

Lithium Neurotoxicity Within the Therapeutic Serum Range

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Abstract

A 56-year-old Chinese woman who had been receiving lithium treatment for 25 years subsequently developed acute encephalopathy while the lithium was within the therapeutic serum range. The acute mental changes subsided after cessation of lithium, with a concomitant normalisation of electroencephalographic tracing. No other organic causes for the encephalopathy could be identified. This case, plus a review of the various clinical features associated with lithium neurotoxicity, its detection, and possible causation is discussed.

Key words: *Lithium, Neurotoxicity, Encephalopathy, Normal therapeutic serum level*

Lithium was first introduced into psychiatry in 1949 for the treatment of bipolar affective disorder. Lithium is indicated in the treatment and prophylaxis of bipolar affective disorder, recurrent depression, and aggressive or self-mutilating behaviour. Despite its undoubted efficacy, lithium is a potentially toxic substance.¹ Lithium salts have a narrow therapeutic/toxicity ratio and doses are adjusted to achieve serum lithium concentration of 0.4 to 1.0 mmol/L (normal therapeutic range, 0.6 to 1.2 mmol/L) 12 hours after the preceding dose. However, there is large variation among patients in relation to what constitutes a toxic serum lithium level and it is generally recommended that elderly patients should remain at the lower end of the range for maintenance therapy. It appears that the extent of lithium toxicity is probably underestimated and many cases go unrecognised.²

Lithium has been associated with side effects and toxic manifestations in multiple systems, including neurological, gastrointestinal, renal, cardiovascular, endocrine, dermatological, ocular, and haematological systems. The most troublesome toxicity is neurological and accounts for most of the morbidity and mortality. Generally, serum lithium levels above 1.5 mmol/L may be toxic, and those above 2 mmol/L are definitely toxic, requiring urgent treatment. However, clinical toxicity may appear at any time during a course of lithium treatment, even after many years of stable uncomplicated therapy. Depending on the onset, the toxic syndromes can be categorised as either acute or chronic. Although the neurological complications resolve completely for most patients,

irreversible permanent sequelae have been documented.³ In the present review, a patient who developed acute lithium neurotoxicity, after having received stable therapy for nearly 30 years, is presented. This case illustrates the importance of clinical state as the best indicator in the diagnosis of lithium intoxication, and that toxicity can occur within the accepted therapeutic range for serum lithium levels.

Case Report

A 56-year-old married housewife had been diagnosed as suffering from bipolar affective disorder since 1962. She had been taking lithium treatment since 1972. According to her psychiatric history, she had had frequent relapses of illness with repeated admissions to hospital. The detailed clinical presentations and hospital admissions before 1972 could not be traced. However, based on the available records, this patient had presented mainly with manic and mixed affective episodes from 1972 to 1984. Tardive dyskinesia had been noticed since 1980, mainly in the form of oral dyskinesia. She had a major depressive episode in 1985 and was also found to have hypertension. She had been relatively well-maintained with treatment from 1985 to 1988. She was admitted to hospital in 1988 with mixed affective features and was discovered to have thyrotoxicosis. During the period from 1989 to 1990, she suffered from 3 relapses of illness, both with depressive and mixed affective features and was twice admitted to hospital in 1991 for relapse of mania.

In 1992, she suffered a mixed affective episode with the coincidental finding of diabetes mellitus. She was admitted to hospital with mixed affective features in 1993, 1995, and 1996. Since the onset of mental illness, she had been admitted to hospital more than 20 times before the index admission to the Pamela Youde Nethersole Eastern Hospital in January 1997. She was compliant with therapy and was supervised by her supportive husband. She had been receiving lithium prophylaxis for 25 years and the treatment response had been unsatisfactory. Her serum lithium levels were 0.4 to 0.7 mmol/L.

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Prior to her index admission, she was given haloperidol 1.5 mg twice daily, lithium 500 mg twice daily, lorazepam 0.5 mg twice daily, metformin 250 mg twice daily, benzhexol 4 mg twice daily, and carbimazole 10 mg daily.

Prior to admission, the patient was seen at the clinic in January 1997 for insomnia, and depressive and labile mood with crying spells. She could not cope with her household chores and ruminated about unrealistic worries. She was disturbed with irrelevant speech. The doctor diagnosed a depressive episode requiring admission to hospital. On the initial day of admission, this patient appeared perplexed and confused. Her speech was slurred and irrelevant with marked perseverations. For most of the time, she was withdrawn and retarded, but from time to time, she was also rather agitated, restless, and tense. She seemed to be in poor contact with the environment.

Mental state examination revealed that she was disorientated in time and place, and had depressive mood together with irrelevant and repetitive speech. Physical examination revealed coarse hand tremor, involuntary buccal-lingual movements, ataxic gait, dysdiadochokinesia, cogwheel rigidity, and sialorrhoea. Her pulse rate was 96 beats/minute and blood pressure was 110/90 mm Hg. These measures had been stable. She developed a low-grade fever of 37.8°C. Blood investigations revealed normal renal function, liver function, and complete blood count. Fasting blood sugar was 9.6 mmol/l (normal level, <6 mmol/L). Thyroid function tests revealed normal free total thyroxine (T_4) level but a low thyrotropin (thyroid stimulating hormone, TSH) level of <0.04 mIU/L (normal range, 0.32-5.0 mIU/L). Creatinine kinase was 67 IU/L (normal range, 24-180 IU/L). Her lithium level was 0.49 mmol/L. Chest X-ray was clear and investigation for sepsis, which included blood culture, was unrevealing.

Lithium was stopped while the other drugs were continued. Medical opinion was sought 3 days after admission to hospital. However, no diagnosis was given as the cause of her confusion. The patient was clinically euthyroid and her fever subsided 5 days after admission, although the confusion, perplexity, ataxia, tardive dyskinesia and cerebellar signs persisted. She appeared to be agitated and disturbed. Computerised tomography (CT) scan of the brain and electroencephalogram (EEG) were performed at day 10. EEG revealed fairly generalised theta activity at 6 to 7 Hz of 30 to 40 mv, CT scan of the brain revealed no focal brain lesion but poor grey/white differentiation. The findings suggested encephalopathy.

The patient's confusion resolved at day 15. A month after her admission, the cerebellar signs, coarse hand tremor, cogwheel rigidity, and oral dyskinesia disappeared. A follow-up EEG revealed background activity of responsive alpha and anterior beta activity. No slow activities were detected. Concurrently, the follow-up CT scan of the brain was also normal. The patient was treated with valproate 200 mg twice a day, and chlorpromazine 50 mg at night. Her mood became stable and she was discharged 2 weeks later with no evidence of organicity.

Discussion

The above case raised the possibility of lithium encephalopathy, which may have been present for some time, as evidenced by extrapyramidal features, tardive dyskinesia, and cerebellar signs. Prior to the index admission, this patient was in delirious state. EEG indicated diffuse slowing of background. Signs and symptoms resolved spontaneously 2 weeks after cessation of lithium treatment, accompanied by normalisation of the EEG tracing. Organic investigations showed no abnormality or infection, and metabolic or endocrine derangement was unlikely to be causative.

Neurological complications in lithium toxicity encompass a wide spectrum of signs and symptoms referable to the central and peripheral nervous systems.⁴ Reports describe isolated parkinsonian syndrome in the absence of other signs of central nervous system toxicity.⁵ Lithium-induced encephalopathy could also manifest as a confusional state which may appear several hours to days after acute overdose or at any time during maintenance therapy.⁶ Besides the cognitive disturbances, pyramidal signs such as spasticity, hyper-reflexia, extensor plantars, brainstem signs such as nystagmus together with seizures may appear in severe cases. If untreated, these would cause coma and death. Cerebellar features are often absent in the acute phase and only become apparent as the acute phase resolves. Peripheral symptoms of lithium neurotoxicity include myopathy, axonal neuropathy, and myasthenic syndrome.⁷ Other atypical presentations include Creutzfeldt-Jakob-like syndrome, sixth cranial nerve palsy (as a result of increased intracranial pressure), aphasia, transient and permanent hemiplegia, fixed gaze palsies, and motor stereotypes.^{8,9}

Most cases of neurotoxicity are reversible, including acute and chronic forms. David and Lewis reported a patient with cerebellar signs for 6 months who recovered upon cessation of lithium.¹⁰ However, some reports of permanent neurological sequelae after lithium toxicity have been reported. The main brunt was borne by the cerebellum, resulting in gait and limb ataxia, intention tremor, nystagmus, and dysarthria, which is estimated to occur in 10% of patients.¹¹

Lithium-induced neurotoxicity is usually, but not exclusively, related to serum lithium levels. Serum lithium levels as high as 4.5 mmol/L have been reported without any sign of neurological impairment, while levels within the therapeutic range or as low as 0.27 mmol/L have been reported to give rise to neurotoxic syndrome.^{12,13} There are numerous reports of both acute and chronic toxicity occurring at levels within the therapeutic range.¹⁴⁻¹⁶

The following are some explanations for 'normal range lithium neurotoxicity'. Lithium distribution in different body compartments is complex, and uptake of lithium by the brain is not uniform. Heurteaux et al found that, in mice, lithium levels in the thalamus, neocortex, and hippocampus were 6-fold that in plasma while, in the striatum and cerebellum, the levels are 3-fold that in the plasma.¹⁷ There is a wide range of correlation of plasma concentrations and levels in the brain.

Therefore, although plasma concentrations may be within normal limits, concentrations of the drug in the brain may be different. Discrepancies in brain and plasma lithium levels may explain the neurotoxicity within the therapeutic range.

Another possible pathophysiological basis for variations in individual lithium tolerance may be related to the intracellular/extracellular lithium concentration ratio. Plasma lithium levels have not been found to correlate with clinical neurotoxicity or EEG changes. Indeed, animal studies show a better correlation between brain and red blood cell levels. Ratios of red blood cell/serum lithium levels exhibit individual variation, which is likely to be partly under genetic control, but is also subjected to acquired influences. The red cell/plasma ratio has been found to fluctuate with phases of bipolar affective disorders and is increased by phenothiazines. There are reports of lithium neurotoxicity in acutely disturbed patients who rated high scores for anxiety and psychotic behaviour.¹⁸ It appears that some state-related effects of psychiatric illness may increase patients' vulnerability to the toxic effects of lithium. Metabolic studies by Trautner et al,¹⁹ Greenspan et al,²⁰ and Almy and Taylor²¹ suggest that acute manic patients retain significantly more orally administered lithium than healthy controls. Advancing age and long-term treatment make patients more vulnerable to neurotoxicity — receptor site sensitivity secondary to ageing has been postulated. However, such correlation of neurotoxicity with age remains controversial.²² It is interesting that this patient took approximately 2 weeks after the cessation of lithium treatment for her symptoms to resolve. This phenomenon is consistent with the observation that patient's clinical state may continue to worsen for up to 1 week after lithium intake is stopped, and the EEG changes persist after lithium has been cleared from the system. This implies that lithium in the brain may be in a deep compartment in which equilibrium is slow to occur.

Important precipitating causes for toxicity after a long period of stable therapy include the following: incidental medical illness, especially if febrile in nature, dehydration, renal failure, low salt diet, drug interactions (of particular relevance are diuretics such as thiazine, non-steroidal anti-inflammatory drugs such as indomethacin, anticonvulsants such as carbamazepine, and calcium antagonists such as verapamil), and major surgery. However, for some patients, no precipitating cause can be identified. In this patient, the febrile illness may have been the precipitating cause for the delirium. Other confounding factors included diabetes and hyperthyroidism, as reflected in the elevated fasting blood sugar and low TSH, and polypharmacy, which included neuroleptics and other drugs.

The interaction of lithium and haloperidol is a possible precipitating factor for the patient reported here. The role of drug synergism, particularly the combined use of lithium and neuroleptics, is controversial. Cohen and Cohen, in their report of 4 cases of irreversible brain damage in patients receiving lithium and haloperidol, suggest a cumulative toxic effect of this combination.²³ However, lithium-haloperidol toxicity may be difficult to distinguish from lithium toxicity

alone. The neuroleptic malignant syndromes (NMS) further cloud the issue. Characteristic features of NMS have been described following the use of neuroleptics in combination with lithium. Sialorrhoea, tremor, rigidity, dyskinesia, confusional state, and EEG abnormalities are common signs and symptoms noted in both conditions. Spring and Frankel suggested that there may be 2 types of neurotoxicity produced by the interaction between lithium and neuroleptics.²⁴ The first is a pure lithium toxicity syndrome of delirium, seizures, and EEG changes, but with no significant extrapyramidal symptoms. The second is a largely extrapyramidal syndrome that could occur with haloperidol alone, similar to NMS and resembling the cases reported by Cohen and Cohen.²³ Spring and Frankel postulated that neuroleptics other than haloperidol, such as phenothiazines, may predispose a patient to the neurotoxic effects of lithium and that lithium and haloperidol act synergistically on dopaminergic pathways to produce extrapyramidal syndromes.²⁴ Recent evidence suggests that the intracellular lithium levels may be significantly altered by concomitant administration of phenothiazines, particularly thioridazine, which enhance red blood cell lithium level *in vitro* by an increase in passive leak diffusion, whereas haloperidol and tricyclics do not have this effect.²⁵

The disappearance of oral dyskinesia and attenuation of the extrapyramidal side effects is interesting in the patient reported here. The relationship between lithium and the extrapyramidal system is complex. There are reports that lithium may be beneficial for the treatment of the on-off phenomenon in parkinsonism,²⁶ while other reports highlight the accentuation of extrapyramidal dysfunction with lithium treatment. In addition, the use of benztropine, an antiparkinsonian drug, did not abolish or significantly ameliorate this symptom.²⁷ Lithium has been shown to enhance cholinergic activity and cause a dose-dependent decrease in dopamine formation in the striatum, both of which may be responsible for the neurotoxic effects of lithium and exacerbation of extrapyramidal side effects. Lithium has also been noted to precipitate and aggravate tardive dyskinesia and it is possible that it enhances cholinergic activity in the striatum and therefore disturbs the dopaminergic-cholinergic imbalance against dopamine.²⁸

EEG is a useful diagnostic tool in lithium encephalopathy. EEG usually shows characteristic changes, which include a slowing of dominant rhythm, progression to theta and delta activities, and disorganisation of the background rhythm. Widening of the frequency spectrum occurs and synchronous bilateral paroxysms of delta activity may appear. The EEG abnormality correlates with the neurological effects and the correlation is more accurate than that with lithium serum levels. EEG may permit the earlier detection of toxicity, but the lack of specificity and difficulties in quantification are major disadvantages. EEG changes may persist for at least 11 days after the last dose of lithium, as shown in animal studies.²⁹

In summary, the important features of lithium neurotoxicity are the diversity of clinical presentation, different tempo of onset, *i.e.* acute, chronic, or acute-on-chronic toxicity,

despite ‘therapeutic’ serum levels and the development of toxicity even after long-term therapy without adverse effects.

Lithium neurotoxicity is a clinical phenomenon that may be much more common than is currently recognised. Chronic neurotoxicity can remain unrecognised for a long time. Lithium as a cause of neurological symptoms should be considered even when serum lithium levels are low and when symptoms are chronic. A high level of clinical suspicion is necessary.

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