CASE REPORT

From renal salt wasting to SIADH

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SUMMARY

Hyponatraemia is common following major head injury and is associated with significant morbidity and mortality. A 20-year-old man presented with reduced consciousness after head trauma and was found to have a fractured skull base with bilateral frontal contusions. On day 3 of his admission, he developed hyponatraemia with raised urine sodium and osmolality, despite receiving dexamethasone and intravenous fluid therapy. His hyponatraemia worsened after the treatment with fluid restriction and oral salt. He was in negative fluid balance suggesting possible renal salt wasting. A trial of isotonic normal saline resulted in a further fall in serum sodium level. He was subsequently treated for suspected syndrome of inappropriate ADH with a hypertonic (3%) saline infusion. His sodium level and neurological status improved. This case report illustrates the confounding factors that commonly affect clinical decision-making when treating patients with hyponatraemia following head injury. The guidelines for diagnosis and management are discussed.

BACKGROUND

Hyponatraemia occurs in up to 10% of patients following a traumatic brain injury and is associated with a worse prognosis even in mild cases.^{1,2} Differentiating syndrome of inappropriate antidiuretic hormone (SIADH) secretion from renal (cerebral) salt wasting (RSW)³ and other causes is challenging in the presence of concurrent medications and following the administration of saline-containing intravenous fluids.⁴ However, careful consideration of the differential diagnoses may avoid inappropriate treatment that could compromise the optimal clinical outcome.

CASE PRESENTATION

A 20-year-old male university student presented with reduced consciousness (GCS11 E2, V4 and M5) after falling from his skateboard while intoxicated with alcohol. A trauma screen demonstrated that he had sustained a base of skull fracture and bilateral frontal lobe contusions (figure 1). He was started on dexamethasone 12 mg/day to reduce the risk of worsening cerebral oedema. His baseline blood tests were unremarkable, except for mild hypokalaemia and lymphocytosis: haemoglobin 15.7 g/dL (130–180 g/L); haematocrit 0.462 L/L (0.320–0.520 L/L); white cell count $15.1 \times 10^9/L$ ($4-11 \times 10^9/L$); lymphocytes $7.7 \times 10^9/L$ ($1.0-4.0 \times 10^9/L$); platelets $335 \times 10^9/L$ ($150-400 \times 10^9/L$); sodium 142 mmol/L (135–145 mmol/L), potassium 3.3 mmol/L (3.5–5.2 mmol/L), urea 4.1 mmol/L (3.1–8.1 mmol/L),

Figure 1 (Left) CT demonstrates a fracture extending from the right lambdoid suture into the mastoid process is shown. A further longitudinal fracture of the mastoid process and a subtle fracture in the posterior wall of the right sphenoidal sinus were also seen but not demonstrated in this slice. (Right) There are petechial haemorrhages in the inferior aspect of both frontal lobes consistent with brain contusions.

creatinine 100 $\mu\text{mol/L}$ (60–110 $\mu\text{mol/L}$), and thyroid-stimulating hormone 0.24 mIU/L (0.4–3.50 mIU/L) with free T_4 10.5 pmol/L (9–19 pmol/L). He was prescribed supplementary intravenous fluids and this corrected his electrolyte levels over the first 24 hours (sodium 135 mmol/L and potassium 4.0 mmol/L).

On day 3, he developed hypo-osmolar hyponatraemia (serum osmolality 272 mmol/kg and sodium 131 mmol/L). His 24-hour urine output was 3.9 L, and a fluid deficit had been measured since admission (–2.4 L) despite supplementation with 3 L Hartmann's solution (containing 131 mmol/L of sodium). His urine sodium (222 mmol/L) and urine osmolality (742 mmol/kg) were elevated, and he was noted to have normal renal function. The treating team initiated a fluid restriction (1.5 L) and prescribed oral salt tablets (2.4 g per day) for a presumed SIADH.

On day 4, the patient developed worsening hyponatraemia with serum sodium of 125 mmol/L. A specialist endocrinologist opinion was sought. He was noted to have a reduced consciousness level and worsening confusion. A repeat CT scan demonstrated the appearance of his cerebral contusions and associated oedema remained stable. On examination, he appeared clinically euvoalaemic, and his blood pressure (135/75 mm Hg) and pulse (54 bpm) were unchanged. Relevant markers of fluid status such as haematocrit (0.438 L/L), urea (6.9 mmol/L) and creatinine (69 $\mu\text{mol/L}$) were within the reference ranges. His urine output for that day was 2.6 L, and his fluid chart reported an ongoing deficit. His urine sodium (108 mmol/kg)

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Figure 2 Changes in serum sodium.

and urine osmolality (912 mmol/L) remained elevated, and his renal function remained normal.

A saline challenge (1 L of 0.9% saline over 4 hours) was administered with the aim of correcting the volume depletion estimated from his chart. This saline challenge resulted in a further fall in his serum sodium level (123 mmol/L). His urine sodium (169 mmol/L) and urine osmolality (992 mmol/kg) remained elevated.

INVESTIGATIONS

The patient's initial CT head is shown in [figure 1](#). His sodium levels and fluid balance over his admission are shown in [figures 2 and 3](#), respectively.

DIFFERENTIAL DIAGNOSIS

Our case demonstrates the complexity of differentiating between the causes of hyponatraemia after head injury. A thorough history and examination are required to assess for dehydration or volume loss related to trauma and to identify drugs that may contribute to hyponatraemia. A cortisol level, or as appropriate serial cortisol levels, should be ordered to exclude adrenocorticotrophic hormone (ACTH) deficiency. Once these causes have been investigated, RSW and SIADH and should be considered as potential causes of hyponatraemia.

SIADH is a volume-expanded hyponatraemia, caused by inappropriate excessive ADH secretion that leads to renal water reabsorption and dilution of the plasma. In contrast, RSW is a volume-depleted state hyponatraemia that may be explained by two possible mechanisms: a reduction of sympathetic activity and/or increased secretion of atrial natriuretic peptides (ANP) or

Figure 3 Changes in fluid intake, output and balance.

brain natriuretic peptides.⁵ The exact pathophysiology of RSW and SIADH is not fully understood.

Overt SIADH and RSW can be differentiated based on primarily volume status ([Table 1](#)). The hallmark of RSW is volume depletion; whereas the diagnosis of SIADH depends on a coexisting euvoelaemic state. Indeed, SIADH cannot be diagnosed in the presence of a fluid deficit as ADH secretion occurs as an appropriate physiological response to volume depletion. Unfortunately, in practice the two syndromes are often difficult to distinguish using clinical and laboratory criteria.⁶ Clinical assessment of extracellular fluid volume status has been found to have limited sensitivity and specificity in patients who are hyponatraemic.⁷ Invasive measures have been proposed as a more

objective measure of volume status; for example, the use of a central venous pressure (CVP) of <5 cm of water to define hypovolaemia.⁸ However, a systematic review of this methodology failed to demonstrate a relationship between CVP and blood volume,⁹ therefore limiting its efficacy as a diagnostic tool.

An isotonic saline challenge may have some utility in distinguishing SIADH and RSW.² In hypovolaemic hyponatraemia, the saline infusion expands the extracellular volume and removes the overriding volume stimulus to ADH secretion; this allows hypo-osmolality to appropriately inhibit ADH and the consequent free water secretion will correct the hyponatraemia. Conversely, if the patient has SIADH, administration of isotonic saline can result in increased natriuresis and a further decline in serum sodium levels.² This process has been named 'desalination' where the administration of isotonic saline in the presence of inappropriate ADH levels results in dilution due to sodium excretion with excess free water reabsorption.¹⁰ This test may not provide a clear-cut dichotomy, as suggested by Cuesta *et al*, it would not be uncommon for instance, to treat hypovolaemic hyponatraemia with appropriate intravenous fluids, only to discover underlying SIADH to be simultaneously present.¹¹

Patients with neurosurgical conditions provide a particular challenge to the clinician as they are often treated with considerable volumes of saline-containing fluid with consequent dynamic changes in blood and extracellular volumes.⁴ A large volume of saline can lead to an expansion of extracellular fluid volume,¹² but may also result in a pressure natriuresis due to a reduction in renal sodium absorption and release of natriuretic agents.¹³ Furthermore, patients with major brain injuries have elevated levels of adrenergic hormones that have several confounding effects: a contraction of venous capacitance vessels; an increase in arterial blood pressure; renal vasodilation and pressure natriuresis as a renal response to a rise in blood pressure.¹³ In patients with subarachnoid haemorrhage,⁴ the use of norepinephrine (to maintain cerebral perfusion) and calcium channel blockers (to prevent vasospasm) have been found to increase APN¹⁴ and reduce aldosterone levels,¹⁵ which may also contribute to hyponatraemia.

TREATMENT

This patient's negative fluid balance was initially suggestive of RSW, and this should have been considered early as a likely diagnosis. Fludrocortisone can improve hyponatraemia in RSW by reducing natriuresis.⁶ However, a saline challenge on day 4 failed to redress his hyponatraemia and therefore the underlying aetiology remained unclear. An altered neurological status in the context of severe hyponatraemia is a medical emergency. Consequently, he was transferred to a high dependency area for administration of a hypertonic (3%) saline by intravenous infusion. The rate of infusion was calculated using the Adrogue-Madias equation¹⁶ and the sodium level repeated every 2–3 hours to ensure a change of <10 mmol/L/24 hours. The rise in sodium was carefully controlled to avoid rapid overcorrection. There is evidence that rapid correction by more than 10 mmol/L/24 hours (or perhaps less if the hyponatraemia has been present for more than 48 hours) is associated with a risk of osmotic demyelination syndrome; this can manifest as irreversible neurological symptoms including dysarthria, paresis and confusion. Over the following 18 hours, this patient's sodium level improved from 122 mmol/L to 129 mmol/L with an accompanying improvement in his neurological status. On day 7, once the patient was clinically stable, the intravenous fluid was ceased and a fluid restriction (1.5 L) and oral salt tablets (2.4 g per day) were reinstated

to good effect. By day 10, he was alert and orientated, the oral salt was ceased and he was able to drink fluids according to thirst without limitation.

Table 1 Clinical and biochemical differences between RSW and SIADH

	RSW	SIADH	Case
Serum sodium (mmol/L)	<135	<135	<135
Serum osmolality (mOsm/kg)	<285	<285	<285
Urine sodium (mmol/L)	>25	>25	>25
Urine osmolality (mOsm/kg)	>200	>200	>200
Weight	↓	↑	<-->
Fluid balance	↓	↑	↓
Jugular venous distension	–	+	<-->
Haematocrit	↑	↓	<-->
Urea	↑	↓	<-->
Creatinine	↑	↓	<-->
Uric acid	↓	↓	N/A
Bicarbonate	↑	↓	↓
CVP (cm water)	<6	>6	N/A
Pulmonary wedge pressure (mm Hg)	<8	>8	N/A

Adapted from Rahman and Friedman.⁶

CVP, central venous pressure; N/A, not applicable; RSW, renal salt wasting; SIADH, syndrome of inappropriate antidiuretic hormone. Arrows refer to low, high and equivocal.

Patient's perspective

A parent perspective

It is an overwhelming emotional rollercoaster to witness such a life-changing event happen to your child, both initially and progressively over time. The impact of such an ordeal affects you psychologically, emotionally and physically. This is what all parents go through when their child is injured; particularly feelings of despair and helplessness when deterioration is detected. To add to this, I am also an Emergency Nurse of 15 years and Nurse Educator; I found it was both helpful and harmful to have a deeper understanding of the effects of traumatic brain injury. Yet, throughout this experience, I was able to help my family understand what was happening from the time of my son's initial injury, when he deteriorated, and during his successful rehabilitation. As a clinician and educator, I have found this experience to be informative and rewarding. I have a deeper and more personal understanding of the effects of traumatic brain injury and can share the importance of managing hyponatraemia with other clinicians and my students.

Learning points

- ▶ Distinguishing between renal salt wasting (RSW) and syndrome of inappropriate antidiuretic hormone (SIADH) can be clinically challenging.
- ▶ Volume status may differentiate RSW from SIADH. However, current clinical and laboratory markers of volume status are often limited in their accuracy.²⁵
- ▶ Fluid restriction can cause harm in patients with neurosurgical conditions.^{45 19}
- ▶ Hypertonic saline may be a safe approach for treating hyponatraemia in patients with acute brain injury.^{24 19}

OUTCOME AND FOLLOW-UP

The hyponatraemia in this case was likely a consequence of early RSW (natriuresis). The restoration of circulating volume may then have revealed an underlying SIADH (excess renal water reabsorption). The contrasting effect of fluid restriction and oral salt on day 3–4, when compared with the same therapy on day 7–10, supports this theory. However, even in retrospect it is difficult to determine the exact pathophysiology of the hyponatraemia. This case demonstrates the diagnostic complexity that challenges the clinician managing patients with hyponatraemia and head trauma.

It should be noted that the patient's cortisol level was not measured on initial blood sampling as dexamethasone had already been administered; exogenous dexamethasone suppresses endogenous cortisol production. After cessation of dexamethasone therapy (>72 hours) his cortisol level was 379 nmol/L. This level does not definitively exclude ACTH deficiency; however, this was not the cause of his hyponatraemia as he was concurrently on supraphysiological doses of dexamethasone.

In the longer term, the patient's salt and water balance remained normal. However, he experienced significant neurological sequelae of his injury, including a prolonged post-traumatic amnesia. After extensive inpatient rehabilitation, he was discharged to community rehabilitation, and he has since successfully returned to undergraduate education.

DISCUSSION

Several guidelines for the management of hyponatraemia emphasise the importance of differentiating between hypovolaemic, euvoalaemic and hypervolaemic hyponatraemia. Unfortunately, this is often challenging in clinical practice. This has led to a shift away from relying on fluid assessment in order to reduce the risk of misdiagnosis.¹⁷ In some medical guidelines, a urinary sodium level of <30 mmol/L is recommended as an indicator of reduced extracellular space in the non-surgical setting. However, this is less helpful in a neurosurgical setting where RSW is a major differential diagnosis, and both RSW and SIADH are associated with urine sodium levels of >30 mmol/L. Where uncertainty exists, a critical component of the therapeutic approach is the close monitoring of response and appropriate revision of the management plan according to the effect on sodium levels. An elevated fractional excretion of urate has been shown as a useful marker for SIADH in non-surgical patients and could prove to be a useful clinical tool in future.¹⁸

Patients with neurosurgical conditions, and in particular patients with traumatic brain injury, are prone to cerebral ischaemia because of systemic hypotension or intracranial hypertension.¹⁹ This is particularly evident in patients with subarachnoid haemorrhage: these patients carry a high risk of vasospasm, and fluid restriction may consequently prove harmful.⁴ Fluid restriction in a volume-deplete patient with RSW could be fatal. If an appropriate intervention for severe hyponatraemia is not instituted, cerebral oedema may occur with a resultant rise in intracranial pressure.¹⁹

Clinicians should consider the judicious use of hypertonic saline in patients with neurosurgical condition(s) and with significant hyponatraemia. This should be delivered under specialist supervision in a high dependency setting with frequent monitoring. The main concern when using hypertonic saline is the risk of overly rapid correction leading to osmotic demyelination. Careful calculation of the infusion rate using the Adrogué-Madiaz equation¹⁶ and individualisation of the infusion based on the rate of sodium change will ensure patient safety and prompt correction of the electrolyte disturbance to provide optimal care.

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Contributors KW managed the patient. THC, ML, ST and KW gathered data, prepared the manuscript for publication and approved the final version.

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