6. Carlotti APCP , Bohn D , Mallie JP , et al: Tonicity balance and not electrolyte-free water calculations more accurately guide therapy for acute changes in natremia . Intensive Care Med 2001 ; 27 : 921–924 Abstract

7. Kamel KS , Lin SH , Cheema-Dhadli S , et al: Prolonged total fasting : a feast for the integrative physiologist . Kidney Int 1998 ; 53 : 531–539 Citation

8. Schwartz WB , Bennett W , Curelop S , et al: A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone . J Am Soc Nephrol 2001 ; 12 : 2860–2870 Full Text

9. Steele A , Gowrishankar M , Abrahmson S , et al: Postoperative hyponatremia despite isotonic saline infusion : A phenomenon of “desalination” . Ann Intern Med 1997 ; 126 : 20–25 Abstract

10. Robertson GL : Vasopressin . In: The Kidney: Physiology and Pathophysiology . Seldin DW , Giebisch G (Eds). Philadelphia , Lippincott, Williams, and Wilkins , 2000 , pp 1133–1152

11. Gowrishankar M , Lin SH , Mallie JP , et al: Acute hyponatremia in the perioperative period : Insights into its pathophysiology and recommendations for management . Clin Nephrol 1998 ; 50 : 352–360 Abstract

12. Walser M : Phenomenological analysis of electrolyte homeostasis . In: The Kidney: Physiology and Pathophysiology . Seldin DW , Giebisch G (Eds). New York , Raven Press , 1992 , pp 31–44

13. Hollenberg NK : Set point for sodium homeostasis : Surfeit, deficit, and their implications . Kidney Int 1980 ; 17 : 423–429 Citation

14. Schreiber MS , Halperin ML : Paleolithic curriculum : Figure it out (with the help of experts) . Adv Physiol Educ 1998 ; 20 : S185–S194

15. Brater DC : Diuretic therapy . N Engl J Med 1998 ; 339 : 387–395 Citation

16. Heer M , Baisch F , Kropp J , et al: High dietary sodium chloride consumption may not induce body fluid retention in humans . Am J Physiol 2000 ; 278 : F585–F595

17. McCance RA : Medical problems in mineral metabolism: III. Experimental human salt deficiency . Lancet 1936 ; 230 : 823–830

18. Chung HM , Kluge R , Schrier RW : Clinical assessment of extracellular fluid volume in hyponatremia . Am J Med 1987 ; 83 : 905–908 Abstract

19. Schrier RW , Fassett RG , Ohara M , et al: Pathophysiology of renal fluid retention . Kidney Int 1998 ; 54 : S127–S132

20. Kamel KS , Magner P , Ethier J , et al: Urine electrolytes in the assessment of extracellular fluid volume contraction . Am J Nephrol 1989 ; 9 : 344–347 Abstract

21. Oliver WJ , Cohen EL , Neel JV : Blood pressure, sodium intake, and sodium related hormones in Yanomamo Indians, a “No-Salt” culture . Circulation 1975 ; 52 : 146–151 Abstract

22. Maesaka JK , Fishbane S : Regulation of renal urate excretion : A critical review . Am J Kidney Dis 1998 ; 32 : 917–933 Abstract

23. Carlotti APCP , Bohn D , Rutka JT , et al: Estimation of urinary electrolyte excretion in patients in the intensive care unit . J Neurosurgery 2001 ; 95 : 420–424

24. Berendes E , Walter M , Cullen E : Secretion of brain natriuretic peptide in patients with aneurysmal subarachnoid hemorrhage . Lancet 1997 ; 349 : 245–249 Abstract

25. Isotani E , Suzuki R , Tomita K , et al: Alterations in plasma concentrations of natriuretic peptides and antidiuretic hormone after subarachnoid hemorrhage . Stroke 1994 ; 25 : 2198–2203 Abstract

26. Wijdick EFM , Ropper AH , Hunnicut EJ , et al: Atrial natriuretic factor and salt wasting after aneurysmal subarachnoid hemorrhage . Stroke 1991 ; 22 : 1519–1524 Abstract

27. Wijdick EFM , Vermeulen M , Van Brummelen P , et al: Digoxin-like immunoreactive substance in patients with aneurysmal subarachnoid hemorrhage . BMJ 1987 ; 294 : 729–732

28. Yamada K , Goto A , Nagoshi H , et al: Role of brain ouabain-like compound in central nervous system-mediated natriuresis in rats . Hypertension 1994 ; 23 : 1027–1031 Abstract

29. Peerless SJ , Kassell NF , Durward QJ , et al: Treatment of ischemic deficits from vasospasm with intravascular volume expansion and induced arterial hypertension . Neurosurgery 1982 ; 11 : 337–343 Abstract

30. Wijdick EFM , Vermeulen M , Hijdra A , et al: Hyponatremia and cerebral infarction in patients with ruptured intracranial aneurysm : Is fluid restriction harmful . Ann Neurol 1985 ; 11 : 137–140 Abstract

31. Zhang Y , Mircheff AK , Hensley CB , et al: Rapid redistribution and inhibition of renal sodium transporters during acute pressure natriuresis . Am J Physiol 1996 ; 270 : F1004–F1014 Abstract

32. Clifton GL , Zeigler MG , Grossman RG : Circulating catecholamines and sympathetic activity after head injury . Neurosurgery 1981 ; 8 : 10–14 Abstract

33. Israel A , Torres M , Cierco M , et al: Further evidence for a dopaminergic involvement in the renal action of centrally administered atrial natriuretic peptide in rats . Brain Res Bull 1991 ; 27 : 739–742 Abstract

34. Aperia AC : Renal dopamine system and salt balance . Am J Kidney Dis 1998 ; 31 : xlii–xlv Citation

35. Hasan D , Lindsay KW , Wijdicks EFM : The effect of fludrocortisone acetate in patients with subarachnoid hemorrhage . Stroke 1989 ; 20 : 1156–1161 Abstract

36. Cort JH , Yale MD : Cerebral salt wasting . Lancet 1954 ; 1 : 752–754

37. Phelps KR , Lieberman RL , Oh MS , et al: Pathophysiology of the syndrome of hyporeninemic hypoaldosteronism . Metabolism 1980 ; 29 : 186–199 Citation

38. Gadallah MF , Kayyas Y , Boules F : Reversible suppression of the renin-aldosterone axis after unilateral adrenalectomy for adrenal adenoma . Am J Kidney Dis 1998 ; 32 : 160–163 Abstract