CASE REPORT

The effect of a therapeutic lithium level on a stroke-related cerebellar tremor

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SUMMARY

Lithium is a mood stabiliser used in the treatment of acute mania, bipolar disorder and as augmentation for unipolar major depression. Tremor is a common adverse effect associated with lithium at both therapeutic and toxic serum levels. We present a case of dose-dependent changes in the quality and intensity of a stroke-related, chronic cerebellar tremor with lithium treatment at serum levels within the therapeutic range. On admission, the patient in this case had a baseline fine, postural tremor, which increased in frequency and evolved to include myoclonic jerks once lithium therapy was initiated. Although the patient's serum lithium level was never in the toxic range, his tremor returned to baseline on reduction of his serum lithium level. This case highlights that a pre-existing, baseline tremor may lower the threshold for developing myoclonus. It also suggests that caution may be warranted with lithium therapy in the setting of known cerebellar disease.

BACKGROUND

Lithium is an effective and commonly prescribed psychotropic agent. Lithium therapy is used for acute mania, bipolar depression and maintenance therapy in bipolar disorder, as well as in augmentation for unipolar major depression.¹ Lithium is also the only mood stabiliser known to significantly reduce the risk of suicide in patients with bipolar disorder.¹ Despite being a first-line treatment for bipolar disorder, lithium has several disadvantages, including a narrow therapeutic index and adverse effects even at therapeutic levels.

Tremor is a common adverse effect, with studies reporting a dose and serum-level dependent incidence of tremor ranging from 4% to 65% in different populations.² A fine tremor is recognised as an early adverse effect of lithium, whereas a coarse tremor tends to be seen in lithium intoxication.

While the phenomenon of therapeutic levels of lithium-potentiating baseline tremors has been reported, the authors in these cases describe simple exacerbation of a physiological tremor or enhancement of extrapyramidal symptoms.^{3–5} Cases of lithium modifying the quality of pre-existing stroke-related tremors are rare in the literature. This case report may be the first to document the dose-dependent modification of a stroke-associated cerebellar tremor by therapeutic serum lithium levels.

CASE PRESENTATION

The patient is an individual with a history of bipolar I disorder who was admitted to the inpatient

psychiatric unit for a severe major depressive episode with anxious distress and associated suicidality. At the time of admission, the patient's psychiatric medications were olanzapine 10mg po qhs for bipolar disorder and buspirone 5mg up to 12 tabs daily for anxiety. He was also on amlodipine 10mg qhs for hypertension, rosuvastatin 10mg daily for hyperlipidaemia, aspirin 81mg qhs for stroke prevention and pantoprazole 40mg daily for gastro-oesophageal reflux disease. He had no history of previous treatment with lithium.

On admission, the patient had a fine, low-amplitude tremor in his upper extremities bilaterally. It was primarily intentional, though also present at rest, but did not impair the patient's motor functioning or overall quality of life. This tremor was chronic and thought to be the sequela of a hypertension-associated cerebellar haemorrhage suffered several months prior. An MRI of his brain performed several months prior to this admission revealed a 1cm focus of chronic haemorrhage in the left cerebellar hemisphere with no evidence of acute infarction.

At the beginning of his hospital stay, the patient's home medications were continued with the exception of buspirone, and lithium 300mg q12h was initiated for acute bipolar depression. Disulfiram 500mg daily was also started at this time. At a serum lithium level of 0.8 mEq/L, the patient's tremor changed in intensity and quality, becoming coarse and irregular with intermittent myoclonic jerks. Although the myoclonus was most pronounced in the upper extremities, the patient also had occasional jerks of his lower extremities. The new tremor oscillated at a greater frequency with increased amplitude, quite obvious at rest with profound severity on intention. The patient's ability to feed, write and type were markedly impaired, causing significant distress.

The tremor was persistent, with a significant impact on the patient's motor function and quality of life, leading the treatment team to taper the lithium dose, and then later add propranolol to his regimen. As the lithium dose was tapered, antidepressant augmentation with bupropion 75mg daily was initiated and gradually increased to a dose of 300mg daily.

OUTCOME AND FOLLOW-UP

The patient's tremor improved in a dose-dependent manner with reduction in lithium, and a lithium level of 0.4 mEq/L resulted in resolution of the myoclonic jerks and return of the quality and intensity of the tremor to the patient's baseline at

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admission. The depressive episode was stabilised at this lithium dose with antidepressant augmentation, and the patient was discharged home.

DISCUSSION

Tremors associated with lithium treatment are common and well described. They usually appear with initiation or up-titration of lithium dose, and although these tremors tend to improve over time, they can occur at any time during treatment.² While lithium's mechanism of action remains uncertain, it is believed to suppress inositol signalling and inhibit glycogen synthase-3, a multifunctional protein kinase that plays a role in diverse intracellular signalling pathways.⁶ In clinical settings, the usual therapeutic window is from 0.8 to 1.2 mEq/L.⁷

Tremor from lithium therapy is typically described as a fine postural and/or action tremor with a higher frequency than parkinsonian or antipsychotic-associated tremor.⁸ It has also been characterised as an irregular, non-rhythmic tremor of the distal extremities with frequency ranging from 8 to 12 Hz.^{2,9} Lithium-induced tremors tend to improve with continued use of lithium; however, beta-adrenergic antagonists, such as propranolol, have been shown to be effective and are frequently used for alleviating lithium-induced tremors.⁸ In cases of severe lithium intoxication exceeding 2 mEq/L, other movement abnormalities including choreoathetosis, ataxia, dysarthria and aphasia have been reported.^{10–14}

Irregular tremors such as those seen in our patient are usually only observed with toxic lithium levels. Tremor induced by lithium toxicity is typically irregular, more prominent and coarser than a non-toxic tremor, and is often generalised to other parts of the body. It is also usually accompanied by other neurological signs (such as altered mental status) and non-neurological symptoms (such as gastrointestinal disturbances and ECG changes) of toxicity.² This case is unique in that the tremor characteristics resemble lithium toxicity despite a therapeutic serum lithium level. In particular, our patient's symptoms manifested as abnormalities localised to the motor system, without concomitant changes to his mental status or other non-neurological symptoms.

The development of myoclonus is another interesting and unusual aspect of this case. Myoclonus is defined as a sudden, brief, shock-like involuntary movement caused by active muscular contractions. Dopamine-blocking agents, such as antipsychotics have been reported to induce myoclonus, with one study revealing that 38% of patients on long-term antipsychotic therapy develop myoclonus, with patients who develop myoclonus having significantly higher doses of antipsychotics than those without myoclonus.¹⁵ Additionally, it has been reported that tricyclic antidepressant drugs, alone or in combination with lithium, can induce reversible action myoclonus, even when used at non-toxic dosages.¹⁵ This patient had not been treated with tricyclic antidepressants during the current hospitalisation. He had been on a low dose of olanzapine for several months prior to admission without any adverse effects or changes to his baseline tremor. However, his concurrent exposure to olanzapine may have lowered the threshold for his developing myoclonus with increasing serum levels of lithium.

Lithium monotherapy leading to prominent myoclonus in four patients was documented in a study conducted some years ago.¹⁶ Two of the patients in the study had lithium serum levels in the near-toxic range, while lithium levels for the other two patients were not assessed. Although our patient's lithium level was non-toxic, the fact that he had a pre-existing tremor, in

addition to the above-mentioned treatment with olanzapine, may have lowered the threshold for his developing myoclonus.

The mechanism underlying the pathophysiology of lithium-induced tremor remains to be fully elucidated.² This case suggests particular sensitivity of cerebellar injury to lithium therapy, even at non-toxic serum levels. Caution may be warranted when treating individuals with known stroke-related cerebellar pathology, and alternative regimens for mood stabilisation might be considered.

Learning points

- ▶ This case suggests sensitivity of cerebellar injury to lithium therapy, even at non-toxic serum levels.
- ▶ A pre-existing baseline tremor may lower the threshold for developing myoclonus in patients treated with lithium therapy, even at non-toxic serum levels.
- ▶ Caution may be warranted with lithium therapy in the setting of known cerebellar disease.

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