CASE REPORT

A rare neurological complication due to lithium poisoning

CH Chan 陳才雄
Anne KH Leung 梁結雄
YF Cheung 張煜暉
Phillip YC Chan 陳彥璋
KW Au Yeung 歐陽健華
KY Lai 黎鏡堯

Lithium salts have been used in 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 $<0.001 \times 10^9$ /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.

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;

Key words
Bipolar disorder; Giant axonal neuropathy; Lithium compounds; Lithium/poisoning; Peripheral nervous system diseases

Hong Kong Med J 2012;18:343-5

B6, Intensive Care Unit, Queen Elizabeth Hospital, Jordan, Hong Kong
CH Chan, FHKCA, FHKAM (Anaesthesiology)
AKH Leung, FHKCA, FHKAM (Anaesthesiology)
YF Cheung, MRCP, FHKAM (Medicine)
PYC Chan, MB, ChB, MRCP
KW Au Yeung, FHKCA, FHKAM (Anaesthesiology)
KY Lai, MRCP, FHKAM (Medicine)

Correspondence to: Dr CH Chan
Email: stanchan01@yahoo.com.hk

鋰鹽中毒引致的罕見腦神經併發症

鋰鹽在臨床上廣泛應用於治療憂鬱症及躁鬱症上，但文獻指出長期服用鋰鹽可造成多種毒害神經的副作用，如眼球震顫、運動失調、震顫、肌纖維抽動、陣攣、癲癇甚至昏迷。本文報告一個因長期服用鋰鹽而引致全身末梢神經病變的中毒個案。這是罕見的病例，一般發病遲緩及病情迅速惡化。患者於神經傳導速度測驗中會顯示出軸索退化性神經病變。雖然患者神經系統會受嚴重影響，但經支援性治療後，一般患者的病情可逆轉，且預後良好。

Fresenius, Germany), at a blood flow of 150 to 180 mL/min, and ultra-filtration rate of 2 L/h, with bicarbonate-based replacement fluid (HEMOSOL BO, Hospal, Italy). Low-molecular-weight heparin was given as anticoagulation.

After 8 hours of CVVH, the serum lithium had decreased to 0.8 mmol/L and the treatment was stopped. He remained comatose with GCS of 6/15 (E1V1M4) 24 hours after ICU admission. Neurological examination showed total ophthalmoplegia, generalised hypotonia, quadriplegia, and areflexia except for bilateral up-going plantar reflexes. No other cranial nerve involvement was demonstrated. No muscle relaxant had been administered in the ICU, but during CVVH he was sedated for 8 hours with morphine and midazolam.

In view of cranial nerve involvement and long tract signs, magnetic resonance imaging was performed, but showed no abnormal signal intensity over the brainstem in restricted diffusion or contrast enhancement films. Nerve conduction tests confirmed the presence of axonal neuropathy, with a generalised decrease in compound motor action potentials and relatively normal conduction velocity but absent F waves in all four limbs. There was no evidence of demyelinating neuropathy and hence a nerve biopsy was not performed.

Other metabolic causes of neuropathy were excluded. Urine and serum examination for heavy metal (mercury, lead, copper) levels, porphyria, pseudocholinesterase levels, and immune markers were all negative. Cerebrospinal fluid was also negative for anti-GQ1b.

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.

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

Neurotoxicity related to acute lithium poisoning is well recognised. However, frank peripheral neuropathy is a rare presentation, about which there are limited case reports.[3-11]

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,[4,6-9] 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 deterioration on day 4, which was associated with a decrease in GCS, together with generalised

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.[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

1. Dunne FJ. Lithium toxicity: the importance of clinical signs. Br J Hosp Med (Lond) 2010;71:206-10.
2. Amdisen A. Clinical features and management of lithium poisoning. Med Toxicol Adverse Drug Exp 1988;3:18-32.
3. Newman PK, Saunders M. Lithium neurotoxicity. Postgrad Med J 1979;55:701-3.
4. Brust JC, Hammer JS, Challenor Y, Healton EB, Lesser RP. Acute generalized polyneuropathy accompanying lithium poisoning. Ann Neurol 1979;6:360-2.
5. Uchigata M, Tanabe H, Hasue I, Kurihara M. Peripheral neuropathy due to lithium intoxication. Ann Neurol 1981;9:414.
6. Pamphlett RS, Mackenzie RA. Severe peripheral neuropathy due to lithium intoxication. J Neurol Neurosurg Psychiatry 1982;45:656.
7. Chang YC, Yip PK, Chiu YN, Lin HN. Severe generalized polyneuropathy in lithium intoxication. Eur Neurol 1988;28:39-41.
8. Vanhooren G, Dehaene I, Van-Zandycke M, et al. Polyneuropathy in lithium intoxication. Muscle Nerve 1990;13:204-8.
9. Johnston SR, Burn D, Brooks DJ. Peripheral neuropathy associated with lithium toxicity. J Neurol Neurosurg Psychiatry 1991;54:1019-20.
10. Tomasina C, Manzino M, Torrazza A, Pastorino P. Polyneuropathy in lithium therapy [in Italian]. Riv Neurol 1990;60:113-6.
11. Keltner NL, Grant JS. Biological perspectives irreversible lithium-induced neuropathy: two cases. Perspect Psychiatr Care 2008;44:290-3.
12. Podnar S, Vodusek DB, Zvan V. Lithium and peripheral nervous system function in manic-depressive patients. Acta Neurol Scand 1993;88:417-21.
13. Licht RW, Smith D, Braendgaard H. The effect of chronic lithium treatment on the calibre of axons and nerve fibres in the rat sural nerve. Eur Neuropsychopharmacol 1997;7:95-8.
14. Schou M, Baastrup PC, Grof P, Weis P, Angst J. Pharmacological and clinical problems of lithium prophylaxis. Br J Psychiatry 1970;116:615-9.
15. Grueneberger EC, Maria Rountree E, Baron Short E, Kahn DA. Neurotoxicity with therapeutic lithium levels: a case report. J Psychiatr Pract 2009;15:60-3.
16. Schou M. Long-lasting neurological sequelae after lithium intoxication. Acta Psychiatr Scand 1984;70:594-602.