Unusual association of diseases/symptoms

Hyponatraemia associated rhabdomyolysis following water intoxication

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Summary

A young man with bipolar disorder was admitted in a coma. Cerebral oedema secondary to severe hyponatraemia was implicated. This was due to self-induced water intoxication. He developed rhabdomyolysis, a massive creatine kinase (out of proportion to longstanding antipsychotic medication) and acute renal failure. In the intensive care unit, hyponatraemia was corrected, and following appropriate fluid resuscitation, with forced alkaline diuresis, the rhabdomyolysis and renal function normalised, averting renal support. While a full recovery ensued, the persisting risk factors for hyponatraemia, that is polydipsia, and its association with rhabdomyolysis, increased the chances of a recurrence. Closely supervised regulation of his water intake, and monitoring of antipsychotic efficacy (for biochemical homeostasis) are essential for secondary prevention. Rhabdomyolysis is a rare complication of hyponatraemia. When associated with psychogenic polydipsia, the acute and chronic management are challenging. Vaptans, which are aquaretics, that preferentially prevent renal tubular water reabsorption, may be beneficial in this situation.

BACKGROUND

Psychogenic polydipsia, or self-induced water intoxication, can be common among psychiatric patients, affecting up to 20%,¹ and can sometimes lead to hypotonic hyponatraemia. Hyponatraemia has well-recognised neurological complications, which result from cerebral oedema. These include headaches, behavioural changes, confusion and even seizures and coma. However, hyponatraemia, in rare instances has also been linked to rhabdomyolysis, a complication which is under-recognised and has serious consequences. The mechanism of this remains uncertain. We discuss possible mechanisms and treatments of hyponatraemia in this context, while emphasising the importance of monitoring for the development of rhabdomyolysis in hyponatraemic patients.

CASE PRESENTATION

A 39-year-old man with bipolar disorder was admitted to hospital following a seizure and fluctuating level of consciousness. He had a several month history of excess fluid intake, drinking 8–10 litres of diet coke a day, 15–20 cups of coffee and several cups of water every few minutes. During this time he had been complaining of recurrent headaches, treated with simple analgesics. On the day of admission, he became increasingly confused and agitated and subsequently had a witnessed, self-terminating generalised seizure, lasting for 5 min. He had had no other symptoms, had not been drinking alcohol and did not have a head injury. He was known to suffer from bipolar disorder, treated with risperidone (6 mg OD) and sodium valproate (1500 mg OD). He also had early onset dementia from previous alcohol abuse.

INVESTIGATIONS

On examination he had a fluctuant level of consciousness (GCS 7–12). Apart from a small area of petechial rash across his L shoulder, further examination was normal. Blood tests revealed hypoosmolar hyponatraemia (serum Na⁺ 104, serum osmolality 214) and leucocytosis of 21.4 with neutrophilia. Creatine kinase (CK) levels measured a few hours later were 1023 IU/l. Head CT revealed cerebral oedema but no focal lesion. His renal function was normal, urine toxicology, including paracetamol and salicylate levels, was negative, as was screening for HIV, legionella, pneumococcal and meningococcal antigens.

DIFFERENTIAL DIAGNOSIS

The syndrome of inappropriate antidiuretic hormone was excluded in view of urine output was >100/h, with a low urine osmolality.

Hyponatraemia secondary to antipsychotic medication was also considered, but the patient had been taking the same antipsychotic dosages for years.

TREATMENT

The patient was admitted to ITU, was intubated, given phenytoin to prevent further seizures and empirical intravenous ceftriaxone in view of raised inflammatory markers, petechial rash and coma. Risperidone, which can cause and exacerbate hyponatraemia, was stopped until correction of Na⁺ levels. The high CK (1023 IU/l) was initially attributed to the seizure episode, although short lived. To correct his hyponatraemia he was given saline, aiming for a maximum increase in serum Na⁺ of 1 mmol/l/h.

Figure 1 Graph of daily biochemistry results, indicating trends for serum sodium (Na^+) in red, serum creatine kinase (CK) in green and creatinine in blue.

By day 2, the petechial rash resolved and inflammatory markers reduced. Na^+ levels reached 129 mmol/L. However, CK continued to rise, reaching 15 653 IU/L on day 3, and polyuric renal failure ensued, with a creatinine of 306 $\mu\text{mol/L}$. Rhabdomyolysis was confirmed by a positive urine myoglobin test. As Na^+ levels were stable at 128 mmol/L, intravenous hydration rate was increased and adjusted according to the monitored electrolyte levels.

His CK peaked at 16 339 IU/L, and on day 4 creatinine was 511 $\mu\text{mol/L}$ (see figure 1 for daily levels). Forced alkaline diuresis and frusemide infusion were started.

On this treatment, renal function returned to normal by day 8. Antipsychotic medication was restarted on day 5, once serum Na^+ normalised, anticipating the need to re-establish a plateau on waking. The patient was extubated on day 9 and discharged from the intensive care unit on day 11.

OUTCOME AND FOLLOW-UP

On the ward, he was placed on fluid restriction, under 24 h supervision. By day 10 of admission, his renal function and CK was normalising. He was discharged to a psychiatric facility for close supervision and management of his drinking habits.

DISCUSSION

Psychogenic polydipsia, or self-induced water intoxication, is a recognised cause of hyponatraemia (Na^+ serum concentration <135 mmol/L). Clinical presentation varies according to the severity and rate of development of hyponatraemia:

initial symptoms include headache, lethargy and confusion. As hyponatraemia worsens, altered behaviour, and hallucinations ensue. Cerebral oedema develops resulting in seizures, respiratory depression and coma.² Initial treatment of hyponatraemia involves controlled administration of intravenous crystalloids. However, the rate of correction can be crucial, as rapid shifts in plasma osmolality reverse the established cerebral oedema too quickly, a phenomenon that has been associated with central and extra pontine myelinolysis. Thus, in cases where hyponatraemia has developed within 48 h, and brain cells have not yet adapted to the electrolyte changes, clinicians can afford a rapid increase in serum Na^+ concentration, whereas in chronic hyponatraemia (anything more than 48 h) a controlled rate of correction is needed.³ The accepted rate of correction is quoted as 10–12 mEq/L, in the first 24 h.^{2 4}

A lesser known complication associated with hyponatraemia or its correction, is rhabdomyolysis, as described herein. Rhabdomyolysis, that is destruction of skeletal muscle, leads to the release of intracellular contents, such as potassium, myoglobin and CK, into the systemic circulation. Complications such as renal failure, cardiac arrhythmias and compartment syndrome may ensue.

While recognised causes of rhabdomyolysis, include traumatic crush syndromes, physical restraints, seizures and certain drugs (eg, statins),⁵ rhabdomyolysis associated with electrolyte abnormalities, such as hypernatraemia, hypokalaemia and hypophosphataemia are less common.⁶

Rhabdomyolysis associated with hyponatraemia due to psychogenic polydipsia was first described in 1979.⁷ In our patient, no physical restraints or intramuscular injections

were used nor was there evidence of neuroleptic malignant syndrome. The lack of temporal relationship between the short lived seizure and progressive rise in CK makes it an unlikely cause of rhabdomyolysis in this case: the CK levels continued to rise, peaking at day 4, despite the absence of further seizures. Another potential confounder was the use of risperidone: Meltzer *et al* reported a 10% incidence of rising CK in patients treated with antipsychotics, including two cases in which risperidone was used.⁸ However, in contrast to our case, the patients in that series did not develop renal failure and only one had evidence of myoglobinuria. Furthermore, the reported onset of rising CK was up to 2 years from initiating antipsychotic treatment, whereas our patient had already been on risperidone for years. Finally, although our patient was restarted on risperidone prior to resolution of rhabdomyolysis, the CK levels continued to decline. Taking all these factors into account, it seems that the most likely cause for rhabdomyolysis in our patient was hyponatraemia, secondary to psychogenic polydipsia.

The mechanism by which hyponatraemia causes rhabdomyolysis is currently unknown and subject to speculation. One theory suggests that the changing osmotic pressures result in failure of regulation of cell volume, leading to cell lysis.^{9 10} Thus, rhabdomyolysis could be occurring during the development of hyponatraemia, or during its correction, as has been suggested.^{6 9 10} Morita *et al*, compared patients with psychogenic polydipsia, and found that patients developing rhabdomyolysis had a higher maximum serum sodium correction rate per hour (2.0±1.3 vs 0.9±0.7 mEq/L/h) and higher increase in sodium level in the first 24 h (21.3±6.0 vs 10.0±4.6 mEq/L).⁴ A second mechanism involves the Na⁺/Ca²⁺ pumps in muscle cells: as extracellular concentration of Na⁺ falls, less Ca²⁺ is pumped out of the cell, leading to its accumulation. The ensuing activation of cellular proteases would eventually lead to cell lysis.^{6 9}

Whatever the mechanism, the treatment of rhabdomyolysis and the ensuing renal failure remains the same – yet competing with the restrictive strategy for treatment of hyponatraemia. Initial treatment of rhabdomyolysis includes aggressive resuscitation and rehydration, in an attempt to prevent renal failure. Alkaline diuresis, via sodium bicarbonate infusion, protects the kidneys by increasing myoglobin solubility and preventing cast formation within the renal tubules.⁵ Diuretics, such as frusemide, have also been used to increase diuresis and in essence ‘wash out’ the myoglobin and other nephrotoxins, although this remains controversial.⁵

Although the initial treatment of hyponatraemia, even when complicated by rhabdomyolysis and renal failure, is relatively effective, the long term management of psychogenic polydipsia has limited success. Conventionally, patients with psychogenic polydipsia are placed under fluid restriction to about 1 litre or less per day. However, understandably, patient compliance is poor and often requires 24 h supervision. Lithium and demeclocycline are vasopressin (AVP) antagonists, and are effective in limiting hyponatraemia in psychogenic polydipsia. Their use is however being limited by multiple side effects.^{2 11}

Newer developments in the treatment of chronic hyponatraemia are the discovery of AVP-receptor antagonists, known as the vaptans.¹¹ In contrast to diuretics, the

vaptans are aquaretics, acting on the renal tubules to prevent reabsorption of water but not of electrolytes.² One example includes conivaptan, which is an intravenously administered, combined V1a-R and V2-R antagonist and has been shown to increase both serum sodium concentration and plasma osmolality with minimal side effects.¹² Tolvaptan, which is an orally active V2-R antagonist, also increases serum sodium levels while being similarly well tolerated.¹³ Agents like these, may be used in the future instead of fluid restriction, as a more effective and better tolerated method of controlling hyponatraemia in the outpatient setting.¹¹

Learning points

- ▶ Severe hyponatraemia is an under recognised cause of rhabdomyolysis and renal failure.
- ▶ Clinicians need to be aware of this potential complication and monitor CK levels and renal function in patients with severe hyponatraemia.
- ▶ Further research is needed to elucidate the mechanism by which low serum sodium could cause rhabdomyolysis.
- ▶ Although long term treatment is at present ineffective, the discovery of vaptans could, in the future, entirely transform the management of hyponatraemia in psychogenic polydipsia.

Competing interests None.

Patient consent Obtained.

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