A case of cerebral salt wasting syndrome in a patient with central diabetes insipidus and status epilepticus

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Dear Editor,

Cerebral salt-wasting syndrome (CSWS) is a condition of hypotonic hyponatremia associated with natriuresis, polyuria, and extracellular-volume depletion in the setting of intracranial disease, particularly subarachnoid hemorrhage [1]. This rare condition accounts for less than 5% of causes of hyponatremia in neurosurgical patients [1]. Its diagnosis is challenging as it shares some features of the syndrome of inappropriate antidiuresis (SIAD), such that some authors believe that a significant proportion of hyponatremic neurosurgical patients are incorrectly diagnosed with SIAD, when in fact they have CSWS [1]. Given that management of the two conditions is different [1], correct diagnosis is key to proper treatment. Here, we report the case of a patient affected with central diabetes insipidus who developed hyponatremia despite maintenance of desmopressin dose, with the occurrence of polyuria, natriuresis, and volume depletion, leading us to the diagnosis of CSWS [2].

On 29 April 2022, a 27-year-old woman was referred to Cattinara Teaching Hospital (Trieste, Italy) because of seizure worsening in a drug-resistant epilepsy arisen seven years earlier. On her past medical history, she had undergone craniotomy for removing a large craniopharyngioma when she was 10 years, with the subsequent development of hypopituitarism and diabetes insipidus. On admission, she was alert. Weight was 144 kg and height 1.7 m (BMI 49 kg/m^2). The temperature was 36.5 °C, pulse 80 bpm, respiratory rate 16/min, and blood pressure 125/70 mmHg. Neurological examination revealed frontal apathy. Serum sodium was 139 mmol/L (r.r. 135–145), fasting glucose 60 mg/dL (r.r. 65–100) and free T4 10.1 pg/mL (r.r. 5.6–12). The fluid balance record showed a 24-h intake of 2500 mL and an urine output of 2200 mL (Fig. 1). CT scan showed signs consistent with previous neurosurgical approach. EEG showed generalized waveform abnormalities, suggesting mild diffuse encephalopathy. Medications included cortisone acetate 31.25 mg/day, L-thyroxine 200 mcg/day, desmopressin 180 mcg/day, somatropin 0.4 mg/day 5 days per week, levetiracetam 2500 mg/day, lacosamide 200 mg/day, sodium valproate 750 mg/day, and perampanel 8 mg/day. As soon as she was admitted to hospital, cortisone acetate was increased to 50 mg/day, with the recommendation of intravenous hydrocortisone in case of a further and acute worsening of her condition. In addition, anti-epileptic drugs were modified as follows: levetiracetam was increased to 3500 mg/day and sodium valproate was changed to lamotrigine and clonazepam, with initial minor EEG improvements (04 May). Nevertheless, over the following weeks, the patient became increasingly drowsy, lamotrigine was withdrawn (23 May), and two days later (25 May) EEG showed generalized status epilepticus that was immediately managed by neurologists requiring administration of lorazepam 4 mg and a further change of anti-epileptic drugs. Levetiracetam was reduced to 2500 mg/day, perampanel was increased to 16 mg/day, whereas lacosamide and clonazepam were maintained. Two days later, serum sodium and urine output increased to 160 mmol/L and 7600–7800 mL, respectively, a likely consequence of missing a desmopressin dose. This transient condition was promptly corrected: desmopressin was maintained at 180 mcg/day and liquid losses were restored, as shown in Fig. 1. Two weeks later (14 June), despite maintenance of initial desmopressin dose, the patient presented acute hyponatremia, as serum sodium dropped to 122 mmol/L with calculated serum osmolality 260 mOsm/Kg (r.r 280–300). This was associated with marked polyuria

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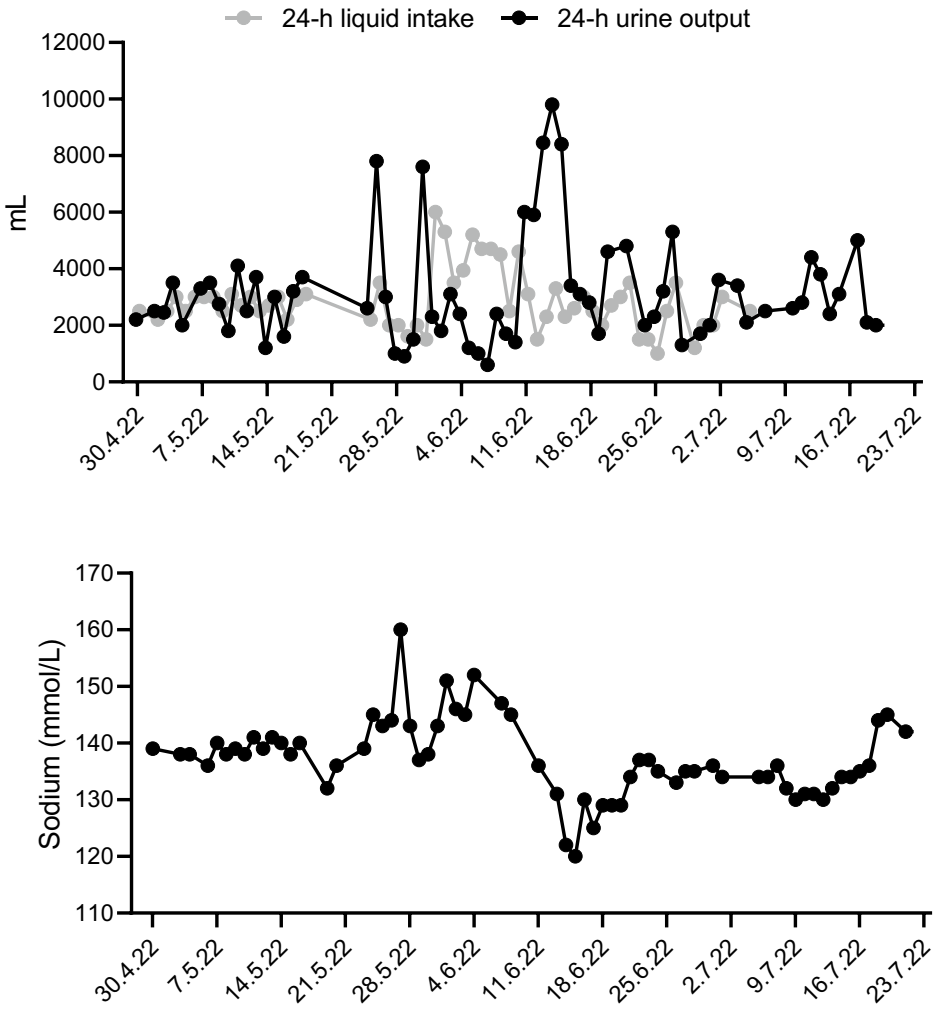

Fig. 1 Fluid balance and serum sodium

(urine output was > 8400 mL) and natriuresis, as urine osmolality was 287 mOsm/Kg (r.r 50–1200) with urinary sodium 124 mmol/L and 594 mmol/24 h (r.r. 40–220), as shown in Fig. 1. Otherwise, potassium, calcium, and phosphates were within reference ranges. In addition, the patient had never taken diuretics, and she had not had any previous bladder obstruction (leading to post-obstruction natriuresis). On physical examination, the patient was awake and her blood pressure was 100/65 mmHg. Overall, the coexistence of hypotonic hyponatremia, polyuria, natriuresis and signs of volume depletion (as assessed by blood pressure reduction and negative fluid balance) led us to the diagnosis of CSWS. Given that acute and severe hyponatremia may rapidly lead to hyponatremic encephalopathy [2], the patient, who had just suffered from status epilepticus, was initially treated with 3% NaCl at 80 ml/h for 5 days, whereby serum sodium increased to 129 mmol/L. This is an effective and potentially life-saving treatment for cerebral edema, as the high extra-cellular sodium concentration of 3% NaCl immediately removes water from the intracellular space [3]. Then, the patient was shifted to 0.9% NaCl with fludrocortisone 0.2 mg/day for 15 days and then 0.1 mg/day for the following 15 days, which was well-tolerated (with no hypokalemia), before full recovery and discharge.

There are only a few reports of CSWS in patients with central diabetes insipidus [4–8]. The most common causes accounting for the coexistence of these two entities are traumatic brain injury [4–6], subarachnoid/intracranial hemorrhage [4, 5], CNS infection [5], hypoxic–ischemic event [5], and pituitary surgery [1, 4, 7]. Nevertheless, consistent with our case, CSWS has been described also in patients with status epilepticus in the post-treatment follow-up [9]. The mechanisms underlying CSWS seem to include: (i) an impairment of sympathetic autonomic system with hyporeninemic hypoaldosteronism and inability of sodium reuptake; (ii) pressure-induced or high-salt-induced renal natriuresis through local dopaminergic system; and (iii) increase of natriuretic peptides. In line with these mechanisms, apart from the impairment of sympathetic drive, we cannot completely exclude that transient hypernatremia might have induced renal natriuresis through local dopaminergic system. By contrast, the involvement of levetiracetam

is unlikely, because hyponatremia developed 1 month after levetiracetam change, the mechanism whereby levetiracetam seems to lead to hyponatremia is ADH secretion [10], which is impaired in central diabetes insipidus, and reduced extracellular volume would not be expected with this medication.

The management of water metabolism in patients with diabetes insipidus and acute intracranial disease is challenging [11]. Clinicians should be alert to the possibility of CSWS in patients with hypotonic hyponatremia, central diabetes insipidus and status epilepticus. Key features include polyuria (with negative fluid balance), natriuresis, and volume depletion. Treatment is directed at replacing volume status. Fludrocortisone can be taken into account for a few weeks [12].

Data availability The raw data supporting the conclusions of this article will be made available by the authors, upon reasonable request.

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Research involving human participants and/or animals This study does not contain any studies involving human participants and/or animals performed by any of the authors.

Informed consent For this type of study, consent is not required.

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