Continuing Nephrological Education (CNE)

Hyponatraemia in a neurosurgical patient: syndrome of inappropriate antidiuretic hormone secretion *versus* cerebral salt wasting

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Introduction

Hyponatraemia is a common electrolyte disorder in the setting of central nervous system disease and is often attributed to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). This syndrome is characterized by hyponatraemia with an inappropriately concentrated urine, increased urine sodium concentration, and evidence of normal or slightly increased intravascular volume. By contrast, there are patients with intracranial disease who develop hyponatraemia with similar characteristics but differ in that there is clinical evidence of a contracted extracellular fluid (ECF) volume. This form of hyponatraemia is due to excessive renal sodium excretion resulting from a centrally mediated process and is termed cerebral salt wasting (CSW). While fluid restriction is the treatment of choice in SIADH, the treatment of CSW consists of vigorous sodium and volume replacement. Given the divergent nature of the treatment and the potential for improper selection of fluid therapy to worsen the underlying clinical condition it is of paramount importance for the clinician to be able to recognize and differentiate between these two entities.

Case

A 44-year-old black man was admitted to an outside hospital after a fall with loss of consciousness. His past medical history was significant for chronic alcoholism complicated by alcohol withdrawal seizures and delirium tremens. On physical examination, the patient was found to be a thin black man who appeared older than his stated age. Vital signs showed: temperature 98.6°F, heart rate 100/min, respiratory rate 18/min, BP 140/60 mmHg without orthostatic changes. The remainder of the physical examination was only signi-

ficant for neurological findings. He was lethargic, disoriented to person, place, and time, and had increased tremulousness. Cranial nerves II–XII were intact. Muscle strength was 5/5 throughout. Reflexes were 2+ and symmetrical and the Babinski sign was negative bilaterally. Initial laboratory examination was unremarkable. A CT scan of the head without contrast showed evidence of a subarachnoid haemorrhage with extra axial haemorrhage adjacent to both frontal lobes. A cerebral angiogram was normal with no evidence of aneurysm or vascular malformation.

The patient was transferred to Parkland Memorial Hospital and admitted to the neurosurgery service. He was treated with librium for his tremulousness, dilantin for seizure prophylaxis, and thiamine, folate and multivitamins. Over the following days his mental status improved to baseline.

On hospital day 10 the patient was noted to be confused and hypotensive. His physical examination was notable for orthostatic changes in pulse and blood pressure. The following data was obtained (mmol/l): Na 118, K 5.2, Cl 85, HCO_3 22. Other laboratory tests obtained showed a serum creatinine concentration of 0.8 mg/dl, glucose 88 mg/dl, and a serum osmolality of 258 mosm/l. The uric acid was 3.4 mg/dl. Tests of both thyroid and adrenal function were normal. Urine electrolytes showed (mmol/l): Na 204, K 20, Cl 191. The urine creatinine concentration was 71 mg/dl and the urine osmolality was 633 mosm/l.

In summary, this 44-year-old man developed significant hyponatraemia in association with a recent subarachnoid haemorrhage. Two potential causes of hyponatraemia in this setting are SIADH and CSW. Distinguishing between these disorders will be the primary focus of this review. To better understand how these disorders differ from other causes of hyponatraemia, a brief overview on the general approach to the hyponatraemic patient will be provided. For a more detailed discussion on this topic, the reader is referred to two recent reviews [1,2].

Approach to the hyponatraemic patient

The initial approach to a patient with hyponatraemia is to measure the serum osmolality in order to deter-

Correspondence and offprint requests to: Biff F. Palmer MD, Professor of Internal Medicine, Director of Clinical Nephrology, Department of Internal Medicine, Division of Nephrology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75235, USA.

mine whether the hyponatraemia is representative of a hypo-osmolar state (Figure 1). A normal serum osmolality would suggest the presence of pseudohyponatraemia as seen in patients with hyperglobulinaemia or hypertriglyceridaemia or an increased concentration of some other osmole such as glucose.

If a hypo-osmolar state is confirmed the next step is to determine whether the kidney's ability to dilute the urine is intact. In the setting of hyponatraemia, the normal response of the kidney is to elaborate a maximally dilute urine (<100 mosm/l). In general, because the normal kidney is able to excrete 20–30 l of water per day, it is difficult to become hyponatraemic with an intact diluting mechanism. However, this can occur in a few rare patients who ingest water in amounts that exceed the kidney's ability to excrete water. These patients should have a urine osmolality <100 mosm/l. Another unusual condition in which more modest amounts of fluid intake can lead to hyponatraemia in association with a maximally dilute urine is when solute intake is extremely limited. This condition is often referred to as beer potomania syndrome [3]. In addition to chronic alcoholics, this syndrome has also been described in other patients with extremely limited solid food intake [4].

In hyponatraemic patients with an inappropriately concentrated urine one needs to next assess the effective arterial blood volume (EABV). Most of the causes of hyponatraemia result from a decrease in EABV, which causes baroreceptor stimulation of arginine vasopressin secretion (AVP) and leads to decreased distal delivery of filtrate to the tip of the loop of Henle. Clinical determination of EABV is usually straightforward. Determining the presence or absence of a postural change in blood pressure or pulse is particularly important in this regard. Urinary electrolytes are also extremely useful in the assessment of EABV. Patients with a low EABV will tend to have a low urinary sodium, low urinary chloride, and low fractional excretions of sodium and chloride in the urine. Patients with euvolaemic hyponatraemia, however, will be in balance and will excrete sodium and chloride at rates that reflect dietary intake of sodium and chloride. Thus, generally they have urinary sodium and chlorides >20 mmol/l and fractional excretions of these electrolytes >1%.

Plasma composition can also be used to assess EABV. The blood urea nitrogen (BUN) is particularly sensitive to EABV. In patients with normal serum creatinines, a high BUN suggests a low EABV and a low BUN suggests a high EABV. The plasma uric acid can also be used as a sensitive index of EABV. In comparison with patients suffering from SIADH and other causes of hyponatraemia, patients with low EABV tend to have an elevated serum uric acid. In patients with SIADH, serum urate is not elevated but is actually depressed as these patients are volume expanded, although it is clinically difficult to detect the degree of volume expansion.

Referring back to the case presentation it can be concluded that a hypo-osmolar state is present (258 mosm/l) and that the urine is inappropriately concentrated (633 mosm/l). The increased urinary sodium concentration and decreased serum uric acid suggest a volume-expanded state such as SIADH. However, as discussed below, increased urinary sodium excretion and depressed serum uric acid are also characteristic of CSW. The finding of an orthostatic change in blood pressure and pulse in this patient strongly suggests the presence of a contracted EABV and thus confirms a
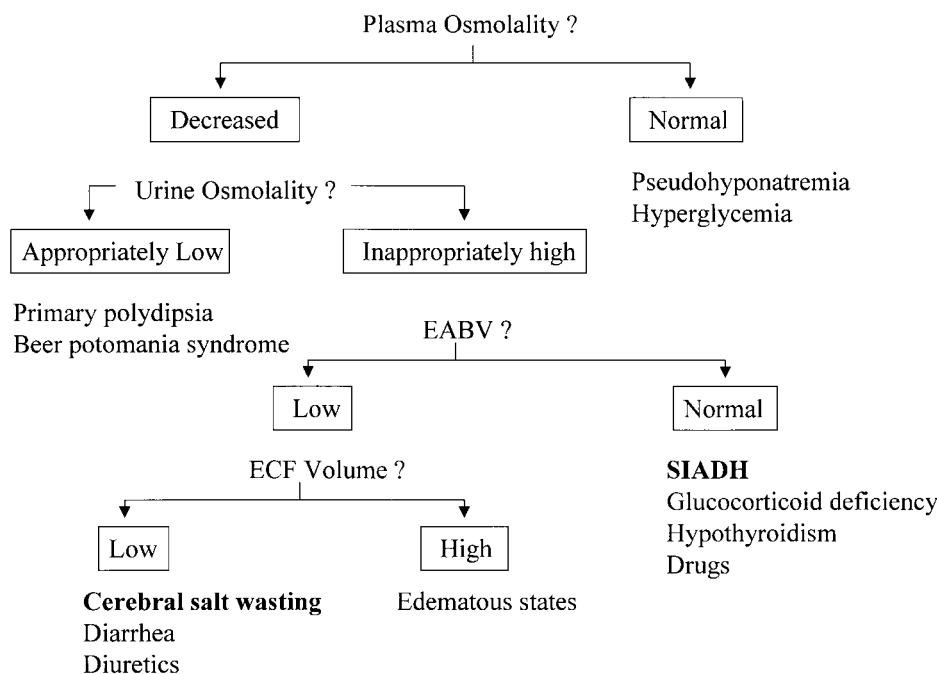

Fig. 1. Approach to the hyponatraemic patient (EABV: effective arterial blood volume, ECF: extracellular fluid volume).

diagnosis of CSW. While the laboratory features of CSW and SIADH show considerable overlap the mechanisms by which they develop are quite distinct. The laboratory abnormalities in SIADH can be traced to changes in renal function that accompany expansion of ECF volume. Much less is known about the development of laboratory abnormalities in CSW. Indirect evidence suggests a primary impairment in the efficiency of solute reabsorption in the proximal nephron mediated by decreased neural input to the kidney and/or effects of a circulating natriuretic factor. In addition there is evidence of a suppressed renin–angiotensin–aldosterone axis. These issues are discussed below.

SIADH is a volume-expanded state

The primary pathogenic mechanism underlying SIADH is excessive ADH release causing renal water reabsorption and resulting in expansion of the ECF volume. Evidence for a volume expanded state in SIADH initially came from studies of normal individuals given exogenous pitressin [5]. In these experiments administration of pitressin resulted in an abrupt decrease in urine volume and increase in urine osmolality (Figure 2). The water retention produced by this antidiuretic effect resulted in an increase in body weight and dilution of the serum sodium concentration. After several days of pitressin administration, a large increase in urine sodium and chloride excretion was noted. This subsequent increase in urine electrolyte excretion was triggered by the progressive expansion of total ECF volume as reflected by the increase in body weight. If fluid intake was kept low during the administration of pitressin, body weight remained unchanged and urine electrolyte excretion did not increase. These findings were reproduced several years later when the first clinical cases of SIADH were described in two patients with bronchogenic carcinoma [6].

During exogenous administration of vasopressin when water intake is not limited and body weight is allowed to increase a steady state is eventually reached in which urine sodium excretion stabilizes and is equal to dietary sodium intake. At this time severe dietary sodium restriction will lead to excretion of urine that is essentially sodium free whereas administration of a large isotonic sodium load is followed by rapid and almost quantitative urinary excretion of the infused solute [7]. The establishment of normal renal sodium handling despite a decreased serum sodium concentration is a characteristic feature of SIADH.

In SIADH expansion of ECF volume is not typically accompanied by overt signs of hypervolaemia such as oedema or distended neck veins since only one-third of retained water is distributed in the ECF space. Nevertheless modest expansion of the intravascular volume results in increased glomerular filtration rate and increased renal plasma flow. In addition the volume expansion leads to decreased proximal sodium reabsorption and urinary sodium excretion is increased and equal to dietary sodium intake. Substances such as uric acid and urea nitrogen, that are reabsorbed in concert with sodium proximally, also tend to be reduced because of diminished proximal reabsorption.

CSW is a volume-depleted state

The concept of a CSW syndrome was first introduced by Peters and colleagues in 1950 in a report describing three patients with neurological disorders who presented with hyponatraemia, clinical evidence of volume depletion, and renal sodium wasting without an obvious disturbance in the pituitary–adrenal axis [8]. This same constellation of findings was subsequently confirmed in additional patients with widely varying forms of cerebral disease [9,10]. In these initial reports, it was theorized that cerebral disease could lead to renal salt wastage and subsequent depletion of ECF volume by directly influencing nervous input into the kidneys. However, with the subsequent description of SIADH by Schwartz et al. [6], the clinical entity of cerebral salt wasting became viewed as either an extremely rare disorder or a misnomer for what was truly SIADH. Only in recent years has cerebral salt wasting again come into favour as a distinct entity. This recognition of CSW has been particularly striking in the field of neurosurgery where CSW is viewed by some as a more common disorder than SIADH.

Part of this new found appreciation for the diagnosis of CSW can be traced to reports in which measurement of blood and plasma volume were found to be decreased in patients who met the traditional laboratory criteria for SIADH. Nelson et al. studied 12 unselected hyponatraemic neurosurgical patients with subarachnoid haemorrhage, intracranial aneurysm, and head injury [11]. The hyponatraemia developed on an average on the tenth day of the patients illness and was associated with increased urine Na concentration (>25 mmol/l) and an inappropriately concentrated urine. As compared to neurosurgical patients without intracranial disease, 10 of the 12 patients had significant reductions in plasma volume and total blood volume. These same investigators then examined sodium balance in a monkey model of subarachnoid haemorrhage [12]. Following the haemorrhage, seven of nine animals developed hyponatraemia in association with natriuresis and negative salt balance. There was a slight decline in plasma volume, although it was not statistically significant. In contrast, sham-operated control animals did not become hyponatraemic or natriuretic and plasma volume did not change. Wijdicks et al. determined sodium balance and measured plasma volume in 21 patients with subarachnoid haemorrhage [13]. On an average of 7 days following the event, nine patients developed hyponatraemia that met the criteria for a diagnosis of SIADH. Eight of nine patients were found to be in negative sodium balance, which preceded the development of hyponatraemia. Body weight declined in all of the hyponatraemic patients, with six demonstrating a $>10\%$ decrease
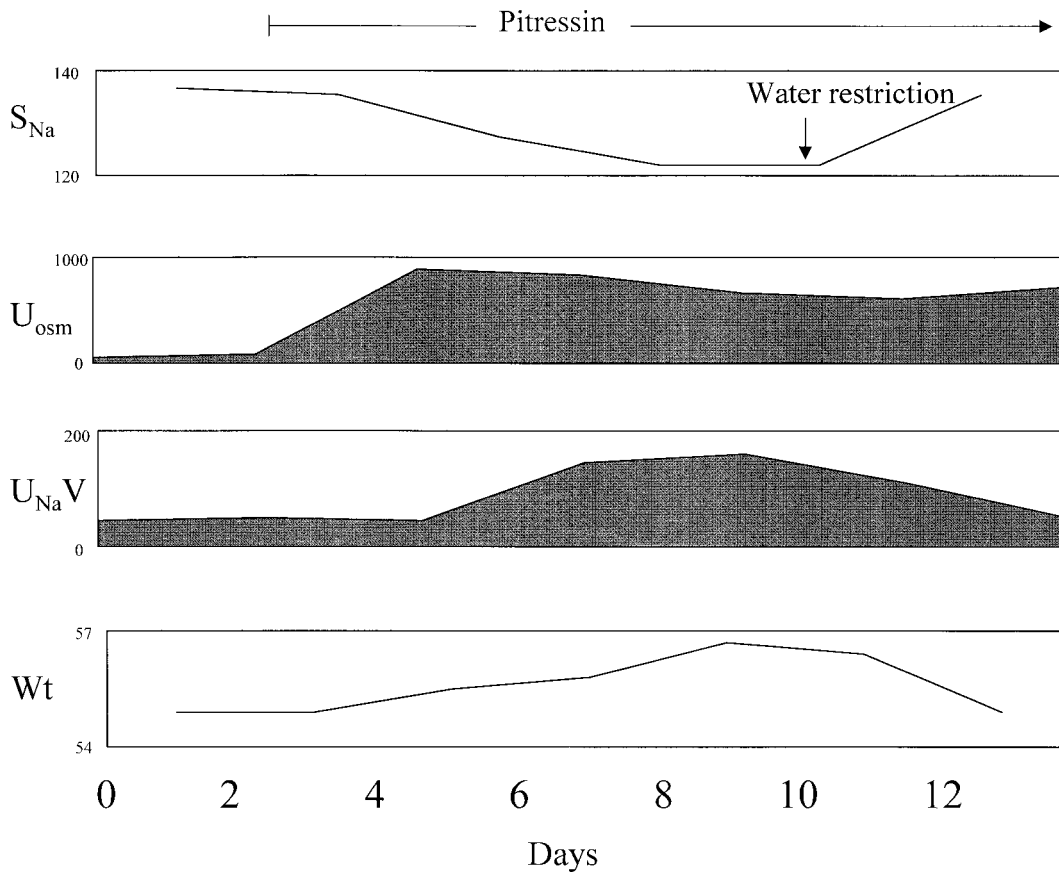
Fig. 2. The administration of pitressin to a normal human subject results in an abrupt increase in urine osmolality (U_{osm}). As water is retained and body weight (Wt) increases, there is a rise in urinary sodium excretion ($U_{Na}V$). A fall in body weight induced by water restriction leads to a decrease in urinary sodium excretion despite the presence of a persistently concentrated urine. These results support the notion that increased urinary sodium excretion in SIADH is the result of ECF volume expansion (S_{Na}, serum sodium concentration) (Adapted from reference 5, with permission).

in plasma volume. Interestingly, of the 12 patients without hyponatraemia negative sodium balance developed in four patients and plasma volume decreased in eight. In one additional report of 21 neurosurgical patients with hyponatraemia associated with increased urine sodium concentration and an inappropriately concentrated urine, volume status was assessed by measurement of total blood volume and central venous pressure and determining the response to volume supplementation [14]. Despite fulfilling the laboratory criteria for SIADH, these patients all showed evidence of a contracted ECF volume.

In summary, a substantial number of neurosurgical patients who develop hyponatraemia and otherwise meet the clinical criteria for a diagnosis of SIADH have a volume status inconsistent with that diagnosis. Rather the evidence of negative salt balance and reductions in both plasma and total blood volume in these patients is more consistent with a diagnosis of cerebral salt wasting.

Pathophysiology of cerebral salt wasting

The mechanism by which cerebral disease leads to renal salt wasting is not well understood. The most likely process involves disruption of neural input into the kidney and/or central elaboration of a circulating natriuretic factor (Figure 3). By either or both mechanisms, increased urinary sodium excretion would lead to a decrease in EABV and thus provide a baroreceptor stimulus for the release of AVP. In turn, increased AVP levels would impair the ability of the kidney to elaborate a dilute urine. In this setting, the release of AVP is an appropriate response to the volume depletion. In contrast, release of AVP in SIADH is truly inappropriate since EABV is expanded.

A likely site for depressed renal sodium absorption in CSW is the proximal nephron. Since this segment normally reabsorbs the bulk of filtered sodium, a small decrease in the efficiency of this segment would result in the delivery of large amounts of sodium to the distal nephron and ultimately into the final urine. Decreased sympathetic input to the kidney would be a likely explanation for impaired proximal reabsorption, since the sympathetic nervous system has been shown to alter salt and water handling in this segment through a variety of both indirect and direct mechanisms. Since the sympathetic nervous system also plays an important role in the control of renin release, decreased sympathetic tone may explain the failure of circulating
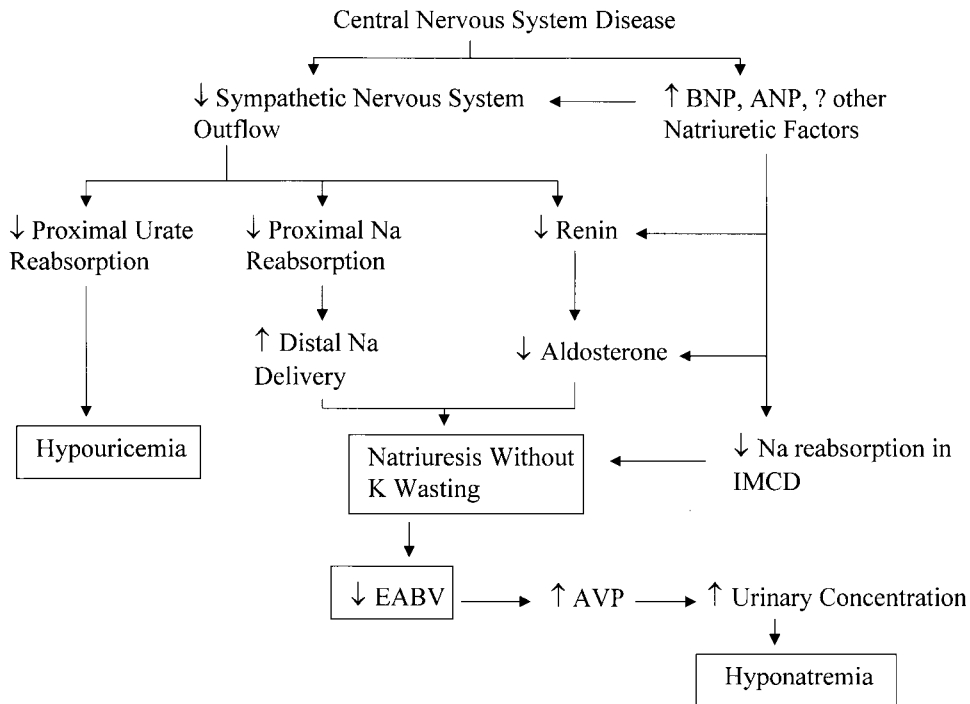
Central Nervous System Disease

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                    ↓ Sympathetic Nervous System  ◄──────  ↑ BNP, ANP, ? other
                    Outflow                                  Natriuretic Factors

  ↓ Proximal Urate      ↓ Proximal Na       ↓ Renin  ◄───────────
  Reabsorption          Reabsorption                             │
                             │                    │              │
                        ↑ Distal Na          ↓ Aldosterone ◄─────
                        Delivery

  ┌──────────────┐     ┌─────────────────┐         ↓ Na reabsorption in
  │ Hypouricemia │     │ Natriuresis Without │ ◄───  IMCD
  └──────────────┘     │ K Wasting          │
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              ┌────────┐
              │ ↓ EABV │ ────► ↑ AVP ────► ↑ Urinary Concentration
              └────────┘
                                            ┌──────────────┐
                                            │ Hyponatremia │
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Fig. 3. A proposed mechanism for the pathogenesis of cerebral salt wasting. IMCD, inner medullary collecting duct; EABV, effective arterial blood volume; AVP, arginine vasopressin; BNP, brain natriuretic peptide; ANP, atrial natriuretic peptide.

renin and aldosterone levels to rise in patients with CSW [15,16]. The failure of serum aldosterone levels to rise in response to a decreased EABV can account for the lack of renal potassium wasting despite the large increase in distal delivery of sodium. In this regard, hypokalaemia has not been a feature of CSW and in the current case the serum potassium was actually slightly increased.

In addition to decreased neural input to the kidney, release of one or more natriuretic factors may also play a role in the renal salt wasting observed in CSW. Atrial and brain natriuretic peptide (ANP, BNP) have several effects that could lead to the clinical syndrome of cerebral salt wasting. For example, infusion of either of these peptides into normal human subjects results in a natriuretic response that is unrelated to changes in blood pressure [17]. The ability of these compounds to increase glomerular filtration rate accounts for some of the natriuresis, however, even in the absence of a change in GFR urinary sodium excretion increases due to a direct inhibitory effect on sodium transport in the inner medullary collecting duct [17].

These peptides are also capable of increasing urinary sodium excretion without causing hypokalaemia. For example, ANP and BNP are associated with decreased circulating levels of aldosterone because of direct inhibitory effects on renin release in the juxtaglomerular cells of the kidney as well as direct inhibitory effects on aldosterone release in the adrenal gland. In addition, inhibition of sodium reabsorption in the inner medullary collecting duct would not be expected to cause renal potassium wasting since this segment is distal to

the predominant potassium secretory site in the cortical collecting duct.

ANP and BNP have also been shown capable of directly decreasing autonomic outflow through effects at the level of the brain stem [17,18]. In this manner, natriuretic peptides may act synergistically with central nervous system disease to decrease neural input to the kidney. A recent review has summarized the evidence both for and against ANP as well a circulating ouabain-like factor as important factors in the development of CSW [19].

Of the various natriuretic compounds, Berendes *et al.* has provided evidence to suggest that BNP may be the more likely candidate to mediate renal salt wasting [16]. He compared 10 patients with subarachnoid haemorrhage who underwent clipping of an aneurysm to a control group consisting of 10 patients who underwent craniotomy for resection of cerebral tumours. All of the patients with subarachnoid haemorrhage and none of the control group showed an increase in urine output accompanied by increased urinary sodium excretion that tended to peak 3–4 days following the procedure. Sodium and fluid loss in the urine was matched by intravenous replacement in order to prevent the development of hyponatraemia. As compared to the control group, significantly greater levels of BNP were found in the subarachnoid haemorrhage patients both prior to surgery as well as through postoperative day 8. The BNP concentration was significantly correlated with both urinary sodium excretion as well as intracranial pressure. By contrast there were no differences in ANP concentration or digoxin-like

immunoreactive substances between the two groups. Plasma renin concentration was the same in both groups but plasma aldosterone concentrations were suppressed and varied in an opposite direction to that of BNP in the subarachnoid haemorrhage group.

BNP in humans is primarily found in the cardiac ventricles but is also found in the brain [17,20]. It is not known whether brain or cardiac tissue or both contribute to the increased BNP concentration found in these patients with subarachnoid haemorrhage. Increased release of cardiac BNP could be part of a generalized stress response to the underlying illness while increased intracranial pressure may provide a signal for brain BNP release. In this regard one could speculate that teleologically the development of renal salt wasting and resultant volume depletion in the setting of intracranial disease is a protective measure designed to limit extreme rises in intracranial pressure.

Differentiation of SIADH and cerebral salt wasting

Distinguishing between CSW and SIADH in clinical practice can be difficult given the similarity in laboratory values and the overlap in associated intracranial diseases. As emphasized in the foregoing discussion determination of ECF volume remains the primary means of distinguishing these two disorders (Table 1). ECF volume tends to be slightly increased in SIADH, whereas it is low in CSW. Physical findings that support a diagnosis of CSW include orthostatic changes in blood pressure and pulse, dry mucous membranes, and flat neck veins. Weight loss or negative fluid balance as determined by review of hospital flow sheets are particularly strong pieces of evidence in support of a declining ECF volume. Laboratory findings that are useful include evidence of haemoconcentration as reflected by an increased haematocrit and increased serum albumin concentration and the finding of an elevated serum bicarbonate concentration, since decreased ECF volume is an important factor in the maintenance of metabolic alkalosis.

Normally the serum level of uric acid would be a useful tool in this situation. As previously mentioned uric acid levels are depressed in patients with SIADH

Table 1. Differential diagnosis of cerebral salt wasting (CSW) vs syndrome of inappropriate secretion of antidiuretic hormone (SIADH)

	CSW	SIADH
Extracellular fluid volume[a]	⇓	⇑
Haematocrit	⇑	normal
Albumin concentration	⇑	normal
BUN/creatinine	⇑	⇓
Potassium	normal or ⇑	normal
Uric acid	normal or ⇓	⇓
Treatment	normal saline	fluid restriction

[a]ECF volume is the primary means of distinguishing CSW from SIADH (see text for discussion).

reflective of the slight increase in ECF volume. By contrast, uric acid levels in patients with hyponatraemia occurring in the setting of decreased ECF volume are either normal or slightly increased. Although not well studied, serum uric acid levels in CSW tend to be unexpectedly low [21]. In fact hypo-uricaemia and increased fractional urate excretion may be a common feature of intracranial disease in general [21,22]. Maesaka et al. studied 29 consecutive neurosurgical patients with a variety of intracranial diseases [23]. Eighteen of the patients had fractional excretion of urate values >10% and 16 had a serum urate concentration ≤4 mg/dl. Only one patient in the series had coexistent hyponatraemia. In this patient the hypo-uricaemia and increased fractional urate excretion persisted after correction of the serum sodium concentration. While not always accompanied by hyponatraemia, hypouricaemia and increased renal uric acid excretion has also been noted in patients with Alzheimer's disease and in patients with the acquired immunodeficiency syndrome [22,24]. While correction of the serum sodium concentration in SIADH leads to a normalization of uric acid handling by the kidney [25], hypouricaemia and increased renal uric acid excretion remains a persistent finding following the correction of the serum sodium concentration in CSW [21].

Treatment of CSW and SIADH

Making the distinction between CSW and SIADH is of particular importance with regard to therapy. Fluid restriction is employed in SIADH since the primary abnormality is expansion of the ECF volume with water. Administration of NaCl is indicated in CSW as ECF volume is decreased as a result of renal salt wasting. Failure to distinguish properly between these disorders such that therapy indicated for one disorder is inappropriately employed for the other can potentially result in an adverse outcome.

The potential for fluid restriction to worsen the underlying neurologic condition in the setting of CSW was suggested by Wijdicks et al. [26]. In a retrospective study of patients with subarachnoid haemorrhage, 44/134 patients were found to have developed hyponatraemia between 2 and 10 days following the haemorrhage; 21/44 patients treated with fluid restriction developed a cerebral infarction including 15/17 patients who clinically met the criteria for SIADH. While the volume status of the patients was not defined, the authors raised the possibility that many of these patients may have had CSW as a cause of the hyponatraemia. If so, fluid restriction would tend to aggravate an already decreased plasma volume. Maintenance of an adequate intravascular volume is important in the management of subarachnoid haemorrhage in order to minimize cerebral ischaemia induced by vasospasm. A decrease in plasma volume could potentially worsen cerebral blood flow by increasing blood viscosity and decreasing cardiac output.

In patients with CSW intravascular volume needs to be vigorously maintained with intravenous saline. Once patients are capable of taking oral medications, salt tablets can be utilized. Although not well studied, CSW tends to be transient in nature with evidence of renal salt wasting usually resolving after 3–4 weeks.

Just as fluid restriction can potentially worsen the underlying condition in CSW, intravenous saline given to patients with SIADH can cause a further lowering of the serum sodium concentration and potentially result in symptomatic hyponatraemia. This potentially deleterious response is the result of SIADH being a disorder in which renal water handling is impaired but renal sodium handling is normal. Consider the response of a patient with SIADH given 1 litre of normal saline (308 mosm). Assuming a urine osmolality of 616 mosm/l, the entire load of NaCl will be excreted in 500 ml of fluid. The remaining 500 ml of administered fluid will remain within the body and cause a further lowering of the serum Na concentration. In order to avoid worsening hyponatraemia in this setting the osmolality of the fluid given must exceed the osmolality of the urine.

Summary

In summary, SIADH and CSW are two potential causes of hyponatraemia is patients with neurosurgical disorders. Distinguishing between these two disorders can be challenging, since there is considerable overlap in the clinical presentation. The primary distinction lies in the assessment of the EABV. SIADH is a volume expanded state due to ADH-mediated renal water retention. CSW is characterized by a contracted EABV resulting from renal salt wasting. Making an accurate diagnosis is important since the therapy of each condition is quite divergent. Vigorous salt replacement is indicated in patients with CSW while fluid restriction is the treatment of choice in patients with SIADH. Therapy indicated for one disorder but used in the other can potentially result in untoward clinical consequences.

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