

# Delirium associated with therapeutic levels of lithium in bipolar disorder

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**Lithium has been associated with neurotoxicity even at 'therapeutic' levels. This case report describes a patient with bipolar disorder who developed signs of delirium following an increase in her dose of lithium, even though her serum levels remained in the therapeutic range.**



Lithium is widely used for the treatment of bipolar affective disorder and as an augmentation agent for antidepressant medication. Despite concerns about adverse effects and poor patient adherence, as well as its known narrow therapeutic index, it remains an effective pharmacological agent, particularly in the prevention of manic relapse in bipolar affective disorder.<sup>1</sup>

Lithium is an element that is chemically similar to sodium and is therefore likely to alter many sodium-linked processes, making it difficult to establish its exact mechanism of action.<sup>2</sup> Lithium's side-effects are well known, commonly causing gastrointestinal upset, fine tremor, polyuria and polydipsia (by causing nephrogenic diabetes insipidus) among other effects. Longer term, it is associated with the development of hypothyroidism and hyperparathyroidism. At toxic levels, it is also associated with significant gastrointestinal and CNS effects, which can in rare cases lead to coma and death.<sup>3</sup> Recent research has investigated possible neuroprotective or neurotoxic effects. The literature is inconclusive regarding this, although evidence is mounting for a neurotoxic effect.<sup>4,5</sup>

Lithium toxicity typically presents to the general hospital and general physicians will be aware of the therapeutic range for lithium. However, lithium has been known to cause neurotoxicity even at therapeutic levels<sup>6</sup> and its endocrine effects may lead to deterioration in both physical and mental health. We present the case of a patient in whom a delirium-like picture developed following an increase in lithium dose, despite lithium levels remaining in the 'therapeutic' range. The patient returned to normal on withdrawal of lithium.

## Presentation

A 61-year-old woman with a history of bipolar affective disorder was admitted to the general hospital mute, with poor intake of food and fluid and a mild tremor. Her mental state had been stable for 10 years on lithium monotherapy. Her only other significant medical history was hypothyroidism, which was treated with levothyroxine. Her relatives had noticed a deterioration in her mood over the previous two weeks with little oral intake for one week.

One week prior to admission, her GP had increased her longstanding lithium carbonate therapy from 600mg at night to 800mg at night due to lowering of her mood. On the day of admission, she had been found wandering outside seminaked and had held a knife limply

against her arm. Assessment by the community mental health team led to concerns about possible lithium toxicity and she was transferred to the emergency department.

Initial blood tests showed a serum lithium level of 0.84mmol per litre [normal range 0.5-1.0mmol per litre]. She was found to have a raised white cell count ( $14.8 \times 10^9$  per litre [ $4.0-11.0 \times 10^9$  per litre]) with neutrophilia ( $12.6 \times 10^9$  per litre [ $2.0-7.5 \times 10^9$  per litre]) and slightly raised C-reactive protein (10mg per litre [0-7.5mg per litre]). Calcium levels were not tested at this stage. Initial blood tests were otherwise unremarkable and physical examination was normal.

A Mental Health Act Assessment was requested by the emergency physicians. At this assessment, there was evidence of psychomotor retardation and mutism. A provisional diagnosis of severe depression with catatonic symptoms was made and sertraline 50mg daily was commenced with advice to commence benzodiazepine treatment for her catatonic symptoms. Medical admission was recommended to rule out a physical cause for the presentation, such as delirium secondary to infection. Lithium was continued since her lithium levels were within the normal range, indicating that she was not toxic.

The patient remained an inpatient in the general hospital for 15 days. Shortly after admission, she

became incontinent of urine and was commenced on oral antibiotics for a suspected urinary tract infection. Creatine kinase was noted to be moderately high at 788iu per litre [ $<145$ iu per litre], but this spontaneously reverted to normal over the next four days. She developed urinary retention and was catheterised. Her pyrexia, which had been consistent at a low grade since admission, worsened and she was commenced on broad-spectrum IV antibiotics (piperacillin with tazobactam, gentamicin). Urine and blood cultures were, however, negative for bacterial growth and no other source of infection was identified. At this stage, blood tests revealed hypercalcaemia (corrected calcium of 2.79mmol per litre [2.15–2.6mmol per litre]). It was initially suspected that this was due to dehydration and IV fluids were administered.

The patient remained mostly mute and confused. A CT head scan showed old ischaemic change only. She was seen by neurologists who recommended lumbar puncture, an MRI head scan and an EEG. Lumbar puncture was unremarkable and the MRI corroborated the CT findings, showing non-specific changes consistent with small vessel disease. EEG revealed no seizure activity. There was mild diffuse slowing with multifocal sharp waveforms, which was reported to be consistent with lithium therapy.

Regular blood tests continued, demonstrating a persistent hypercalcaemia despite the administration of IV fluids. The patient went on to develop hypernatraemia with sodium peaking at 160mmol per litre in the absence of clinical dehydration. Endocrinology review was requested. At this assessment, it was suggested that the hypernatraemia and hypercalcaemia may be due to nephrogenic diabetes insipidus secondary to lithium. Despite this, lithium was continued. Subclinical

hyperthyroidism was noted with a thyroid stimulating hormone (TSH) level of 0.56mU per litre [0.34–5.6mU per litre] and a free thyroxine (FT4) level of 26.3pmol per litre [7.5–21pmol per litre] on levothyroxine, leading to a dose reduction of her levothyroxine dose. Parathyroid hormone levels were marginally raised at 7.3pmol per litre [1.8–6.8pmol per litre] but not as high as would be expected in primary hyperparathyroidism.

The patient was reviewed by the psychiatric liaison team. She was no longer mute but remained confused – scoring 11/30 on the Mini-Mental State Examination (MMSE) – and talked about witches dying and people removing body parts from her. She appeared to be suspicious of staff. She was commenced on quetiapine 50mg daily and her lithium was reduced to 600mg daily in view of her ongoing hypernatraemia. The hypernatraemia started to improve and a Mental Health Act assessment was completed leading to detention under Section 2 and transfer to an acute psychiatric ward.

On admission to the psychiatric ward, the patient presented as confused, disorientated and thought disordered. She continued to hold ongoing delusional beliefs about the removal of body parts and was convinced she would die in hospital despite having no suicidal thoughts. Following a review of her medical notes, her lithium was reduced and then stopped over the course of one week. Her sertraline and quetiapine doses were increased to 100mg daily and 250mg daily respectively. The patient made a rapid recovery and was able to go home on leave within 10 days of admission.

Blood results all normalised. She was reassessed two weeks later and was euthymic, with no evidence of delusional beliefs or thought disorder. Her MMSE improved to 28/30 and she

reported that her head felt clearer than it had been in years. She was discharged from inpatient care.

## Discussion

Was lithium to blame for this patient's physical and mental health deterioration despite therapeutic levels? The patient in question had been on lithium for many years, but serum levels had always been lower than at admission (0.33–0.61mmol per litre for past three years although the most recent level, recorded one month prior to admission, was even lower at 0.17mmol per litre). Her lithium had been increased shortly prior to the medical admission, and although a level of 0.84mmol per litre is considered therapeutic, it was higher than it had been in this patient for some time.

The patient made a rapid physical and psychiatric recovery when the lithium was eventually withdrawn. The presence of pyrexia and a raised white cell count were initially thought to be suggestive of a concurrent infective process, but the absence of any microbiological evidence of infection on blood and urine culture should cast doubt on this assumption. Pyrexia and urinary incontinence could be explained in the context of the patient's catatonic presentation. Catatonia shares many clinical features with neuroleptic malignant syndrome, a syndrome in which pyrexia is a cardinal symptom. Lithium has been shown to cause a raised white cell count,<sup>7</sup> an effect used therapeutically in cases of clozapine-induced neutropenia.

The literature includes case reports of lithium-induced delirium occurring at therapeutic levels<sup>8,9</sup> with the suggestion that this is more likely to occur in the context of advanced age, in combination with antipsychotics or in the presence of acute psychotic symptoms. In this patient, calcium levels were not checked until sev-

eral days into the admission, when they were found to be high. Hypercalcaemia may have been present at admission and may have played a role in the initial presentation. Hypernatraemia was not present on admission so is unlikely to account for her initial deterioration in mental health but is likely to have contributed to her ongoing confusional state.

There are case reports in the literature of delirium caused by lithium-induced hypercalcaemia.<sup>10</sup> One article published in an endocrine journal describes a similar case in which a patient on long-term lithium therapy was admitted with sepsis and developed hypercalcaemia 10 days later, which resolved on withdrawal of the lithium.<sup>11</sup>

During her admission, our patient was diagnosed with nephrogenic diabetes insipidus (NDI) by the endocrine team. NDI is the most common adverse effect of lithium, occurring in up to 40 per cent of patients.<sup>12</sup> Chronic lithium treatment is believed to cause antidiuretic hormone (ADH) resistance, reducing the diffusion of water through the pores in the collecting tubules, leading to polyuria and polydipsia. In a normal situation, the ensuing polydipsia will cause an increase in fluid intake and restore any electrolyte imbalance. If, however, the patient is unable to increase his fluid intake, dehydration can occur with a corresponding increase in plasma sodium and calcium levels and possible physical symptoms including delirium. Our patient's hypercalcaemia continued despite rehydration, so although NDI may have played a role, perhaps other factors were involved.

Lithium-induced hypercalcaemia may occur in 5-40 per cent of patients with or without hyperparathyroidism.<sup>13</sup> The prevalence of hyperparathyroidism is 10-15 per cent in patients treated for more than 10

years.<sup>14</sup> The mechanism of lithium-induced hyperparathyroidism and hypercalcaemia is not well understood. Proposed mechanisms include lithium causing an increase in calcium reabsorption within the loop of Henlé. Alternatively, lithium may cause an alteration in feedback mechanisms within the parathyroid gland. By altering the sensitivity of calcium-sensing receptors, the threshold for calcium needed to suppress the release of parathyroid hormone by the parathyroid is increased. Another suggestion is that lithium may directly stimulate parathyroid hormone production.<sup>15</sup> NDI and metabolic acidosis tend to occur within weeks or months of lithium initiation, whereas chronic nephropathy and hypercalcaemia are most likely to develop after years of lithium treatment.

In our patient, we believe that her delirium-like state was a result of lithium-induced hypercalcaemia and hypernatraemia, in the context of a recent increase in her lithium dose. The patient's blood results and mental state normalised after withdrawal of lithium. Once recovered and off lithium, our patient reported greater clarity in thinking than she had experienced in years. The clouded thinking may relate to her bipolar affective disorder being inadequately treated with residual depressive symptoms, but it also raises the question of whether her lithium treatment had contributed to this in the longer term.

## Conclusion

Toxic effects of lithium should be considered in patients on lithium therapy even in the context of 'therapeutic' blood levels. Lithium can induce hypercalcaemia and hypernatraemia, which may contribute to a confusional state.

## Declaration of Interests

Zoe Clough is an academic clinical

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*Zoe Clough is a CT2 Trainee in Psychiatry, Rebecca Henry is a Clinical Pharmacist and Anders Ekelund is a Consultant Psychiatrist in General Adult Psychiatry, Southern Health NHS Foundation Trust, Southampton*

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