CASE REPORT

Acute renal failure induced by markedly decreased appetite secondary to a depressive episode after discontinuation of long-term lithium therapy in an elderly patient with bipolar disorder

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SUMMARY

Some elderly patients on chronic lithium therapy for bipolar disorder and their doctors may be faced with a therapeutic dilemma over whether or not to continue prescribing/taking lithium given their increased risk of reduced renal function. We present the case of a 78-year-old woman with bipolar disorder who discontinued lithium therapy due to increased risk factors for renal injury. After discontinuation, she experienced markedly decreased appetite secondary to a depressive episode, and developed acute renal failure, which subsequently progressed to a more advanced stage of chronic kidney disease. This case suggests that extreme care must be taken to prevent the recurrence of depression in elderly patients with bipolar disorder who discontinue lithium therapy, even when they had been emotionally stable for a long time while receiving lithium. Medications other than lithium for bipolar disorder may be needed at the time lithium therapy is discontinued.

BACKGROUND

Lithium is a highly effective drug for the treatment of bipolar disorder and is frequently used long term to prevent recurrence of the disease and suicide.^{1–4} However some studies have indicated that long-term administration of lithium and advanced age are among the risk factors for renal injury.^{5–7} Therefore, elderly patients treated with lithium over a long term and their doctors face a potential therapeutic dilemma over whether or not to continue prescribing/taking lithium.

We present the case of an elderly woman treated by long-term lithium therapy for bipolar disorder who developed acute renal failure induced by markedly decreased appetite secondary to a depressive episode after discontinuation of lithium therapy. The findings in this case provide insight into the problems that can occur in elderly patients with bipolar disorder when lithium therapy is withdrawn.

CASE PRESENTATION

The patient is a 78-year-old woman with mood disorders. Since receiving a diagnosis of bipolar I disorder at the age of 43, she had been receiving lithium therapy at a local psychiatric hospital. She sometimes presented with a hypomanic or depressive state associated with sleep disorder but had been treated on an outpatient basis excluding the

hospitalisation for a manic episode at the age of 43. At the age of 73, she visited the psychiatry department of our hospital on referral from her previous doctor for evaluation and treatment of comorbid renal disorder and bipolar disorder. At the initial visit, she was prescribed lithium 600 mg/day, but showed poor drug compliance and presented with mild manic symptoms. Laboratory results showed a serum lithium level of 0.45 mEq/L (therapeutic range 0.6–1.2 mEq/L), serum creatinine level of 72.7 µmol/L and normal serum electrolytes. Renal function was estimated using the estimated glomerular filtration rate (eGFR) calculated from serum creatinine values according to the Modification of Diet in Renal Disease Study Group equation modified for Japanese.⁸ Moreover, the classification of chronic kidney disease (CKD) proposed by the Kidney Disease Improving Global Outcomes was used.⁹ Her eGFR was 53.3 mL/min/1.73 m² which was comparable to stage 3a (mild-to-moderate reduction in kidney function). She had no history of smoking, hypertension or diabetes mellitus. A specialist in internal medicine advised periodic check-ups for renal function. She was continued on lithium 600 mg in a single bedtime dose because of the possibility of renal tubular regeneration¹⁰ and given zopiclone 7.5 mg for insomnia. Her manic symptoms and insomnia subsided within 1 month after the first visit. At this time, her serum lithium level was 1.09 mEq/L and eGFR was unchanged. Thereafter, she was emotionally stable and her blood pressure, blood sugar and serum uric acid levels were maintained within the normal range. In addition, she showed no symptoms of polyuria or polydipsia.

At the age of 76, she complained of the sudden onset of tremor in both hands and fatigue. Laboratory results showed a serum lithium level of 2.86 mEq/L and stage 3b renal function (moderate-to-severe reduction in kidney function). Other results including serum electrolytes and liver function tests were within normal limits. According to the patient, she had visited an orthopaedic surgery hospital because of acute lumbago and was prescribed the non-steroidal anti-inflammatory drug loxoprofen 180 mg/day for 10 days. Therefore, as a drug–drug interaction of lithium and loxoprofen might have caused her symptoms, loxoprofen was discontinued and lithium was reduced from 600 to 400 mg/day. Her symptoms disappeared within

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1 month, when her serum lithium level was 1.12 mEq/L. She continued lithium treatment at 400 mg in a single bedtime dose. After 6 months, laboratory results showed a serum lithium level of 0.56 mEq/L, a serum creatinine level of 81.8 $\mu\text{mol/L}$ and an eGFR of 46.2 mL/min/1.73 m^2 (stage 3a). She developed no symptoms of polyuria or polydipsia.

At the age of 78, although the CKD remained unchanged at stage 3a, discontinuation of lithium therapy came up for discussion because despite having multiple risk factors for lithium-induced nephropathy, including current lithium therapy, long-term administration of lithium, episodes of lithium intoxication and advanced age,¹⁰ she had not experienced any change in mood for more than 12 months after the lithium dose reduction. The patient and her family decided to discontinue lithium therapy, rather than benefit from its positive effects. Consequently, lithium usage was tapered over 2 months. At the point of discontinuation, she refused to take an alternative drug because she had been emotionally stable for a long time after the lithium dose reduction. However, 1 month later she experienced sleep disorder and a sense of fatigue and subsequently showed depressive mood, loss of interest in usual activities, diminished daytime activities and markedly decreased appetite. After about 1 week of exhibiting these symptoms, she was hospitalised on a general internal medicine ward due to dysarthria and disturbed consciousness. Laboratory results showed dehydration and declined renal function (stage 4: severe reduction in kidney function). No symptoms of polyuria and polydipsia were observed during hospitalisation. She showed symptomatic improvement with fluid replacement therapy and was discharged from the hospital 2 weeks later. However, she remained with stage 4 CKD at the time of discharge.

INVESTIGATIONS

From the initial visit to lithium intoxication, the patient's serum lithium levels ranged from 0.45 to 1.09 mEq/L (mean lithium level, 0.78 mEq/L), serum creatinine levels from 72.7 to 81.8 $\mu\text{mol/L}$ and eGFR from 53.3 to 46.4 mL/min/1.73 m^2 (stage 3a; 45–59 mL/min/1.73 m^2) on eight occasions over 3 years. Thyroid hormone levels (free triiodothyronine, free thyroxine and thyroid-stimulating hormone), blood urea nitrogen (BUN), serum sodium (Na), serum potassium (K), serum calcium (Ca) and serum phosphate (P) were all within normal limits over 3 years.

At the time of lithium intoxication, maximum values were serum lithium 2.86 mEq/L, serum creatinine 90.9 $\mu\text{mol/L}$ and eGFR 41.4 mL/min/1.73 m^2 (stage 3b: 30–44 mL/min/1.73 m^2). Thyroid hormone levels, BUN, Na, K, Ca and P were within the normal ranges.

Signs and symptoms of lithium toxicity include tremor, confusion, ataxia, drowsiness, anorexia, nausea/diarrhoea, fatigue, lethargy, altered arousal, slurred speech and seizure.¹¹

The patient developed tremor, fatigue, lethargy and slurred speech. The patient and family were informed of the continuous need for monitoring in a general internal ward but they did not wish to stay in the hospital. The next day, the patient's symptoms subsided with fluid replacement therapy, and the MRI of the brain was cancelled. However, they did not attend her scheduled appointment on the second day after visiting our department because of lithium toxicity. Therefore, in the evening of the second day, the author confirmed via telephone that tremor, fatigue, lethargy and slurred speech had subsided and that other symptoms of lithium toxicity such as confusion were not present. Moreover, she was advised to receive treatment if any of these symptoms reappeared.

From the improvement of lithium intoxication to the discontinuation of lithium therapy, her serum lithium level was 0.56 mEq/L, serum creatinine level was 81.8 $\mu\text{mol/L}$ and eGFR was 46.2 mL/min/1.73 m^2 (stage 3a).

At the time of acute renal failure after discontinuing lithium therapy, her serum creatinine level was 200 $\mu\text{mol/L}$ and her eGFR was 17.3 mL/min/1.73 m^2 (stage 4: 15–29 mL/min/1.73 m^2). Brain MRI and CT of the kidney showed no organic changes.

In the 18 months following acute renal failure, her serum creatinine levels have ranged from 181.8 to 172.2 $\mu\text{mol/L}$ and her eGFR ranged from 19.1 to 20 mL/min/1.73 m^2 (stage 4).

DIFFERENTIAL DIAGNOSIS

Physical diseases such as hypertension, liver function diseases and hyperthyroidism and organic brain diseases that induce tremor, fatigue, lethargy and slurred speech should be included in the differential diagnosis of lithium intoxication associated with their symptoms. In addition, diuretics and ACE inhibitor, as well as non-steroidal anti-inflammatory drugs, should be considered drugs that interact with lithium. Physical diseases such as brain infarction, brain haemorrhage and hypoglycaemia that induce acute disturbance of consciousness should be included in the differential diagnosis of acute renal failure after discontinuing lithium therapy.

TREATMENT

The patient had been treated with lithium for bipolar disorder from the age of 43–78. At the time lithium was withdrawn, no further drugs were administered for bipolar disorder.

OUTCOME AND FOLLOW-UP

For 18 months after discharge, the patient has been treated with olanzapine 5 and zopiclone 7.5 mg/day for bipolar disorder and insomnia, respectively, and has remained emotionally stable. She was also referred to a specialist in internal medicine for management of stage 4 CKD.

DISCUSSION

Many patients on chronic lithium therapy for bipolar disorder carry an increased risk of reduced renal function with advancing age.¹² Bocchetta *et al*⁵ indicated that patients aged 60 years or older who are treated with lithium for 30 years are likely to develop stage 3 or more severe CKD (ie, eGFR <60 mL/min/1.73 m^2 ; calculated from serum creatinine values using the equation proposed by the Modification of Diet in Renal Disease Study Group). Rej *et al*¹³ reported that at 5-year follow-up, a trend towards clinically important decreases in renal function was observed in patients who had used lithium continuously for more than 2 years following chronic renal failure (CRF), but not in geriatric patients with CRF who had discontinued lithium. Therefore, whether or not elderly patients with poor renal function on long-term lithium therapy should continue lithium may need to be questioned.

Our patient chose to discontinue lithium therapy because of increased risk factors for renal injury, including episodes of lithium intoxication and advancing age, and because she had been emotionally stable for more than 12 months after lithium dose reduction. However, she experienced markedly decreased appetite and became dehydrated, possibly caused by the recurrence of depression around 1 month after discontinuing the lithium. As a result, she developed prerenal acute renal failure, which subsequently progressed to stage 4 CKD.

The present case suggests that extreme care must be taken to prevent the recurrence of depression in elderly patients with

bipolar disorder who discontinue lithium therapy, even if they have been emotionally stable for a long period. Medications other than lithium for bipolar disorder (eg, olanzapine, aripiprazole, quetiapine, valproate and lamotrigine) with reference to the National Institute for Health and Care Excellence (NICE)¹⁴ and The British Association for Psychopharmacology (BAP)¹⁵ guidelines may be needed for these patients at the point of discontinuing lithium therapy.

Learning points

- ▶ Risk factors for renal injury, including drugs that interact with lithium, should be avoided as much as possible in elderly patients on chronic lithium therapy for bipolar disorder.
- ▶ At the time of lithium intoxication, the patient should be carefully monitored in a hospital if possible.
- ▶ Extreme care should be exercised to prevent the recurrence of depression when such patients discontinue lithium, even if they have been emotionally stable for a long time.
- ▶ Medications other than lithium for bipolar disorder (eg, olanzapine and aripiprazole) may have to be administered at the time of discontinuing lithium therapy for these patients.

Contributors AO identified and managed the case, and is the guarantor of the paper.

Competing interests None.

Patient consent Obtained.

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