Case report

Hyponatraemia: the importance of obtaining a detailed history and corroborating point-of-care analysis with laboratory testing

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SUMMARY

We describe a 67-year-old man admitted from a mental health unit with an incidental finding of hyponatraemia on routine blood tests. Laboratory investigations were in keeping with syndrome of inappropriate antidiuretic hormone secretion (SIADH). He had been recently commenced on mirtazapine. During his inpatient stay, he became increasingly confused. Review of a previous admission with hyponatraemia raised the possibility of voltage-gated potassium channel antibody-associated limbic encephalitis, although subsequent investigations deemed this unlikely as a cause of hyponatraemia. Although his sodium levels improved with fluid restriction, serial point-of-care testing proved misleading in monitoring the efficacy of treatment as inconsistencies were seen in comparison with laboratory testing. The cause of hyponatraemia may have been medication-induced SIADH and/or polydipsia. This case highlights the importance of collating detailed histories and laboratory blood testing to guide management in cases of hyponatraemia of unknown aetiology.

BACKGROUND

Hyponatraemia is a common electrolyte abnormality seen in hospital inpatients. Investigations to determine the underlying cause are essential in order to direct and optimise management.

The patient we describe did not initially reveal that he had been feeling excessively thirsty prior to admission. Additionally, news of a previous hospital admission with hyponatraemia only became apparent later during the admission. A thorough history coupled with obtaining extensive information regarding a patient's presenting complaint can help yield diagnoses in cases where there appear to be no obvious cause of hyponatraemia.

The management of hyponatraemia requires close monitoring of serum sodium levels. In clinical practice, both point-of-care and laboratory analysers are used to monitor patients. Our case demonstrates the pitfalls of using point-of-care testing to guide management in cases of severe hyponatraemia.

CASE PRESENTATION

A 67-year-old man was admitted to the local mental health unit having presented with catatonic depression and suicidal ideation, attributed to financial pressure. Two days later, he was transferred to an acute medical ward at a different hospital because of an incidental finding of hyponatraemia on routine blood tests (sodium 121 mmol/L).

On admission, he was fatigued and systems screen was negative. He established minimal eye contact and was low in mood both subjectively and objectively, with a flat affect. He was fully orientated to time, place and person. No significant changes in his psychiatric condition had been reported in 2 days since commencing mirtazapine. He was clinically euvolaemic and haemodynamically stable. Physical examination was unremarkable and there were no focal neurological signs.

In the first few days of his admission, clinical staff noted that he displayed increasing symptoms of attention deficit, reduced concentration and memory impairment. On review by the psychiatric team he remained low in mood with no evidence of catatonia, but instead was perplexed with some volatility of mood and obvious distress, characteristic of trauma-related dissociative disorder with fragments of thought relating to his financial worries. Following this, the possibility of a diagnosis of pseudodementia was considered.

Seven days into the admission, the patient had a generalised tonic-clonic seizure lasting 2 minutes, with a gradual recovery over 20 minutes. His sodium was 135 mmol/L on laboratory tests at that time. In view of new seizure activity, behavioural changes and hyponatraemia, the history was revisited. The medical team ascertained that 5 years prior to the index admission he had presented to hospital with a 1-day history of acute confusion, pressure of speech, flight of ideas and impaired concentration on a background of a resolving chest infection 2 weeks prior. He also developed symptoms of psychotic depression during his inpatient stay. Laboratory workup at the time revealed hyponatraemia (sodium 121 mmol/L which improved to 127 mmol/L on discharge) and weakly positive voltage-gated potassium channel (VGKC) antibody in blood (113 pmol/L). He was treated for viral encephalitis with aciclovir and then for presumed VGKC antibody-mediated limbic encephalitis with intravenous methylprednisolone then oral prednisolone. He improved significantly and returned to his cognitive baseline. Follow-up in neurology clinic 7 months later showed weakly positive VGKC antibody titres (154 pmol/L), but no other cause for the admission was found. In view of the history gathered from this prior admission, a relapse of VGKC

antibody-mediated limbic encephalitis was suspected as a cause of the patient's new presentation and a neurology consultation was sought in an effort to investigate for this.

INVESTIGATIONS

Initial laboratory tests showed a raised white cell count of 12.5×10^9/L, neutrophils of 10.0×10^9/L, plasma sodium of 121 mol/L and plasma chloride of 89 mmol/L. The sodium on a concurrent point-of-care test was 116 mmol/L. A random urine sodium was 49 mEq/L. Paired osmolalities revealed serum osmolality of 245 mOsm/L and urine osmolality of 220 mOsm/L, in keeping with SIADH although it was felt that his urine osmolality was lower than that might have been expected. The rest of his laboratory workup including full blood count, electrolytes, liver function tests, thyroid function tests and cortisol levels were unremarkable.

The patient's increasing confusion and suspected diagnosis of autoimmune limbic encephalitis led to further investigations. An initial computed tomography (CT) of the head demonstrated mature lacunar infarcts within the anterior right parietal lobe and right superior frontal gyrus. Magnetic resonance imaging (MRI) of the head confirmed numerous non-specific subcortical and deep white matter signal changes that appeared stable. Subsequently a CT scan of the chest, abdomen and pelvis revealed an anterior mediastinal well-defined homogenous soft tissue density with mildly enlarged mediastinal nodes.

Cerebrospinal fluid (CSF) from a lumbar puncture had 1 white blood cell/μL, 1 red blood cell/μL, glucose 4.1 mmol/L (plasma glucose 6.1 mmol/L), protein 0.42 g/L, with negative oligoclonal bands and showed no growth at 2 days. Viral polymerase chain reaction (PCR) was negative for herpes simplex virus, varicella zoster virus and enterovirus. An electroencephalogram performed towards the end of his admission revealed diffuse non-specific slowing with no epileptiform activity.

DIFFERENTIAL DIAGNOSIS

- Mirtazapine-induced SIADH.
- Severe depression causing pseudodementia with hyponatraemia related to polydipsia.
- VGKC antibody-associated limbic encephalitis.

TREATMENT

In view of SIADH, the patient was fluid restricted to 750 mL of fluid per day. He did not receive intravenous fluids at any point during this admission. Both laboratory and point-of-care sodium were taken at regular intervals with an aim to slowly (<10 mmol/L per 24 hours) correct the patient's hyponatraemia (figure 1). This showed a slow and incremental improvement in sodium readings. After 4 days of fluid restriction, the patient's sodium levels returned to within the normal range (135 mmol/L).

In addition to correction of the hyponatraemia he received a 3-day course of aciclovir, stopped when the results of the viral PCR on CSF were negative. He was started on levetiracetam following the single seizure episode. The patient was subsequently treated with intravenous methylprednisolone for 3 days for presumed autoimmune limbic encephalitis. He was weaned off the mirtazapine and started on lofepramine and aripirazole. He was also discharged on a reducing regime of prednisolone and levetiracetam.

OUTCOME AND FOLLOW-UP

Although very rare, patients with thymoma-associated paraneoplastic encephalitis often have VGKC-complex antibodies.[1]

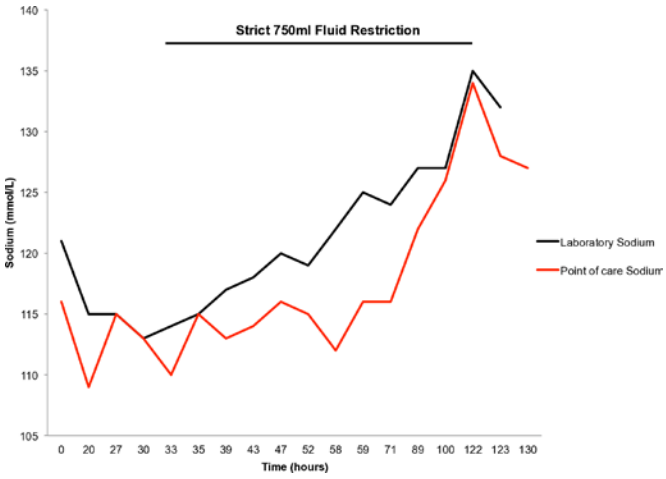

Figure 1 Graph depicting the levels of sodium (mmol/L) as analysed by point-of-care testing and by the laboratory at similar time points during the patient's inpatient stay. Note particularly the discrepancies between laboratory and point-of-care readings from 33 to 122 hours, resulting in disproportionate representation of sodium levels when using point-of-care testing to monitor incremental changes in sodium.

Further imaging was performed in order to discern the anterior mediastinal mass found on the CT scan. An MRI of the heart and thorax with contrast and a full-body positron emission tomography (PET) scan confirmed a likely benign pericardial cyst. This was compared with a previous PET scan performed in 2013, and no change in size had been noted over a 5-year time frame. This was subsequently discussed at a lung nodule multi-disciplinary team meeting. No follow-up was required.

Follow-up antibody testing for blood and CSF LGI1, Caspr2 and anti-VGKC antibodies was negative. The patient has now been reviewed in neurology clinic, with the opinion that his behaviour may have been a pseudodementia in the context of significant mood disturbance. He has now been weaned off the prednisolone and the levetiracetam has now been stopped, as he has had no further seizures since. Recent neuropsychological assessments confirm that he has no significant specific cognitive deficits and he continues to show cognitive improvement following completion of the course of steroids.

DISCUSSION

In view of this man's severe hyponatraemia and its potential to cause serious complications, serial point-of-care sodium measurements using venous blood measured in a point-of-care analyser (GEM4000, Werfen, Italy) were taken in the initial stages of his management. These were corroborated with samples taken at similar (or the same) time points and measured in the hospital laboratory (Architect c16000, Abbott, Illinois, USA). Our findings demonstrated inconsistencies in readings of laboratory and point-of-care sodium readings. We believe that while point-of-care testing is useful in detection of hyponatraemia, its utility in monitoring response to treatment is more questionable. There is a need for reliable results to establish the rate of increment in blood sodium concentrations in order to avoid complications such as central pontine myelinolysis.

Ion-sensitive electrodes are used to measure serum sodium concentrations. Previous studies have demonstrated statistically significantly raised readings with laboratory analysers when compared with point-of-care analysers.[2] The underestimation of sodium when using point-of-care testing has been postulated

to be affected by many factors including the dilution of sample volume attributed to using heparin-flushed syringes to take the blood sample, as well as the overestimation of sodium in hypoalbuminaemia by laboratory analysers.[3–7] Neither of these theories were applicable to our patient, however he consistently had higher sodium values on laboratory testing compared with point-of-care testing in keeping with this finding (figure 1).

Additionally, our results demonstrate that sodium measurements using point-of-care testing were erroneous when used serially to monitor treatment response. They showed a drop in sodium concentration, which did not correlate to the rising levels seen with laboratory testing at similar points in time (figure 1). A previous study has shown an increase in the absolute difference in sodium readings between laboratory and point-of-care testing as patients move from hyponatraemic to euvolaemic statuses,[3] which may correlate with this finding.

The causes of hyponatraemia in acute medical patients can usually be identified,[8] however a relatively small proportion of patients with SIADH have an unexplained aetiology, particularly in the elderly population.[9] The instigation of mirtazapine therapy 2 days prior to admission may have been a relevant factor. However, evidence of mirtazapine-induced hyponatraemia is scarce with only a small number of studies demonstrating a link,[10–13] and other studies demonstrating none at all.[14] Mirtazapine is a serotonin receptor blocker, which also effects norepinephrine release through alpha-2-mediated adrenergic antagonism. Antidepressant-mediated antagonism of serotonin receptors is thought to be responsible for the release of antidiuretic hormone,[15] resulting in SIADH. The measured osmolalities were found to be in keeping with an SIADH, and as such the introduction of mirtazapine presents a possible explanation for the patient's presentation. In a small number of previous case studies of mirtazapine-induced hyponatraemia, with doses as low as 7.5 mg, the range to significant hyponatraemia (ranging between 112 and 130 mmol/L) was between 4 and 10 days,[12] and as our patient had hyponatraemia out of this time frame following the introduction of mirtazapine, this may not be a directly related link.

The previous finding of hyponatraemia and positive VGKC antibody titres in the patient's serum during a hospital admission 5 years prior to the present admission suggested an alternative diagnosis.[16] The importance of obtaining a thorough history was underpinned following this discovery of the previous admission. This raised a possible diagnosis of VGKC antibody-associated limbic encephalitis as an explanation for the patient's clinical presentation. This condition tends to be responsive to immunotherapy,[17] and while the diagnosis had not been confirmed, the potential for corticosteroid treatment to reverse the patient's neuropsychiatric presentation resulted in a clinical decision to initiate empirical treatment. VGKC antibodies are associated with limbic encephalitis.[17] Of these, up to 80% are associated with hyponatraemia, the majority confirmed to be SIADH.[17 18] VGKC antibodies are not directed to the VGKC itself but its associated proteins. Antibodies directed against the leucine-rich glioma-inactivated 1 (*LRG1*) gene tend to be associated with hyponatraemia. Recurrence rates of LRG1- associated limbic encephalitis are relatively low at 0%–20%.[19] In our patient, the negative follow-up antibody testing and continued cognitive improvement following the completion of steroids deem limbic encephalitis a far less likely cause of this patient's hyponatraemia.

Learning points

- Obtaining a detailed history is important to ascertain causes of hyponatraemia where there is no apparent cause.
- Point-of-care analysers should be used with caution when used to monitor sodium levels in severe hyponatraemia.
- Patients may not always disclose clinical symptoms when initially presenting to hospital and as such it is important to continuously revise and revisit their 'history of presenting complaint'.

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Reminder of important clinical lesson