CASE REPORT

Lithium-induced nephrogenic diabetes insipidus in older people

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Abstract

Presentation: we report two patients. The first is a 68-year-old woman who presented with a 2-day history of vomiting. She was hypernatraemic and her elevated serum sodium concentration did not improve initially, despite adequate fluid replacement. She subsequently developed polyuria and polydipsia. The second patient, a 77-year-old woman, presented with delirium and severe hypernatraemia after being treated for a chest infection 1 week earlier. Both patients were on long-term lithium treatment.

Investigation: in both the cases, a supervised water-deprivation test done after normalization of the blood biochemistry showed partial nephrogenic diabetes insipidus.

Outcome: lithium was discontinued.

Conclusion: older people on lithium—especially those requiring supportive care—are at risk of severe hypernatraemia after an acute illness or if their fluid intake is restricted.

Keywords: hypernatraemia, lithium, nephrogenic diabetes insipidus

Introduction

Drug-induced diabetes insipidus is almost always of the nephrogenic type. Lithium is the commonest drug implicated [1]. We report two cases of lithium-induced nephrogenic diabetes insipidus which highlight a relatively common but under-appreciated problem occurring in some older people who take this medication.

Case reports

Case 1

A 68-year-old woman was admitted with a 2-day history of vomiting after eating pork. She had been taking lithium for the last 8 years for recurrent depression. The clinical examination was unremarkable, apart from signs of moderate dehydration. Investigations revealed hypernatraemia (sodium 149 mmol/l), pre-renal azotaemia (urea 30.3 mmol/l, creatinine 306 µmol/l), normal serum potassium, glucose and calcium, and normal plasma lithium level (<0.2 mmol/l).

We made a diagnosis of food poisoning and she was treated with intravenous 5% dextrose. The vomiting did not improve. The serum urea rose, despite adequate fluid replacement via a central venous line with monitoring of the central venous pressure. On the third day, endoscopy revealed the presence of a paraoesophageal hernia. Three litres of fluid were aspirated from the stomach. She was given nothing by mouth and was subsequently managed with nasogastric suction and intravenous dextrose saline infusion. However, nasogastric suction yielded only 300–350 ml of fluid per day.

Her vomiting improved gradually with conservative management. She was discharged after 2 weeks with a diagnosis of a spontaneously resolved gastric volvulus and oesophageal hiatus hernia. On discharge, her blood urea and electrolytes were normal. At follow-up 2 weeks later, she complained of polyuria and excessive thirst. In view of her lithium treatment, we considered the possibility of nephrogenic diabetes insipidus. A review of her inpatient record showed her serum sodium had been persistently elevated (144–149 mmol/l) despite adequate hydration (4–4.5 l/day). She had an urine output of between 2.2 and 3.4 l/day over the same period. She was re-admitted for a supervised water-deprivation test (Table 1), which suggested a diagnosis of partial nephrogenic diabetes insipidus. After consultation with the consultant psychiatrist, lithium was stopped. She is now under regular follow-up.
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Table 1. Water-deprivation test results

<table>
<thead>
<tr>
<th></th>
<th>Osmolarity (mosmol/kg)</th>
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<th></th>
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<tbody>
<tr>
<td></td>
<td>Pre-test</td>
<td>After dehydration</td>
<td>After desmopressin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
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<tr>
<td>Case 1</td>
<td>295</td>
<td>460</td>
<td>305</td>
<td>605</td>
</tr>
<tr>
<td>Case 2</td>
<td>302</td>
<td>518</td>
<td>307</td>
<td>587</td>
</tr>
</tbody>
</table>

Case 2

A 77-year-old woman from a residential home was admitted with delirium. She had been treated for chest infection a week earlier by her general practitioner. She had a long history of manic depressive illness and had been on lithium for the past 10 years. On admission, she was severely hypernatraemic (sodium 163 mmol/l) with pre-renal azotaemia (urea 25 mmol/l, creatinine 253 μmol/l). Her blood potassium, glucose and calcium concentrations were normal. Her lithium level was 1.4 mmol/l. Her serum osmolality was 358 mosmol/kg and a simultaneous urine osmolality was 513 mosmol/kg.

We made a diagnosis of lithium-induced nephrogenic diabetes insipidus and managed her with intravenous fluid replacement (5% dextrose) via a central line. After normalization of renal function and sodium level, we carried out a supervised water-deprivation test (Table 1). This showed a picture suggestive of partial nephrogenic diabetes insipidus. The lithium was stopped. She was discharged and continues outpatient follow-up.

Discussion

Lithium is the recommended treatment for the prophylaxis of bipolar affective disorder. It is also used in the prophylactic treatment of recurrent unipolar depression, short-term treatment of mania and to augment antidepressant drugs in cases of resistant depression [2]. About one in 1000 of the general population is on lithium treatment [3] and about 20% of these patients are over 65 [4]. Over the age of 65 years the point prevalence of lithium therapy is 0.27% [5]. Lithium can cause major disturbance in water balance, manifested by polyuria and secondary polydipsia. This is because of decreased urinary concentrating ability—a consequence of impaired responsiveness of the distal nephron to the anti-diuretic action of arginine vasopressin [6] (nephrogenic diabetes insipidus).

Lithium interferes with arginine vasopressin-mediated activation of adenylate cyclase in the principal cells of the distal tubule and collecting duct of the kidney, thereby decreasing intracellular cyclic AMP generation and protein kinase A stimulation, and reducing the abundance of water channels in the apical membrane of the cells and subsequent water transport [7, 8]. Aquaporin-2 is the vasopressin-regulated water channel. It is found only in the collecting duct. In the experimental rat model, immunoblotting reveals that lithium treatment has been associated with marked down-regulation of aquaporin-2 expression (to 31 ± 8% after 10 days and to 4 ± 1% after 25 days of treatment), coincident with development of severe polyuria, which only partially reversed by cessation of therapy [9].

In most cases, there is a correlation between impaired urinary concentrating ability and duration of lithium therapy or total lithium dose [7]. Chronic lithium administration may cause focal interstitial nephritis, distal renal tubular dilatation and microcyst formation. Patients developing these lesions can be identified clinically by impaired urinary concentrating ability, which progresses with the duration of lithium treatment [7, 10]. The current practice is to maintain the serum lithium level between 0.5 and 0.8 mmol/l. The incidence and severity of adverse effects are greater at higher serum concentrations [2]. Between 20 and 40% of patients currently taking lithium have a moderate increase in urine volume (> 2.5 l/day) as a result of the concentrating defect. Up to 12% have frank nephrogenic diabetes insipidus characterized by polyuria (urine volume > 3 l/day), excessive thirst, nocturia, delirium, tachycardia, hypotension, hypernatraemia and even hyperosmolar coma [8, 11].

Lithium-induced nephrogenic diabetes insipidus is usually reversible on stopping therapy but a few patients remain symptomatic long after the lithium has been discontinued [12] (a case of persistent nephrogenic diabetes insipidus has been reported 8 years after discontinuation of lithium [13]). These patients are at risk of severe hypernatraemia if their fluid intake is restricted, if they receive inadequate intravenous fluid peri-operatively or during episodes of vomiting or diarrhoea or during acute illness [13, 14]. This is particularly important in institutionalized older people who require supportive care with feeding. Furthermore, the patients are at increased risk if the importance of current or past lithium use is under-estimated.

In the first case, the onset of vomiting led to inadequate replenishment of excreted water and the patient presented with hypernatraemia and severe dehydration. Subsequently, although volume-depleted, she never had a tendency to conserve body water. The acute illness unmasked lithium-induced nephrogenic diabetes insipidus. That lithium might be contributory to her biochemical derangement was considered only at outpatient follow-up. During her hospital stay, polyuric data were overlooked because of a normal serum lithium level on presentation.

In the second case, the patient was care-dependent and a recent chest infection led to restriction of oral fluid intake. Perhaps the carers were not aware of her need for increased hydration. It is likely that in both cases, urinary concentrating ability was progressively impaired as a consequence of long-term maintenance.
therapy with lithium (8 years and 10 years respectively) and was at a critical level before the onset of an acute illness. It is possible that an acute illness alone may produce similar hypernatraemia in older people [15, 16] but urine output will always be low in that situation.

Nephrogenic diabetes insipidus in adults is usually partial with mild symptoms [17]. Usually the serum sodium is normal or mildly elevated, the plasma osmolality is within normal range, the urine osmolality is low (<300 mosmol/kg) and the urine volume is between 2.5 and 6.0 1/day [8, 17]. However, when patients are fluid-depleted, there is a marked rise in serum sodium, a rise in plasma osmolality and a urine osmolality that may exceed that of plasma [8]. The water-deprivation test is useful in diagnosis: the urine osmolality is usually <300 mosmol/kg after dehydration with no further or a minimal (<9%) rise after desmopressin. In partial nephrogenic diabetes insipidus, the urine osmolality is between 300 and 750 mosmol/kg after dehydration and is <750 mosmol/kg after desmopressin [8, 17].

To find out the result of water-deprivation tests in healthy older people, we conducted a Medline search between the years 1984 and 2000 (keyword: water deprivation test). The results are shown in Table 2 [18–20]. The findings of the three studies varied, possibly because of the different mean age of the study populations and the duration of water deprivation. It seems that with increasing age there is a reduction in the maximal urinary concentrating ability during water deprivation. In view of the finding of a lower concentration of arginine vasopressin after water deprivation as compared with healthy young adults, studies have suggested that the older people might be in a state similar to partial cranial diabetes insipidus [18, 19]. However, in neither of our cases did the urine osmolality rise further after desmopressin administration, suggesting unresponsiveness of the distal nephron rather than a central cause.

Symptomatic stable patients with lithium-induced nephrogenic diabetes insipidus may respond to a reduction in lithium dosage or discontinuation of lithium [6, 21]. If the urine volume exceeds 4 l/day, treatment with thiazides and amiloride has been advocated [1, 22].

Nonsteroidal anti-inflammatory drugs such as indomethacin [23, 24] and intravenous ketorolac [25] may be used in severe refractory cases. Preventive measures include education of patients and their carers about maintaining adequate hydration. The serum lithium level should be kept between 0.5 and 0.8 mmol/l. Annual measurement of the 24-h urine volume is a simple and effective screening test [1].

Physicians caring for older people should be aware of the development of lithium-induced nephrogenic diabetes insipidus and should consider it in the differential diagnosis of patients with unexplained hypernatraemia.

Key points

- Lithium is the commonest drug causing nephrogenic diabetes insipidus.
- The prevalence of lithium therapy is higher in those over 65 years than in the general population.
- Those taking lithium may develop severe hypernatraemia during acute illness or after fluid deprivation.
- Institutionalized dependent people are at increased risk if carers are not educated about the need to maintain adequate hydration.
- Lithium must be considered in the differential diagnosis of patients with unexplained hypernatraemia.

Table 2. Studies of the water-deprivation test in healthy older people

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study population</th>
<th>Results after test</th>
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<tbody>
<tr>
<td></td>
<td>Authors</td>
<td>Mean age (years)</td>
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<tr>
<td>Li et al., 1984</td>
<td>Li et al.</td>
<td>76.5</td>
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<td>Faull et al., 1993</td>
<td>Faull et al.</td>
<td>68</td>
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<tr>
<td>Jian et al., 1995</td>
<td>Jian et al.</td>
<td>65.2</td>
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<tr>
<td>Men</td>
<td>Men</td>
<td>65.8</td>
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AVP, arginine vasopressin; NA, not available.

References

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