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CASE REPORT
Heart failure

Resistant hyponatraemia in a patient with follicular lymphoma and heart failure with reduced ejection fraction: a case report

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Background Hyponatraemia is a common problem in patients with heart failure. It can be difficult to treat, especially in the presence of the patient's needs for diuresis and manipulation of the renin–angiotensin–aldosterone system (RAAS).

Case summary This concerns a 74-year-old woman with follicular lymphoma and severe global left ventricular systolic dysfunction secondary to treatment with R-CHOP chemotherapy. She presented a difficult challenge in the management of her decompensated heart failure alongside hyponatraemia as low as 113 mmol/L. This was resistant to standard treatment. The resistance to usual measures necessitated treatment with Tolvaptan, a selective arginine vasopressin V2 inhibitor used to treat hyponatraemia in syndrome of inappropriate anti-diuretic hormone. This, along with a strict fluid restriction of 500 mL/day, resolved the patient's hyponatraemia and enabled her discharge home on tolerated heart failure treatment. She has now remained stable for almost 12 months.

Discussion The potential causes of hyponatraemia are discussed along with the role of Tolvaptan in its management.

Keywords Hyponatraemia (D007010) • Heart Failure (D006333) • Tolvaptan (D000077602) • Lymphoma (D008223) • Case Reports (D002363)

Learning points

- Hyponatraemia is a common part of acute medical presentations, especially in the elderly. It is closely related to patients' overall fluid status and can be caused or exacerbated by heart failure treatment.
- Tolvaptan is a selective arginine vasopressin V2 inhibitor that promotes free water excretion and helps to normalize sodium levels. It can lead to a sudden rise in the sodium level. Therefore, it should be initiated under specialist supervision, and with close monitoring of U+Es.
- Sudden significant sodium rise, especially in pre-existing chronic hyponatraemia, can precipitate osmotic demyelination syndrome, a debilitating and potentially irreversible degenerative neurological condition.

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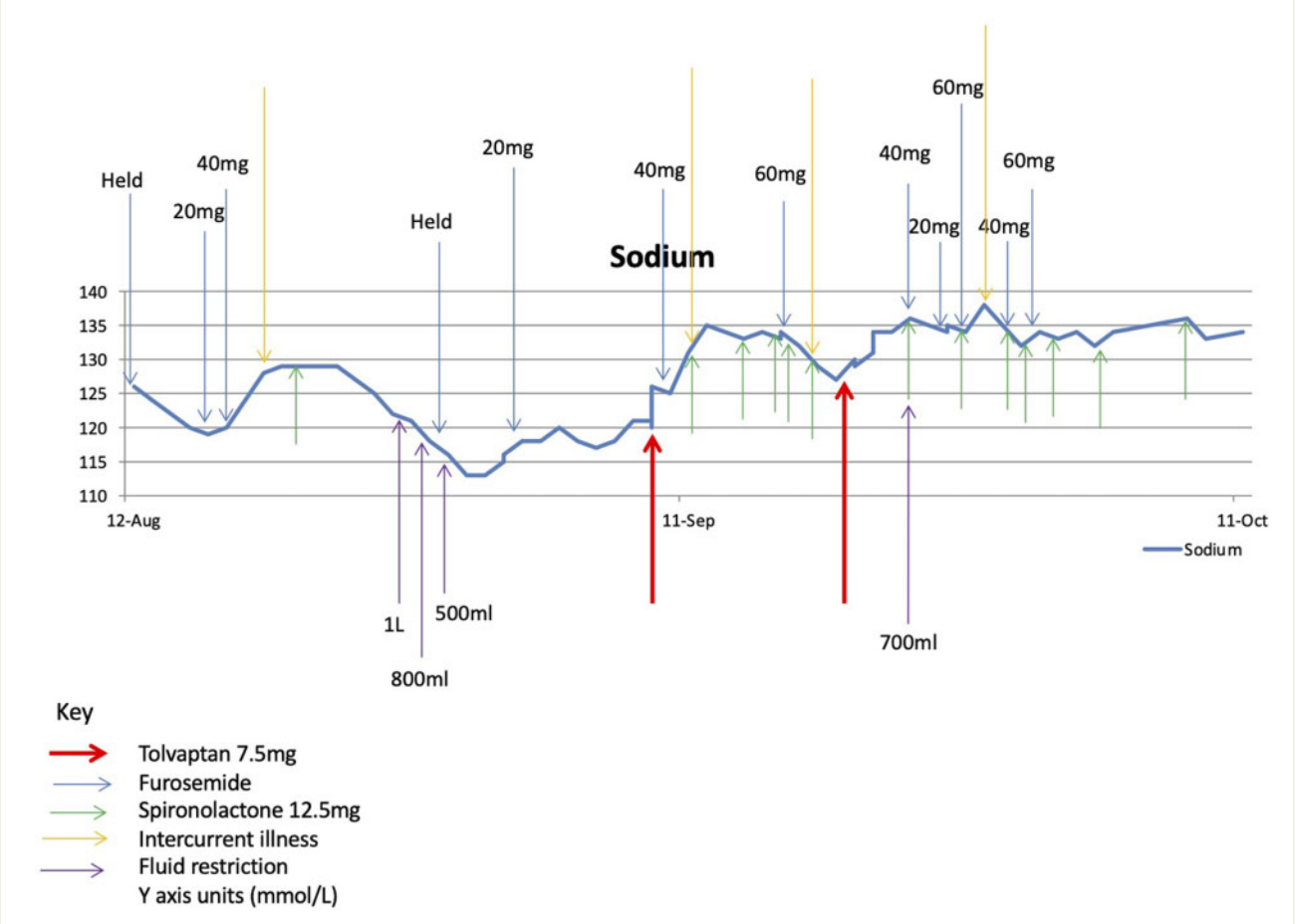
Introduction

Hyponatraemia is common in clinical practice, reported to occur in 15–30% of adults.[1] The Organized Program to Initiate Life Saving Treatment in Patients Hospitalized for Heart Failure (OPTIMIZE-HF) registry showed that 25.3% of the 47 647 patients with heart failure (HF) had hyponatraemia on admission to the hospital.[2]

The following case illustrates important learning points on fluid status management and specialist input into the management of hyponatraemia in HF.

Timeline

The timeline of the patient's admission against the level of the serum sodium with indicators of therapeutic interventions or intercurrent illnesses in order to demonstrate the complexity of the multiple factors affecting the patient's serum sodium.



Case presentation

A 74-year-old female with follicular lymphoma presented to the haematology unit with increasing breathlessness and peripheral oedema. She was commenced by her general practitioner on Furosemide 40 mg o.d. Her past medical history included follicular lymphoma. She was found to have left-sided pleural effusion. She received chemotherapy with R-CHOP for lymphoma 6 months earlier. Following pleural tap, the effusion was found to be a transudate in keeping with HF. She remained dyspnoeic, with peripheral oedema up to the thighs and she had free fluid in the abdomen. Transthoracic echocardiography (TTE) showed severe global left ventricular systolic dysfunction. It was determined that this was likely due to dilated cardiomyopathy secondary to chemotherapy, as her previous TTE in 2018 showed no more than mild left ventricular systolic dysfunction. She was treated with furosemide 40 mg o.d., bisoprolol 1.25 mg o.d., and ramipril 1.25 mg o.d. She developed hyponatraemia which responded initially to the omission of ramipril. Her eGFR was 66 mL/min/1.73 m^2, her bilirubin was slightly raised at 26 µmol/L, and her alkaline phosphatase measured 156 IU/L. The latter two were in keeping with congestion. She remained fluid overloaded and hypotensive, hence, her transfer to our cardiology unit for further management.

Progress

Whilst on the cardiology ward attempts were made to treat her with therapy for HF with reduced left ventricular ejection fraction (HFrEF)

(*Timeline*), to improve her symptoms and reduce long-term morbidity and mortality. Her blood pressure was too low to restart ramipril (at best her systolic pressure was 90 mmHg). Unfortunately, the introduction of spironolactone 12.5 mg o.d. with the furosemide resulted once again in hyponatraemia.

Initially, the hyponatraemia was mild (around 125–130 mmol/L). Her furosemide was reduced to 20 mg o.d., while on bisoprolol 1.25 mg o.d. in an effort to reduce renal sodium loss. In addition, her fluid intake was initially restricted to 1.5 L/day, dropping gradually to 0.5 L/day which was maintained for 4 weeks.

Her lowest serum sodium was 113 mmol/L. At that point, she was experiencing nausea, vomiting, and mild early morning confusion which are symptoms of significant hyponatraemia. Her course was complicated by a Stage 2 acute kidney injury. She was given 500 mL of 0.9% saline over 12 h in addition to her restricted oral intake of 0.5 L/day.

The maximum serum sodium achieved with this plan was 125 mmol/L. This prevented the reintroduction of spironolactone or ramipril and hindered any increase in the dose of furosemide. Having failed to respond to stringent and prolonged fluid restriction, the serum sodium responded to a single dose of tolvaptan 7.5 mg orally rising from 123 mmol/L to 134 mmol/L. The plan was for her to receive the tolvaptan once every 2 weeks to avoid sudden rises in sodium with consequent impact on the brain. However, following the second dose of tolvaptan, her serum sodium remained normal. At that point, spironolactone was added initially at 12.5 mg every 2 days and then daily, without recurrence of the hyponatraemia (*Timeline*).

The patient continued to improve clinically and was discharged from the hospital. She has been in the community for 12 months, with minimal HF symptoms (NYHA Class II).

Cardiac magnetic resonance (CMR) imaging was performed 5 months after discharge from hospital. The CMR showed severe left ventricular systolic impairment, left ventricular ejection fraction of 28%, and no myocardial scarring on late gadolinium imaging. This confirmed that she had HFrEF was non-ischaemic in origin, most likely due to the cardiotoxic effects of her R-CHOP chemotherapy.

Discussion

This patient presented a difficult challenge, with hyponatraemia, hypervolaemia, severe HFrEF, and hypotension. The complex interaction of these factors necessitated a long inpatient stay.

Hyponatraemia is divided into three categories: first is hypervolaemic hyponatraemia (in advanced liver cirrhosis, renal disease, or HF) is associated with fluid overload, raised arginine-vasopressin (AVP) secretion, raised total body sodium with disproportionately increased total body water. The second is euvolemic hyponatraemia which can result from excess free water intake but usually results from the syndrome of inappropriate anti-diuretic hormone secretion (SIADH). The latter is characterized by increased AVP.[3] Euvolemic hyponatraemia is defined by a serum osmolality < 270 mosm/L and a urine osmolality > 100 mosm/L. The third category is hypovolaemic hyponatraemia, where there are reduced total body fluid and total body sodium. This is commonly seen in the elderly and can be caused by prolonged use of diuretics and some intrinsic kidney diseases.[4] The most common management intervention is with slow intravenous sodium-containing IV fluids.

The role of renin–angiotensin–aldosterone system (RAAS) is vital in HF and hypervolemic hyponatraemia.[5] In chronic HF, the cardiac output and circulating blood volume are reduced. This triggers a compensatory RAAS response preserving blood pressure by retaining water and sodium.[5] This is associated with sympathetic stimulation, causing renal vasoconstriction.

Severe hyponatraemia can lead to cerebral oedema and neurological disturbances, while rapid correction of hyponatraemia could lead to osmotic demyelination syndrome.[6] Thus, it is vital to monitor serum sodium and carefully manage the medications particularly in older patients (usually female) with low body mass who are most at risk of hyponatraemia in HF.[7]

Tolvaptan is a selective (AVP) V2 inhibitor which promotes free water excretion in patients with SIADH, helping to normalize sodium levels. It can be used in the treatment of HF exacerbations, allowing the addition of diuretic treatment in patients with low sodium levels.[8,9] It normalized our patient's sodium levels, relieved the symptoms of hyponatraemia, and allowed administration of diuretics and spironolactone. The latter allowed us to suppress the RAAS. We kept ramipril stopped due to persistent hypotension. Spironolactone provides a prognostic benefit through the reduction of hospitalization and improving overall survival.[10]

Hyponatraemia is a negative prognostic indicator in HF[4] and can be difficult to manage. Affected patients are often complex, with multi-morbidity, and are frail. Their medications must be managed cautiously and gradually introduced.

Conclusion

This case demonstrates the complexity of treating hyponatraemia complicating HFrEF in a hypotensive, fluid overloaded patients. Tolvaptan is an effective last resort therapy in hyponatraemia.

Lead author biography

Dr Jennifer Butler is a Foundation Year 2 Doctor at the Northern General Hospital, Sheffield. She has BA (Hons) in Classics from the University of Oxford and graduated with Honours from the University of Southampton Medical School. She is a winner of the Donald Acheson First Prize for achievement in Finals. She has ambitions to work in Anaesthetics and Critical Care.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing these cases and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

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