Central pontine myelinolysis: Case report and short overview

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Abstract
Central pontine myelinolysis is a rare and potentially life-threatening complication of a sudden rise in serum osmolality. Here we describe a 51-year-old male with alcohol dependence syndrome who was treated for severe hyponatraemia. The clinical course was complicated by neurological symptoms, eventually recognised as the consequence of evolving central pontine myelinolysis. This case report underlines the importance of recognising risk factors predisposing the patient to the development of central pontine myelinolysis.

Introduction
Central pontine myelinolysis (CPM) is a syndrome that is characterised by rapid destruction of myelin sheaths of mainly oligodendritic cells,[1] generally caused by a rapid rise in serum osmolality. Along with extrapontine myelinolysis, it is part of the osmotic demyelination syndrome (ODS). In most cases, ODS occurs in patients with chronic hypotonic hyponatraemia which is corrected too quickly. Known risk factors include severe hyponatraemia, alcoholism, thiazide use, hypokalaemia and malnourishment.[3] The exact incidence is unknown; a study by Singh et al. demonstrated that central pontine myelinolysis was present in 29% of postmortem examinations of liver transplant patients.[2] A relatively recent study by Louis et al.[8] showed that mortality rates might be close to 31%, much lower than previously thought.[4] Initial symptoms include confusion, quadriplegia and pseudobulbar palsy which occur 2-6 days after a rise in serum osmolality.[5] The advised rate of correcting chronic hyponatraemia, especially in high-risk patients, is 4-6 mmol/l for any 24-hour period with an advised maximum of 8 mmol/l to prevent ODS.[5]

Case report
A 64-year-old male with a history of alcohol dependence syndrome, gout and hypertension was admitted to the emergency department with slowly progressing lower back pain, weakness and collapse. After initial examination which showed hypotension (95/57 mmHg), a regular heart rate of 93 beats/min and a haematoma in the left lumbar region, the patient was resuscitated as a trauma patient with intravenous fluids in the ambulance (500 ml of Ringer’s lactate) and in the emergency department (1500 ml NaCl 0.9%) because of potential internal haemorrhage due to his fall. Laboratory testing revealed elevated inflammatory parameters, a mild elevation in liver enzymes, hypo-osmolar hyponatraemia (osmolality: 261 mmol/l, sodium: 115 mmol/l), hypokalaemia and acute renal failure (creatinine: 199 µmol/l) supposedly because of hypovolaemia due to inadequate fluid intake in combination with the use of a thiazide diuretic (ultrasound renal imaging showed no abnormalities). His urine analysis revealed a urine osmolality of 276 mmol/l with a sodium level of 10 mmol/l, which fitted with the supposed hypovolaemia and might also be related to inadequate sodium intake or extra-renal loss. After initial treatment in the emergency department, the patient was admitted to the medical ward.

The patient received intravenous potassium chloride and was to be given 2000 ml of NaCl 0.9% in the first 24 hours of treatment with an expected rise in serum sodium levels of 5.2 mmol/l as calculated: 1500 ml in the emergency department and 500 ml for the rest of the 24-hour period on the medical ward (figure 1). Also, thiamine, vitamin B and ascorbic acid were prophylactically started to prevent Wernicke encephalopathy. Approximately 16 hours after admission, the sodium levels showed a rise of 115 mmol/l to 308 mmol/l which was calculated by the Adrogue-Madias formula:

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\text{Change in serum Na}^+ = \frac{\text{Infusate Na}^+ + \text{Infusate K}^+ - \text{serum Na}^+}{\text{Total body water(l) + 1}}
\]

Adapted from Adrogue and Madias:²⁶ 308 mmol – 115 mmol/l/(60 kg x 0.6) + 1) = 5.2 mmol/l

Figure 1. Adrogue-Madias formula
increased to 124 mmol/l after which the infusion was switched to NaCl 0.45% and glucose 2.5%. The patient received glucose 5% infusion when sodium levels increased another 2 mmol/l to 126 mmol/l within the first 24 hours (figure 2).

In the following week the sodium levels normalised with a daily increase of 1-3 mmol/l. The potassium levels normalised quickly as well. However, during this period, the patient developed ataxia, resting tremors and a disturbance in rump balance. An MRI of the brain, performed to rule out cerebellar pathology, showed only global cortical and cerebellar atrophy. Vitamin doses were switched from prophylactic to therapeutic because Wernicke encephalopathy was suspected. Furthermore, benzodiazepines were started to prevent potential alcohol withdrawal syndrome. In the following days the patient developed an increasingly incomprehensible speech and ptosis of the right eye. In order to rule out new cerebral focal pathology, a cerebral CT was performed, showing no other lesions than previously described on MRI. Eventually, he was admitted to the ICU because of ongoing neurological symptoms and sepsis of unknown origin (blood culture was positive for *Enterococcus faecalis*) for which he received amoxicillin-clavulanic acid and a single gift of tobramycin. Additional lumbar puncture revealed no pathogens and normal glucose and white blood count levels. When the fever subsided but the neurological symptoms persisted, he was admitted to the stroke care unit where his EMV score gradually deteriorated. Opsoclonus myoclonus syndrome was considered along with a paraneoplastic syndrome, investigated by conducting paraneoplastic antibody testing (the results turned out to be negative). He was readmitted to the ICU because of difficulty in swallowing and the MRI was repeated demonstrating central pontine myelinolysis (figures 3A-C). In the following days the patient’s neurological status deteriorated eventually leading to a ‘locked in’ state, when he was only able to open and move his eyes.

After excessive multidisciplinary deliberation, weighing his medical history, limited social network and poor prognosis, it was decided to abstain from oxygen therapy and antibiotic treatment, and palliative care was started, after which the patient died the following day.

**Discussion**

Here we present a case of hypo-osmolar hyponatraemia in a patient with a history of alcohol dependence syndrome, complicated by central pontine myelinolysis probably due to an overly rapid correction of plasma osmolality. Although sodium correction exceeded the advised rate (maximum of 8 mmol/l in 24 hours) by only 3 mmol/l, the clinical course was complicated by severe neurological symptoms eventually leading to death.

**Central pontine myelinolysis**

Under pathophysiological conditions, cells protect themselves against oedema due to chronic hyponatraemia by adjusting cellular osmolality via the release of organic osmolytes. With this form of slow adaption, cells can only adjust their osmolality to balance a fall in serum osmolality by a certain rate. If, subsequently, the serum osmolality rises too quickly, e.g. due to a rapid correction of the plasma osmolality, the brain cells are unable to rapidly compensate for their relatively hypo-osmotic state putting them at risk for myelinolysis.[1] In our patient it seems that the combination of multiple (known) risk factors eventually led to CPM.
Potential risk factors leading to an unexpected rise in serum sodium levels

Besides the correction in osmolality, we hypothesise that several other factors contributed to the changes in osmolality during our treatment, predisposing the development of CPM. First, a sudden correction of (chronic) hypovolaemia could have led to a fall in antidiuretic hormone secretion. In turn, this would lead to less retention of water in the collecting tubules of the nephron resulting in a rise of plasma sodium concentrations (autocorrection).[7] Second, cessation of a thiazide diuretic also predisposes a more rapid rise in serum sodium levels. By withdrawing the thiazide diuretic, the Na/Cl co-transporter in the distal tubule of the nephron is reactivated leading to retention of sodium.[8] The Adrogue-Madrias formula does not take both of these factors into account, which could explain the unexpected distinct rise in sodium osmolality in the first 24 hours of admission. Third, hyponatraemic patients with chronic alcoholism often suffer from polydipsia (although in our patient this was not proven) and malnourishment, which may cause a deficiency in organic osmolytes preventing the brain from reabsorbing these solutes to balance the rapid rise in serum osmolality.[9] Fourth, our patient presented with hypokalaemia, which is often described as a predisposing factor to developing CPM, although the exact mechanism remains unclear.[10] In our patient the combination of all of the above (hyponatraemia, alcoholism, hypokalaemia, malnourishment, use of a thiazide diuretic and hypovolaemia) seems to have contributed to the fierce increase in sodium concentrations, with the correction of chronic hypovolaemia and the cessation of the diuretic agent as the most important causative factors. We would like to stress that when dealing with severe hyponatraemia, all known risk factors should be taken into account when treating your patient.[11,12]

Recommendations

In retrospect, the chronological presentation of symptoms, reflecting extensive neurological deterioration (from corticobulbar fibre involvement, to corticospinal tract involvement, and finally to total pontine failure) are consistent with the known literature.[1] Nonetheless, the recognition of CPM was difficult in our patient; possibly the combination of the extremely low incidence of CPM, the absence of pontine damage on the primary MRI scan and/or not recognising and weighing all risk factors delayed the diagnosis.

The development of CPM might have been prevented by early recognition of the pitfalls described above. Even though a number of different possible diagnoses were considered, such as alcohol withdrawal, Wernicke encephalopathy, opsoconus-myoclonus syndrome and paraneoplastic encephalopathy, CPM was only diagnosed after the neurological course progressed and the second cerebral MRI scan was performed. The characteristic (extra)pontine lesions of CPM might become apparent on MRI within days up to four weeks after the onset of clinical symptoms.[11,12] Therefore an early MRI might not lead to the early detection of CPM. Unfortunately, when the second MRI was performed, the symptoms were already considered irreversible.

Despite adequately using the Adrogue-Madrias formula, frequent control of sodium levels and treatment with NaCl0.9%, NaCl 0.45% and eventually glucose 5% infusion, the sodium levels increased too quickly (only once; 11 mmol/l in the first 24 hours). Given the fact that our patient had multiple risk factors in combination with severe hyponatraemia (<120 mmol/l) he would likely have benefited from a more intensively controlled rise in serum sodium levels or more aggressive lowering of sodium levels when overcorrection became apparent. Lowering of sodium levels in the early stages of neurological deterioration,[13] either by glucose 5% at an early stage and/or by administration of desmopressin according to the Dutch guideline,[14] has shown favourable outcomes. Moreover, in patients with hyponatraemia without other risk factors or symptoms, a safe and adequate rise in sodium levels might initially be achieved without intravenous sodium suppletion, but solely by fluid restriction with or without regular oral electrolyte supplements.[15]

Conclusion

Although CPM is a rare complication of a rapid correction of serum osmolality (as is often the case in chronic hyponatraemia), clinicians should always be aware of this irreversible complication. Especially in patients with multiple risk factors, CPM might be prevented by frequent control of electrolytes and osmolality in combination with volume status and urinary output. New methods such as point-of-care testing could be helpful to monitor shifting electrolyte levels more closely and thereby this could provide physicians ways to treat severe hyponatraemia more adequately. When these methods are not readily available, intensive care treatment should be considered.

Disclosures

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