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. 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. Up to 10% of patients can be left with permanent neurological sequelae if lithium toxicity is left untreated. 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
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/mm$^3$, a red blood cell count of 7650/mm$^3$, a protein level of 0.91 g/L, and a glucose level of 6.2 mmol/L (spot serum glucose, 10.1 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 mmol/L and 0.89 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 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.$^4$

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.$^5$

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.
Thiazide diuretics, by inducing sodium depletion, can lead to a 25% reduction in lithium clearance after a week of therapy. 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. 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. 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. The acute neurological manifestations may persist for days to weeks and severely intoxicated patients can develop permanent neurological sequelae, even after prompt haemodialysis.

Apart from causing a typical diffuse slowing on EEG, lithium neurotoxicity can also present as NCSE. Non-convulsive status epilepticus is not an uncommon condition, especially in those who are critically ill. It carries a high morbidity and mortality and is often unrecognised as the cause of coma. 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. Nevertheless, recognition of NCSE is often delayed because its clinical manifestations mimic psychiatric disturbances, metabolic encephalopathies, and postictal confusional states. 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.
References