CASE REPORT

Lithium neurotoxicity presenting as dementia with therapeutic serum lithium levels

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SUMMARY

After 25 years of continuous lithium therapy, a woman with moderate intellectual disability and bipolar disorder developed symptoms suggestive of dementia. In fact, she had developed lithium neurotoxicity, but this was overlooked for 18 months as serial lithium levels were in the therapeutic range.

BACKGROUND

Lithium neurotoxicity is a well-recognised problem, usually identified clinically and confirmed by lithium levels above 1.0 mmol/L. However, there are reports of neurotoxicity caused by lithium in people in whom the lithium level has remained within therapeutic levels.^{1–9} These cases may be misidentified and misdiagnosed. This literature is examined later in the Discussion section.

Lithium neurotoxicity classically presents with muscle weakness, drowsiness, ataxia, coarse tremor, muscle twitching, disorientation and seizures. Individuals vary in their propensity to develop symptoms of toxicity and, in some cases, neurological effects are irreversible even after cessation of lithium.

This case describes a woman who developed symptoms of reversible dementia while on treatment with lithium carbonate at therapeutic levels. Her symptoms largely resolved following reduction in the dose of lithium after 18 months. A review of the literature identified only a handful of similar published cases suggesting that this is either rarely reported or rarely identified. On reflection, a number of risk factors can be identified which increased her susceptibility to developing toxicity. Lithium toxicity should be considered in all individuals who present with insidious cognitive impairment while on lithium treatment, even if serum levels are within the normal range and there are no obvious neurological signs.

CASE PRESENTATION

This individual was a 50-year-old woman with moderate intellectual disability possibly caused by meningitis in infancy. She had no family history of intellectual disability or neurological disease. She lived in residential accommodation with 24 hours support provided by paid carers.

Her first episode of hypomania occurred at the age of 23 years and she was started on lithium 2 years later. Over the following 25 years, her illness was unstable with at least one episode of hypomania

per year, usually lasting several weeks, and generally treated with benzodiazepines. She only ever had three short-lived episodes of depression and never exhibited psychotic symptoms. A number of psychotropic medications were trialled including thioridazine, chlorpromazine, olanzapine, risperidone, zuclopenthixol, quetiapine, carbamazepine, sodium valproate and lamotrigine. She remained on lithium throughout, with the maximum dose reaching 1000 mg per day.

From a physical point of view, she developed renal disease in 2013 and hypothyroidism in 2014, both probably caused by long term lithium therapy. Extrapyramidal side effects developed early in the course of her illness and tardive dyskinesia more recently.

At the onset of her cognitive symptoms, her psychotropic medication was lithium carbonate 700 mg/day, sodium valproate 1250 mg/day and quetiapine 300 mg/day. She also took levothyroxine, omeprazole, trimethoprim (long-term prophylactic therapy) and regular laxatives.

At the age of 50 years, after 25 years of lithium treatment, she presented with progressive cognitive impairment initially characterised by lethargy, aggression, shouting and the onset of ruminative thoughts. Disorientation and confusion followed, with impairment of attention and memory, and loss of ability to perform basic skills of daily living. In addition, she exhibited muscle twitches, loss of manual dexterity, loss of visual perception, incontinence of urine and faeces, irrational fear of bathing, polydipsia and worsening mobility. She was noticed to be responding to auditory and visual hallucinations at times and developed marked extrapyramidal symptoms of bilateral cogwheel rigidity, resting tremor and pill-rolling tremor.

INVESTIGATIONS

Serial lithium levels were all noted to be 1.0 mmol/L or lower, estimated glomerular filtration rate (eGFR) varied between 33 and 53 mL/min, electrolytes and liver function were normal. Repeated urine cultures were negative.

A CT brain scan was unremarkable and showed no evidence of intracranial haemorrhage, acute infarcts or space-occupying lesions. An MRI brain scan showed slightly reduced cortical perfusion in the right posterior parietal and anterior occipital region and in the left frontal region. There was no specific pattern suggestive of Alzheimer disease or frontotemporal dementia.

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DIFFERENTIAL DIAGNOSIS

The principal working diagnosis was unspecified dementia (International Classification of Diseases 10 F.03) due to the presence of symptoms of cognitive decline and confusion. Attempts were made to classify the dementia through neuroimaging, but results were inconclusive.

A relapse of bipolar disorder was excluded as her symptoms were not typical of previous hypomanic episodes, and she appeared more confused. There was no evidence of elation or overactivity.

Physical issues that can frequently cause confusion and agitation in people with intellectual disability such as constipation, urinary tract infections and pain were excluded.

A neurological cause such as a space-occupying lesion was excluded following neuroimaging.

Lithium toxicity was considered but repeat lithium levels were within the therapeutic range and misled health staff into thinking this was not a valid differential diagnosis.

TREATMENT

After 18 months of serial normal lithium levels, a further routine lithium level was found to be raised at 1.5 mmol/L. The dose of lithium was reduced. Subsequently, the lithium level was still raised at 1.1 mmol/L and the dose reduced again to 400 mg/day. Within 2 weeks of these two small reductions in dose, she displayed an improvement in levels of confusion and disorientation, with complete resolution of ataxia, incontinence, hallucinations and all other symptoms with the exception of extrapyramidal symptoms. The temporal association between the reduction in dose of lithium and the resolution of symptoms implicates lithium neurotoxicity as the cause of her cognitive decline.

OUTCOME AND FOLLOW-UP

Given her propensity to develop toxicity, and her marked renal dysfunction, most likely caused by lithium therapy, it was decided to withdraw the lithium completely. This was done slowly over several months, following which she remained well on a combination of sodium valproate and quetiapine.

DISCUSSION

This case highlights how clinicians can easily be misled by falsely reassuring serum lithium levels. The handful of cases described in the literature of reversible delirium or pseudodementia caused by lithium toxicity, show similar features to our patient and the authors have considered a number of putative contributory factors.

Soriano-Barceló *et al*⁹ presented a similar case to the one described here: a man in his 50s who developed reversible dementia symptoms after treatment with lithium carbonate, although the duration of treatment of 4 years was much shorter. His symptoms continued for 2 years and lithium levels were all 0.91 mmol/L or less. However, after increasing doses of quetiapine and risperidone, the lithium level was found to be 1.94 mmol/L, suggesting that individuals on combinations of lithium and antipsychotic medication may be more vulnerable to developing neurotoxicity.

In contrast, Peng⁸ describe a woman in her teens who was started on lithium as treatment for an episode of mania. Within a few weeks, and with a relatively low lithium level of 0.57 mmol/L, signs of neurotoxicity were seen with disturbed consciousness and hyperactive tendon reflexes. Once lithium was stopped, and following treatment with mannitol, her symptoms resolved.

In the case described by Goyal and Ali,⁷ the issue of concomitant physical ill health is raised. Their patient had bleeding from an anal carcinoma and subsequent iron deficiency anaemia. After 25 years of stability on lithium, he then developed lithium neurotoxicity with serum lithium levels in the lower end of the therapeutic range.

Other case reports are remarkably similar to the patient described here, but with some notable variations. For example, Grueneberger *et al*⁵ presented a young man with rapidly developing neurotoxic symptoms culminating in the sudden onset of bilateral myoclonic jerks and generalised tonic-clonic seizures. Mesquita *et al*⁶ showed that electroencephalogram (EEG) changes during the period of neurotoxicity were the only subsidiary examination indicating intoxication (serum lithium levels and brain CT were normal). The importance of considering advancing age in patients susceptible to neurotoxicity is discussed by Arya⁴ whose patient's age was 73 years and who was also taking antipsychotic medication.

Lithium is frequently used as a mood stabiliser for people with a range of mood disorders. It is particularly effective in the treatment of acute mania and for long-term maintenance of bipolar disorder. There is emerging evidence in the field of intellectual disabilities, that lithium and other mood stabilisers may be beneficial in reducing severe self-injurious and aggressive behaviours in those with more severe intellectual disabilities.¹⁰ However this comes with ethical issues about initiating potentially toxic medication which requires blood monitoring in individuals who cannot give informed consent.

Despite its use over many decades, there is still no clear explanation for the mode of action of lithium in the brain. Broadly speaking, lithium reduces excitatory neurotransmission (via dopamine and glutamate) and increases inhibitory neurotransmission (via gamma-aminobutyric acid). But at intracellular and molecular levels many other pathways are employed that further modulate neurotransmission and may ultimately be neuroprotective.¹¹ For example, lithium has effects on adenyl cyclase and phosphoinositide pathways; it increases protective proteins such as brain derived neurotrophic factor and B cell lymphoma 2; it alters phosphorylation of certain proteins of the cytoskeleton; and it promotes changes in transcription of specific genes.¹¹

Therapeutic levels for lithium were arbitrarily defined in the 1980s for populations. Gelenburg *et al* recommended that higher lithium levels were more effective, despite the higher drop out rate among participants in their study.¹² However, for individuals, there may be a very fine line between a therapeutic index and frank toxicity. For each individual, the risk of toxicity will depend on other comorbid factors.

With regard to this individual, it is possible, with hindsight, to identify a number of possible risk factors for the development of lithium neurotoxicity. Lithium toxicity is significantly more likely to occur in women and in those with an affective disorder rather than schizophrenia.¹³ There is also evidence that having a pre-existing neurological disorder may increase the likelihood of developing toxicity.⁵ Kemperman *et al* hypothesised that there is a diminished capacity for lithium removal in pathologically transformed brain tissues; it is possible that neurological damage leading to intellectual disability may also act in the same way. Long-term administration of lithium is likely to be associated with higher tissue concentrations of lithium which may not be identified from serum lithium measurements alone.^{6 14} Experimental studies in rat models have shown that lithium tends to accumulate in brain tissue, particularly following chronic treatment,¹⁵ leading to high brain intracellular concentrations which do not correlate with low plasma or CSF levels.

There have been reports of individuals being more susceptible to neurotoxicity when treated with an antipsychotic medication in addition to lithium. Most reports involve the use of haloperidol or risperidone, but Miodownik *et al* specifically described neurotoxicity on a combination of lithium and quetiapine as seen in this individual (although the duration of administration of lithium was only a few days).¹⁶

The individual developed both thyroid dysfunction and impaired renal function. These are recognised adverse effects of long-term lithium administration, but have also been identified as independent clinical risk factors for the development of lithium neurotoxicity.¹⁷

This case highlights the importance of monitoring for early signs of toxicity, even when blood parameters are within the therapeutic range. This is particularly pertinent for people with intellectual disabilities who may have a number of concurrent risk factors for toxicity, who may display unusual symptoms and who may be less able to communicate their distress.

Learning points

- ▶ Lithium neurotoxicity should always be considered when unusual symptoms are present, even when serial lithium levels in the normal range.
- ▶ There is an increased chance of diagnostic overshadowing in people with intellectual disability, whereby signs and symptoms are attributed to a certain diagnosis rather than considering other possible causes.
- ▶ Where medication is required, doses should start low. People on long-term psychotropic medication should have regular reviews, and consideration should be given to lowering doses wherever possible.
- ▶ Psychotropic polypharmacy should be avoided in all patients, particularly those with pre-existing neurodevelopmental disorders.

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