Hyponatraemic syndrome in a patient with tuberculosis—always the adrenals?

Keywords: hyponatraemic; tuberculosis; meningitis

Quiz

A 42-year-old African man was admitted to our Nephrology Department for the management of a severe hyponatraemia (117 mmol/l).

The patient had been hospitalized 1 month earlier for generalized weakness, weight loss (30 kg in the past 3 months), abdominal pain, cough, dyspnoea, haemoptysis and confusion. His clinical examination was unremarkable except for severe malnutrition. His Glasgow coma scale was 15, with no focal neurological signs. Blood pressure was 100/70 mmHg with orthostatic hypotension and tachycardia (120 pulse/min). Routine blood tests revealed hyponatraemia at 117 mmol/l, plasma osmolarity of 250 mOsm/l, serum glucose level 5.5 mmol/l and normal serum potassium level (4.5 mmol/l). Chest X-ray showed an excavated shadow of the right superior lobe. Head CT scan was normal. CSF examination revealed a lymphocytic reaction (130 cells/cm) with a protein of 1.9 g/l and glucose of 2.3 mmol/l. Meanwhile, the patient was found to be HIV-1 positive with disseminated tuberculosis (i.e. pulmonary and meningitis). Based on the clinical and biological findings, the patient was treated for adrenal insufficiency with glucocorticoid substitution and normal saline perfusion with an improvement in plasma sodium level (from 117 to 123 mmol/l). However, since Synacthen test remained normal, steroid substitution was stopped and the serum sodium decreased to 118 mmol/l. Urine output increased (51 in 24 h). Biochemical parameters are summarized in Table 1.

Question

What is your diagnosis?

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Range</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At baseline</td>
<td>Under treatment</td>
</tr>
<tr>
<td>Serum parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum sodium (mmol/l)</td>
<td>136–142</td>
<td>118</td>
</tr>
<tr>
<td>Serum osmolality (mOsm/l)</td>
<td>285–295</td>
<td>260</td>
</tr>
<tr>
<td>Serum creatinine (µmol/l)</td>
<td>70–100</td>
<td>35</td>
</tr>
<tr>
<td>Serum urea (mmol/l)</td>
<td>2.5–5</td>
<td>8</td>
</tr>
<tr>
<td>Serum uric acid (µmol/l)</td>
<td>240–350</td>
<td>100</td>
</tr>
<tr>
<td>Serum ADH (pg/ml)</td>
<td>&lt;14</td>
<td>20</td>
</tr>
<tr>
<td>Serum BNP (pg/ml)</td>
<td>&lt;100</td>
<td>330</td>
</tr>
<tr>
<td>Serum ANP (pmol/l)</td>
<td>&lt;14</td>
<td>12.6</td>
</tr>
<tr>
<td>Serum renin (pg/ml)</td>
<td>3.5–19</td>
<td>10.5</td>
</tr>
<tr>
<td>Serum aldosterone (pg/ml)</td>
<td>12–125</td>
<td>&lt;12</td>
</tr>
<tr>
<td>Synacten test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum cortisol (before) (ng/ml)</td>
<td>60–249</td>
<td>292</td>
</tr>
<tr>
<td>Serum cortisol (after) (ng/ml)</td>
<td>195–400</td>
<td>402</td>
</tr>
<tr>
<td>Urinary parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary sodium (mmol/l)</td>
<td>143</td>
<td>120</td>
</tr>
<tr>
<td>Urinary osmolality (mOsm/l)</td>
<td>650</td>
<td>300</td>
</tr>
</tbody>
</table>

NA, not available.
Answer to the quiz on the preceding page

**Diagnosis**

Acute hyponatraemia due to cerebral salt-wasting syndrome (CSWS) during tuberculosis meningitis (TBM) in an HIV-1-infected patient.

**Clinical follow-up**

Hyponatraemia associating TBM has three main differential diagnoses: Adrenal insufficiency, inappropriate secretion of antidiuretic hormone syndrome (SIADH) and CSWS.

Absence of hyperkalaemia and negative Synacten test suffice to eliminate adrenal insufficiency. Diminished extracellular volume associated with natriuretic hyponatraemia excludes SIADH. We therefore, considered the diagnosis to be CSWS, the following are supporting arguments:

- Severe volume depletion (postural hypotension with tachycardia), high urinary sodium concentration and excretion, and correction of hyponatraemia and volume status with saline and fludrocortisone therapy, features atypical on SIADH and favouring CSWS. Furthermore, demonstration of elevated BNP levels in our patient with TBM would support this diagnosis.
- Hypertonic saline given at the dose of 12 g the first day and then 6–10 g/day for the following seven days, associated with 21 of normal saline/day along with increasing doses of fludrocortisone (up to 0.5 mg/day) stabilized the serum sodium concentration at the level of 130 mmol/l. However, normalization of higher brain functions was not obtained until CSF TBM subsided (decreased cellularity 100–50 lymphocyte/ml, negative ADA level). Two months later, plasma sodium level remained stable at 138 mmol/l.

**Discussion**

CSWS is defined as renal loss of sodium during intracranial diseases, leading to hyponatraemia, excessive natriuresis, volume depletion and clinical response to volume and salt replacement. It was first described by Peters et al. [1] in 1950, 7 years before the identification of SIADH [2]. As early as 1951, Rapoport et al. [3] described a salt-losing state as a possible cause for hyponatraemia in TBM. Up to 1993, however, hyponatraemia in TBM was thought to be caused by SIADH.

A variety of processes have been linked with CSWS, including central nervous system injury, subarachnoid haemorrhage, encephalitis, tuberculous meningitis, craniotomy, poliomyelitis, and pituitary adenoma, among others [4]. It can occur between 6 months and 65 years of age, and the exact underlying pathophysiology is unclear. The main pathophysiological mechanisms involved in CSWS are a decrease in the sympathetic nervous system outflow during intracranial disease leading to decrease sodium reabsorption in the proximal tubules, inhibition of the RAS, and also the release of some natriuretic factors such as brain natriuretic factor (BNP), ANP and some other natriuretic proteins [5,6]. The net effect of all these changes is the induction of natriuresis, which in turn causes polyuria and a decrease in the effective circulating volume, thus leading on to hypotension and hyponatraemia. Our patient presented suppressed RAS, inappropriately normal ANF and elevated BNP levels as reported in the literature. Indeed, Narotam et al. [7] described a state of inappropriate ANF secretion with suppressed or inappropriately normal RAS and ADH levels as the cause of hyponatraemia in 65% of patients with TBM. Berendes et al. [8] have provided evidence that BNP might be the more likely candidate to mediate CSWS.

The main differential diagnosis is SIADH. A thorough clinical and laboratory examination is essential to distinguish between the two and attention to extracellular volume status is critical. Despite apparent similarities, the pathophysiology, biochemistry and treatment of these two conditions are quite different (Table 2). The major difference between CSWS and SIADH is that CSWS involves renal salt loss, resulting in hyponatraemia and extracellular fluid volume decrease, whereas SIADH involves physiologically inappropriate secretion of ADH or increased renal sensitivity to ADH, leading to renal conservation of water and euvoalemic or hypovolaemic hyponatraemia. Conversely, an elevated serum ADH does not exclude a diagnosis of CSWS as it may be raised physiologically in response to hypovolaemia [9]. Misdiagnosis of CSWS as SIADH can be fatal, as water restriction is detrimental to patients with CSWS.

Other causes of hyponatraemia, such as drug therapy and adrenal insufficiency, must also be excluded. The possibility that our patient had some degree of hypothalamus pituitary–adrenal axis suppression is a confounding factor in the diagnosis of CSWS. Both AIDS and tuberculosis can cause suppression of the hypothalamus pituitary–adrenal axis and destruction of the adrenal gland [10,11] and may have accounted for the mild hyponatraemia seen.
on admission. This may lead to adrenal insufficiency and subsequent hyponatraemia. However, the high urinary potassium levels, as well as the absence of hyperkalaemia and normal adrenal stimulation test, make this diagnosis less likely. Patients with AIDS or AIDS-related complex can also develop acute hyponatraemia from diarrhoea and vomiting as well as renal insufficiency [12]. Our patient had normal renal function and had no evidence of gastrointestinal losses.

Therapy of SIADH and CSWS is diagonally opposed, i.e. volume restriction in SIADH vs volume and salt replacement in CSWS. Volume restriction in CSWS would be potentially disastrous, in causing a further decrease in the cerebral perfusion pressure. The volume replacement achieved with 0.9% (or 3% sodium chloride if necessary) is the cornerstone of treatment of CSWS. The rapidity of salt replacement depends on the rate at which the hyponatraemia developed. Treatment of hyponatraemia developing at a rate of ≥0.5 mmol/l/h should be aggressive, as it is a life-threatening complication and may cause death from severe cerebral oedema and cerebral herniation [13]. Unlike chronic hyponatraemia, rapid correction of serum sodium level is associated with marked neurological improvement, with less danger of developing central pontine myelinolysis [14]. As ANP can inhibit mineralocorticoid secretion in patients with CSWS, administration of an agent with mineralocorticoid activity, such as fludrocortisone, has also been shown to be effective in returning serum sodium levels to normal [15], by acting directly on the renal distal tubules to enhance sodium reabsorption [16]. Ishikawa et al. [16] reported a resolution of CSWS with fludrocortisone acetate at a dose of 0.2–0.4 mg/day. Adverse effects of fludrocortisone including hypertension, hypokalaemia and pulmonary oedema should be monitored.

In our patient, sodium deficit was replaced within 3 weeks (plasma sodium level, 138 mmol/l) by intravenous hypertonic (although within the recommended limit of 0.5 mmol/l/h for the first days), then normal saline perfusion and mineralocorticoid substitution (fludrocortisone 0.5 mg daily dose).

This case shows the difference between CSWS and SIADH, and the importance of correct diagnosis and treatment. Mineralocorticoid supplementation seems to be a safe and effective treatment for CSWS, whereas normal saline and hypertonic saline could be a temporary measure. However, serum sodium level normalization was obtained only with TBM disease control.

Conflict of interest statement. None declared.

References


Laurent Camous1
José Luis Lopez Zaragoza2
Edward Bourry1
Gilbert Deray1
Hassane Izzedine1

1Department of Nephrology
2Department of Infectious Diseases, Pitie Salpetriere Hospital, Paris, France

Received for publication: 1.1.07
Accepted in revised form: 16.5.07