

# Lithium overdose causing non-convulsive status epilepticus—the importance of lithium levels and the electroencephalography in diagnosis

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We report a case of lithium overdose in a patient who presented in non-convulsive status epilepticus. The lithium toxicity was probably due to interaction with Moduretic. The diagnosis was not suspected until electroencephalography was performed. This case underscores the importance of therapeutic drug level monitoring of lithium, especially where toxicity is suspected, and the indispensable role electroencephalography plays by allowing a correct diagnosis to be made promptly.

## Introduction

Lithium has been a mainstay of treatment for patients with bipolar disorders for more than 50 years, ever since its effects on mania were first described.<sup>1</sup> Close monitoring of plasma lithium levels are nonetheless important because its therapeutic margin is narrow. Toxicity can occur when there is an overdose, particularly in the presence of risk factors such as renal impairment. The neurological manifestations are often non-specific, one of which can be non-convulsive status epilepticus (NCSE), and the diagnosis is often missed initially.<sup>2</sup> Up to 10% of patients can be left with permanent neurological sequelae if lithium toxicity is left untreated.<sup>3</sup> Therefore, physicians must be vigilant about this possible complication and aware that electroencephalography (EEG) can assist with making a prompt diagnosis. We report a case of lithium toxicity and discuss the pitfalls encountered with both diagnosis and management.

## Case report

A 59-year-old woman presented in September 2004 to the emergency department with a sub-acute onset of altered mental state. She had been unwell with intermittent episodes of confused speech, easy weeping, crying for no reason, and poverty of speech for 1 week prior to admission. There had been no psychotic features or suicidal tendencies. She had a history of hypertension managed in a government out-patient clinic and bipolar affective disorder being followed up by a private psychiatrist. Her medications included propranolol 10 mg three times a day, verapamil SR 120 mg daily, sertraline 50 mg daily, lithium sulphate (Lithiofor; Vifor, Geneva, Switzerland) 660 mg twice a day, deanxit (flupentixol and melitracen) 1 tablet daily, flunitrazepam (Rohypnol; Roche, Mannheim, Germany) 2 mg at night, and mirtazapine (Remeron; Organon, Oss, The Netherlands) 30 mg daily. Around 2 months before admission, a doctor at the government out-patient clinic added Moduretic (MSD, Herts, UK) [amiloride/hydrochlorothiazide] one tablet daily to help control her hypertension.

On admission, she was afebrile with stable vital signs. The Glasgow coma scale score was 14/15 due to confused speech. Physical examination revealed no focal neurological deficit. Her chest X-ray, electrocardiogram, and brain computed tomography scan were all normal. Blood tests, including a complete blood picture, liver and renal biochemistry, thyroid function tests and arterial blood gases were unremarkable except for a slightly elevated creatinine level of 116 mmol/L (reference range, 53-97 mmol/L). Serum and urine toxicology screens were negative.

In view of the apparent absence of any organic pathology, a psychiatrist was consulted 1 day after admission and a provisional diagnosis of psychotic depression was suggested. She was later noticed to have a low-grade fever and a sepsis work-up, including a lumbar puncture, was done. The cerebrospinal fluid (CSF) was blood stained from a traumatic tap, with a protein level of 3.48 g/L, glucose 4.9 mmol/L (concomitant spot serum glucose, 6.5 mmol/L). The cell count could not be reliably interpreted because of the numerous red blood cells. She was empirically treated as having encephalitis and given

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## 鋰中毒引致非抽搐性癲癇持續狀態： 鋰用量水平和使用腦電圖診斷的重要性

本文報告一個鋰中毒的個案，病者出現非抽搐性癲癇持續狀態，相信是因為服用一種名為Moduretic的藥物所致，診斷時並無懷疑病者是鋰中毒，直至為病者進行腦電圖檢查才發現。這個病例表明對含鋰藥品進行藥物水平監測的重要性，特別是在懷疑中毒時更要注意，也展示了要迅速地作出準確診斷，腦電圖是不可或缺的。

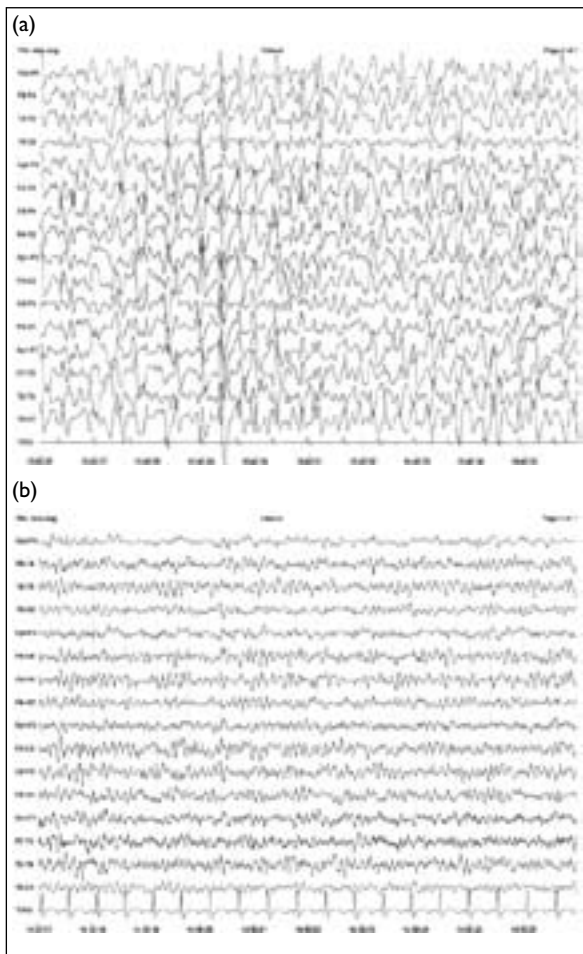


FIG. Electroencephalograms (EEGs) on day 3 after admission and before discharge

(a) EEG on day 3 after admission showing intermittent sharp discharges over both hemispheres and intermittent bursts of high-amplitude generalised electrographic seizure activity bilaterally, suggestive of non-convulsive status epilepticus; (b) EEG before discharge showing complete resolution of the abnormal seizure activity

intravenous acyclovir and cefotaxime. A CSF Gram stain, acid-fast bacilli culture, fungus culture, and herpes simplex virus polymerase chain reaction (PCR) were all negative. All other microbiological work-ups

were negative. An electroencephalogram arranged 3 days after admission showed intermittent sharp discharges over both hemispheres and intermittent bursts of high-amplitude generalised electrographic seizure activity bilaterally, features suggestive of NCSE (Fig a). She was treated with phenytoin and lorazepam, together with supportive measures. A follow-up lumbar puncture showed a white blood cell count of  $7/\text{mm}^3$ , a red blood cell count of  $7650/\text{mm}^3$ , a protein level of  $0.91 \text{ g/L}$ , and a glucose level of  $6.2 \text{ mmol/L}$  (spot serum glucose,  $10.1 \text{ mmol/L}$ ). A sample of clotted blood saved initially on admission was subsequently sent for lithium levels after toxicity was suspected. The lithium levels on admission and after 1 week of hospitalisation came back as  $3.17 \text{ mmol/L}$  and  $0.89 \text{ mmol/L}$ , respectively. A presumptive diagnosis of NCSE due to lithium overdose was made. Haemodialysis was not instituted in view of the already lowered lithium level. In the ensuing days, she showed a gradual improvement in her general mental status that correlated with the return of a normal background alpha rhythm on the EEG done 3 weeks after admission. On discharge she had recovered fully with no apparent neurological deficit or cognitive impairment (Fig b).

### Discussion

Lithium is widely used in the treatment of bipolar disorders, refractory depressive disorders, and in the long-term prophylaxis of cluster headache. It has a narrow therapeutic index. The currently recommended therapeutic serum concentration range is narrow, from  $0.6$  to  $1.2 \text{ mmol/L}$ . Toxicity associated with lithium prescription is prevalent. Between 75 and 90% of patients treated with lithium have symptoms and signs of toxicity at some time during their treatment.<sup>4</sup>

There are basically two types of lithium intoxication—acute and chronic. Acute lithium intoxication occurs when the patient deliberately ingests a large amount when attempting suicide or overdoses accidentally. Chronic lithium intoxication is more common. It occurs when there is gradual accumulation of lithium, usually due to decreased excretion. Impaired renal function, drug interactions, volume depletion, concurrent illnesses like congestive heart failure or cirrhosis all predispose a patient to chronic lithium toxicity.<sup>1</sup>

The interactions between various drug classes and lithium excretion are well-documented (Table). With lithium being excreted exclusively by the kidneys, any drug that alters the glomerular filtration rate or affects electrolyte exchange in the nephron may influence its level. Some examples are diuretics, angiotensin-converting enzyme inhibitors, calcium channel antagonists, or non-steroidal anti-inflammatory drugs.

TABLE. Drugs and physiological states with clinically important interactions with lithium<sup>1</sup>

Drugs and physiological states	Interaction
<b>Diuretics</b>	
Thiazides	Increased plasma lithium level due to decreased lithium clearance; may be used to treat lithium-induced polyuria
Furosemide	Usually no change in plasma lithium level
Amiloride	Usually no change, but may increase plasma lithium level; may be used to treat lithium-induced polyuria
<b>Non-steroidal anti-inflammatory drugs</b>	
Bronchodilators (aminophylline, theophylline)	Decreased plasma lithium level due to increased renal clearance
Angiotensin-converting enzyme inhibitors	May increase plasma lithium level
Neuromuscular blockers	Lithium may prolong the action of blockers
Neuroleptic drugs	Lithium may worsen extrapyramidal symptoms or increase the risk of the neuroleptic malignant syndrome
Anticonvulsant drugs (carbamazepine)	Concurrent use with lithium may result in additive neurotoxicity from combination of drugs
<b>β-Adrenergic-antagonist drugs</b>	
Increased glomerular filtration rate (pregnancy)	Decreased plasma lithium level due to increased renal lithium clearance
Decreased glomerular filtration rate (kidney disease, ageing)	Increased plasma lithium level due to decreased renal lithium clearance
Increased renal tubular reabsorption of sodium (dehydration, decreased sodium intake, extrarenal sodium loss)	Increased plasma lithium level due to decreased renal lithium clearance

Thiazide diuretics, by inducing sodium depletion, can lead to a 25% reduction in lithium clearance after a week of therapy.<sup>5</sup> For our patient, the calculated creatinine clearance was 40 mL/min. Her chronic lithium toxicity was multifactorial in origin and appeared to be due to the interplay of old age, impaired renal function, and the concomitant intake of Moduretic (a combination of amiloride 5 mg and hydrochlorothiazide 50 mg).

Lithium poisoning causes a variety of presentations including nephrogenic diabetes insipidus, renal tubular acidosis, or hypothyroidism but central nervous system toxicity is usually its hallmark. Lithium neurotoxicity can develop even within the therapeutic range.<sup>6</sup> Its neurologic manifestations have a good correlation with serum lithium levels and they are divided into mild, moderate, and severe toxicity.

Mild lithium toxicity correlates with a serum lithium level of 1.5-2.5 mmol/L and it includes features like gastro-intestinal upset, fine tremor, fatigue, and apathy. These symptoms and signs are non-specific and are often mistaken for normal adverse reactions to a lithium intake within the therapeutic range.<sup>7</sup> A moderate lithium overdose matches with a serum level of 2.5-3.5 mmol/L, and may present with an alteration in consciousness and more pronounced neuromuscular abnormalities. The fine tremor will become coarse and irregular. Patients may also have dysarthria, ataxia, hypertonia,

hyper-reflexia, or myoclonus. Severe lithium neurotoxicity is marked by muscle fasciculation, muscle rigidity, choreiform movements, flaccid paralysis, seizures, stupor, or even coma.<sup>8</sup> The acute neurological manifestations may persist for days to weeks and severely intoxicated patients can develop permanent neurological sequelae, even after prompt haemodialysis.<sup>3,9</sup>

Apart from causing a typical diffuse slowing on EEG, lithium neurotoxicity can also present as NCSE.<sup>6,10,11</sup> Non-convulsive status epilepticus is not an uncommon condition, especially in those who are critically ill. It carries a high morbidity and mortality<sup>12</sup> and is often unrecognised as the cause of coma.<sup>2</sup> The disease is confirmed when there is seizure activity on the EEG and concomitant behavioural or cognitive changes lasting more than 30 minutes. A clinical and electroencephalographic response to intravenous benzodiazepine will also help to establish the diagnosis.<sup>13</sup> Nevertheless, recognition of NCSE is often delayed because its clinical manifestations mimic psychiatric disturbances, metabolic encephalopathies, and postictal confusional states.<sup>13</sup> In order to differentiate between NCSE and these other conditions, an urgent EEG should be performed. Physicians must also search carefully for the underlying causes of the NCSE. Besides infection and structural lesions of the brain, metabolic disturbances and toxic aetiologies must be excluded, as illustrated by our case. Our case underscores the importance of the EEG for making a prompt diagnosis

in this situation. To prevent lithium overdosage, an anticipatory approach should be adopted. Drugs that have a potential interaction with lithium are better avoided unless they are strongly indicated and there is no alternative. The lithium level should be monitored periodically and the dose adjusted accordingly. A detailed drug history is essential since toxicology screens do not routinely include lithium. If such a patient develops an alteration of consciousness, lithium neurotoxicity should be suspected and the serum lithium level checked while other causes of confusion are also excluded. An EEG should be performed urgently to rule out NCSE. In acute lithium intoxication, the mortality rate approaches 25% and is 9% in patients with a chronic overdose.<sup>3</sup> Apart from mortality, lithium toxicity causes significant morbidity and economic cost to society due to the lengthy hospital stay required. All these can only be reduced by careful prescription, vigilant clinical and drug monitoring, and a high awareness of the risk factors for toxicity. The importance of strict adherence to

treatment guidelines cannot be overemphasised.<sup>14</sup> Haemodialysis has been the mainstay of therapy for lithium overdoses. It is generally considered when serum lithium levels are higher than 2.5 Eq/L. A forced alkaline diuresis can also be used in the presence of unimpaired renal function when haemodialysis expertise or facilities are not available.<sup>15</sup>

## Conclusion

Lithium intoxication remains a serious medical problem. We report a case of lithium toxicity due to concomitant use of Moduretic, presenting with NCSE, which was not suspected until an EEG was performed. We suggest that the serum lithium level should be checked and an EEG should be considered in any patient on lithium presenting with an altered mental state, especially those with risk factors for toxicity. Early recognition and management of lithium-induced neurotoxicity can save lives and reduce significant morbidity.

## References

1. Price LH, Heninger GR. Lithium in the treatment of mood disorders. *N Engl J Med* 1994;331:591-8.
2. Towne AR, Waterhouse EJ, Boggs JG, et al. Prevalence of nonconvulsive status epilepticus in comatose patients. *Neurology* 2000;54:340-5.
3. Hansen HE, Amdisen A. Lithium intoxication. (Report of 23 cases and review of 100 cases from the literature). *Q J Med* 1978;47:123-44.
4. Groleau G. Lithium toxicity. *Emerg Med Clin North Am* 1994;12:511-31.
5. Petersen V, Hvidt S, Thomsen K, Schou M. Effect of prolonged thiazide treatment on renal lithium clearance. *Br Med J* 1974;3:143-5.
6. Bellesi M, Passamonti L, Silvestrini M, Bartolini M, Provinciali L. Non-convulsive status epilepticus during lithium treatment at therapeutic doses. *Neurol Sci* 2006;26:444-6.
7. Annitto WJ. Recognizing lithium-associated neurotoxicity. *Drug Ther* 1979;9:125.
8. Goldfrank LR, Osborn H, Weisman S. Lithium. In: Goldfrank LR, Fomenbaum NE, Lewin NA, et al, editors. *Goldfrank's toxicologic emergencies*. 4th ed. Norwalk, CT: Appleton & Lange; 1990.
9. Apte SN, Langston JW. Permanent neurological deficits due to lithium toxicity. *Ann Neurol* 1983;13:453-5.
10. Weiner RD, Whanger AD, Erwin CW, Wilson WP. Prolonged confusional state and EEG seizure activity following concurrent ECT and lithium use. *Am J Psychiatry* 1980;137:1452-3.
11. Kuruvilla PK, Alexander J. Lithium toxicity presenting as non-convulsive status epilepticus (NCSE). *Aust NZ J Psychiatry* 2001;35:852.
12. Krumholz A. Epidemiology and evidence for morbidity of nonconvulsive status epilepticus. *J Clin Neurophysiol* 1999;16:314-22,353.
13. Kaplan PW. Assessing the outcomes in patients with nonconvulsive status epilepticus: nonconvulsive status epilepticus is underdiagnosed, potentially overtreated, and confounded by comorbidity. *J Clin Neurophysiol* 1999;16:341-53.
14. Foutoulakis KN, Vieta E, Sanchez-Moreno J, Kaprinis SG, Goikolea JM, Kaprinis GS. Treatment guidelines for bipolar disorder: a critical review. *J Affect Disord* 2005;86:1-10.
15. Amdisen A. Clinical features and management of lithium poisoning. *Med Toxicol Adverse Drug Exp* 1988;3:18-32.