A rare neurological complication due to lithium poisoning

Lithium salts have been used in the prophylaxis and treatment of depression and bipolar disorder for more than 50 years. Neurotoxic side-effects such as nystagmus, ataxia, tremor, fasciculation, clonus, seizure and even coma have been well described in the literature. We present a case of generalised peripheral neuropathy following lithium intoxication. It is a rare presentation with delayed onset and characterised by a rapid downhill course. Diagnosis was confirmed by nerve conduction tests, which showed axonal neuropathy. Despite the profound neurological effects of this toxicity, it is readily reversible with supportive care and the prognosis is good.

Introduction

Lithium salts have been used in the prophylaxis and treatment of depression and bipolar disorder for more than 50 years. The narrow therapeutic range of lithium, together with other well-characterised adverse effects, has limited its use. Patients receiving lithium for bipolar disorders may experience acute or chronic toxicity after starting treatment. Acute toxicity commonly presents as neurotoxicity, nephrogenic diabetic insipidus, or thyroid dysfunction. Among the neurotoxic side-effects, nystagmus, ataxia, tremor, fasciculation, clonus, seizure, and even coma have been well described in the literature.1,2

In this case report, we describe an uncommon but reversible neurological manifestation of lithium toxicity.

Case report

A 49-year-old man who had bipolar affective disorder was receiving treatment with lithium, trifluoperazine and trihexyphenidyl (Artane; Synco, Hong Kong) as therapy for more than 10 years. He was taking sustained-release lithium 400 mg in the morning and 600 mg at night and there had been no recent change in his drug regimen. Apart from the psychiatric illness, he also had cardiomyopathy, for which he was receiving long-term treatment with aspirin, acertil, carvedilol, furosemide, and aldactone. He was noted to have decreased cognitive function in the recent few months, associated with muscle weakness and unsteady gait.

On admission he was confused, with a Glasgow Coma Scale score (GCS) of 13/15 (E4V4M5). Haemodynamically, he was stable with a blood pressure of 110/60 mm Hg and pulse rate of 70 beats per minute and in sinus rhythm. His body temperature was minimally raised (37.9°C). The initial serum lithium level was 3.2 mmol/L (therapeutic range, 0.5-1.0 mmol/L). He was therefore managed as acute lithium toxicity with saline diuresis and achieved a good response.

In view of his decreased cognitive function and body temperature, lumbar puncture was performed after brain computed tomography (CT) to rule out central nervous system (CNS) infection. Brain CT revealed tiny hypodense foci in the right basal ganglion and lumbar puncture showed no evidence of CNS infection. The cerebrospinal fluid (CSF) revealed a white cell count of <0.001 x 10^9/L, Gram smear was negative, protein level was 0.35 g/L (reference range, 0.15-0.45 g/L), and the glucose level was 5 mmol/L (paired serum level, 7.4 mmol/L). Electroencephalography was suggestive of a metabolic encephalopathy.

Four days after hospital admission, his GCS suddenly decreased from 13/15 (E4V4M5) to 5/15 (E1V1M3). Neurological examination revealed generalised hypotonia of all the four limbs, together with bilateral up-going plantar reflexes. He was intubated for airway protection and a repeat brain CT showed no change. Just before his clinical deterioration, the serum lithium level had been 1.6 (down from 3.2) mmol/L.

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The patient was transferred to the Intensive Care Unit (ICU) for further management. Continuous veno-venous haemofiltration (CVVH) was initiated for suspected lithium-related toxicity. The CVVH was performed with the polysulfone filter (Ultraflux AV600S;
Neurotoxicity related to acute lithium poisoning is well recognised. However, frank peripheral neuropathy is a rare presentation, about which there are limited case reports. In our patient, the differential diagnosis of the presenting features included critical illness polyneuropathy, Guillain–Barré syndrome and its variants, hypernatraemia, heavy metals poisoning, pesticide poisoning, and abnormal porphyrin metabolism. All these differential diagnoses were excluded by a carefully taken history and special investigations.

Thus, the urinary heavy metal screen, porphyrin studies, tests for pseudocholinesterase, and immune markers were all negative. The polyneuropathy of critical illness seldom involves cranial nerves and the rapidly reversible neurological recovery made this differential diagnosis unlikely. Guillain–Barré syndrome and its variants were also excluded by the lumbar puncture findings, the negative anti-GQ1b level in the CSF and the absence of demyelinating neuropathy on nerve conduction testing. Hypernatraemia secondary to diabetes insipidus was also unlikely as it occurred at a time the patient’s GCS was improving very significantly (day 3 in the ICU). Acute lithium intoxication with peripheral neuropathy therefore appeared to be the most likely diagnosis.

A literature search yielded a very limited number of case reports, but shared certain presenting features and physical findings encountered in our patient. One feature was a delayed presentation of CNS symptoms, which usually occurred 3 to 5 days after the acute intoxication. All the reports described hypotonia of all four limbs with depressed reflexes. Our case presented a similar picture with an acute decrease in GCS, together with generalised hypotonia of all four limbs with depressed reflexes. The next day he was successfully extubated. After 5 days in the ICU, he made a rapid neurological recovery with return of eye movements and gag reflex. Bulbar function returned to normal and he was able to eat without choking.

After 8 days in the ICU he returned to the general ward, having regained limb power (grade 4/5, with normal reflexes) and never had a demonstrable sensory deficit. His serum sodium level returned to the normal range. He continued to make a speedy recovery and was discharged to a convalescent hospital 10 days after discharge from the ICU. Later, he was discharged home, but walked with a quadripod whilst receiving psychiatric rehabilitation for 4 months. Finally he was able to walk independently without a quadripod.

**Discussion**

The patient was closely monitored in the ICU with supportive therapy. By day 3, he had developed nephrogenic diabetes insipidus; his serum sodium increased from 149 to 160 mmol/L. Fluid replacement therapy was instituted and the sodium level gradually normalised over the next 4 days to 144 mmol/L.

By day 3 in the ICU, the patient had started to improve; he was able to follow commands, gradually resumed spontaneous movement and power in all four limbs, and the next day he was successfully extubated. After 5 days in the ICU, he made a rapid neurological recovery with return of eye movements and gag reflex. Bulbar function returned to normal and he was able to eat without choking.

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Neurotoxicity related to acute lithium poisoning is well recognised. However, frank peripheral neuropathy is a rare presentation, about which there are limited case reports. In our patient, the differential diagnosis of the presenting features included critical illness polyneuropathy, Guillain–Barré syndrome and its variants, hypernatraemia, heavy metals poisoning, pesticide poisoning, and abnormal porphyrin metabolism. All these differential diagnoses were excluded by a carefully taken history and special investigations.

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hypotonia of all four limbs. The diagnosis was confirmed by nerve conduction tests that showed axonal neuropathy. Finally, all the reports described a good prognosis with clinical recovery upon discontinuation of lithium.

The biological mechanism of peripheral neuropathy with lithium toxicity is far from clear. Acute axonal dysfunction seems to be the hallmark, which may be attributed to intracellular accumulation of lithium and interference with propagation of the action potential.\(^8\)\(^,\)\(^9\)\(^,\)\(^12\)\(^,\)\(^13\)

It has been postulated that there could be a discrepancy between the serum lithium level and lithium concentrations in the brain,\(^14\) consistent with intracellular accumulation and much lower serum lithium levels. Worsening of neurological symptoms has also been well-documented even when the serum lithium levels were within the therapeutic range.\(^15\)

Although acute axonal neuropathy is uncommon in lithium toxicity,\(^16\) it carries a good prognosis; clinical recovery occurs within weeks to months after discontinuation of the drug. In our patient, clinical deterioration occurred on day 4 when the serum lithium level had nearly returned to the therapeutic range. The patient started to improve 7 days after stopping the medication and following one session of CVVH to further normalise the serum lithium level. He was discharged to convalescence 21 days after hospitalisation.

**Conclusion**

We present a case of generalised peripheral neuropathy following lithium intoxication, which is a rare presentation characterised by a delayed but rapid downhill course. As in our patient, such neurological deterioration usually occurs 3 to 5 days after the acute intoxication, and is associated with hypotonia of all four limbs and areflexia. Diagnosis was confirmed by nerve conduction tests showing axonal neuropathy. Despite the profound neurological involvement, it is readily reversible with supportive care and the prognosis is good.

**References**