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Case Report

Lithium Toxicity Related Parkinsonism in an Older Woman: Case Report and Literature Review

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SUMMARY

Lithium is commonly used to treat affective disorders. However, it has a narrow therapeutic index and incurs a considerable risk of toxicity, which can occur even within the therapeutic range. For older adults, this toxicity risk is particularly high because of age-related pharmacodynamic and pharmacokinetic changes and other comorbidities.

A 69-year-old widow with bipolar disorder, Parkinsonism, and dementia was managing her conditions with lithium and Madopar. In the month before attending our hospital, she had been experiencing progressive cognitive decline, gastrointestinal discomfort, and general weakness, leading to a functional decline. Additionally, she had experiencing hand tremors, rigidity, and unsteady gait for 1 year. Her lithium serum level was 0.9 mmol/L. A Tc-99m TRODAT-1 brain single-photon emission computed tomography scan revealed normal perfusion in the bilateral basal ganglion, indicating secondary Parkinsonism rather than idiopathic Parkinson's disease. Therefore, lithium-related Parkinsonism was suspected. We tapered the dose of lithium and her condition gradually improved.

We thus present a case of lithium toxicity related Parkinsonism and cognitive impairment and highlight the relevance of monitoring the required dose for older adults and understanding the various toxic effects of lithium, which can manifest even when a therapeutic level of lithium is used.

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1. Introduction

Lithium is the oldest and most commonly-used medication in the acute and long-term maintenance treatment of unipolar and bipolar disorders,[1,2] being a first-line treatment for adult patients with bipolar disorder. In general, measuring a patient's serum lithium concentration 1 week after they commence lithium therapy is recommended. Blood samples should be taken 10–14 h after the most recent drug intake.[4] The general consensus is that the concentration should be maintained at between 0.6 and 1.2 mmol/L. Interestingly, a study that employed Li magnetic resonance spectroscopy reported that the concentration in the brain was weakly correlated with the serum concentration.

However, the pharmacokinetics and pharmacodynamics of lithium varies across age groups, influencing lithium toxicity. Lithium is almost exclusively excreted through the kidneys.[4] Because renal function declines with age, older adults eliminate lithium more slowly and are at higher risk of lithium toxicity than are younger adults. Dehydration, physical illness with fever, heart failure, hyponatremia, and impaired renal function are common late-life comorbidities that increase the risk of lithium toxicity.[2,4,5] Thiazide diuretics, angiotensin-converting enzyme inhibitors, and nonsteroidal anti-inflammatory drugs can contribute to the aforementioned comorbidities by decreasing the body's clearance ability. Angiotensin II receptor blockers, antidepressants, antipsychotics, and antiepileptics have been reported to have similar effects. Furosemide was discovered to increase lithium elimination, and it is regarded as the diuretic of choice for patients receiving lithium.[2] Checking renal function and preventing its impairment is crucial. Regular monitoring of serum calcium, thyroid function, parathyroid function, cardiac function, complete blood count, body weight, and body mass index is also recommended.[4,6,7] Lithium intoxication can occur suddenly without apparent reason and even when lithium is administered at low doses. Between the ages of 40 and 95 years, the total daily dose of lithium required to achieve a given serum concentration decreases by a factor of three.[11] Thus, the recommended dose reduction ranges from 25% to 35% for older adults.

The most severe manifestations of lithium toxicity involve the central nervous system and kidneys, and some of these effects can be permanent. Approximately 4% of older patients treated with lithium were hospitalized for lithium toxicity.[2] Persistent sequelae of lithium intoxication have been named the Syndrome of Irreversible Lithium-Effectuated Neurotoxicity (typically abbreviated as SILENT), which is characterized by lithium-induced demyelination at multiple sites in the nervous system. The typical neurological presentations of SILENT include persistent cerebellar dysfunction, extrapyramidal syndromes, brainstem dysfunction, and dementia with varying de-

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grees of organic brain syndrome. The atypical presentations include downbeat nystagmus, retrobulbar optic neuritis, persistent papilledema, choreoathetosis, peripheral neuropathy, myopathy, and central pontine myelinolysis-related blindness. Several case reports have highlighted the risk of chronic toxicity developing gradually in patients taking small doses of lithium over a long period, with the possibility of severe neurotoxicity occurring even when lithium levels are within the therapeutic range. Notably, the emergence of neurotoxicity does not correlate with serum lithium level, and considerable individual variation has been reported with regard to the threshold of sensitivity to the effects of lithium. Intolerance to lithium has been attributed to concomitant cerebral impairment. Seizure-prone individuals may be more vulnerable to lithium-induced seizure even when their serum level is within the therapeutic range. The accentuation of extrapyramidal symptoms in individuals with Alzheimer's disease who are treated with lithium has been reported. Individuals with pre-existing neurologic illness or cerebral impairment are more likely than those without such conditions to develop persisting sequelae after lithium intoxication and to experience acute intoxication more frequently. The persistent neurologic sequelae of lithium intoxication have increased the awareness of these critical iatrogenic and irreversible conditions among clinicians.[8]

2. Case presentation

A 69-year-old widow with underlying bipolar disorder, Parkinsonism, dementia, chronic obstructive pulmonary disease, gastric ulcer, and lumbar discectomy history had been managing these conditions with regular medication, which comprised lithium (for 20 years), Madopar, betahistine, and domperidone. She lived in a seventh floor apartment with her son and daughter-in-law, and, since her hospitalization approximately 1 month earlier for conscious disturbance and sepsis, she had become partially dependent on assistance to perform her daily activities. She had also been experiencing functional decline. She was readmitted to hospital after experiencing progressive anorexia, nausea, vomiting, general weakness, and fluctuating consciousness for approximately 2 weeks. She had no fever, upper respiratory tract infection symptoms, abdominal pain, diarrhea, or constipation. At admission, she had high blood pressure (172/86 mmHg), but her heart rate, body temperature, and respiratory rate were all within normal ranges. She measured 144 cm tall, weighed 47 kg, and had a body mass index of 22.7 kg/m^2. Initially, the patient presented with delirium and disorientation in place and time. Her complete blood count results revealed normal levels of hemoglobin, white blood cells, and platelets, and her biochemistry profile indicated normal results for albumin, liver function, uric acid, renal function, and electrolytes except for the existence of hypercholesterolemia. Her lithium level was 0.9 mmol/L (reference range: 0.8–1.2 mmol/L). Abdominal X-ray revealed increased bowel gas pattern and fecal material retention.

We conducted a comprehensive geriatric assessment (CGA) and obtained the following findings: a positive result for the confusion assessment method; a score of 7 on the clinical frailty scale; a positive result on the Supportive and Palliative Care Indicators Tool; scores of 0/8 and 25/100 for instrumental activities of daily living and activities of daily living, respectively; a score of 4 on the Short Portable Mental State Questionnaire; a score of 8 on the Ascertain Dementia-8 Questionnaire; scores of 5 and 10 on the Geriatric Depression Scale-5 and Geriatric Depression Scale-15, respectively; and a score of 4 on the Mini Nutritional Assessment—Short Form. On the basis of these CGA results, we concluded that she had delirium, dementia, depression, and malnutrition. According to her son, she had been living alone and capable of performing independent daily activities. However, approximately 1 year previously, she had started experiencing hand tremors, rigidity, unsteady gait, progressive functional decline, cognitive decline, and auditory hallucination. She was recently prescribed Madopar (one tablet 3 times per day) after receiving a diagnosis of Parkinsonism. Because we suspected drug-related gastrointestinal discomfort, we discontinued Madopar and initiated fasting with intravenous fluid supplementation. A survey for delirium did not reveal any electrolyte imbalance, ongoing infection, or severe urinary or stool retention. Subsequently, the patient was able to tolerate a soft diet and regained her orientation. Thus, we resumed Madopar at a low dose. No nausea or gastrointestinal upset was observed thereafter. We also arranged a Tc-99m TRODAT-1 brain single-photon emission computed tomography (SPECT) scan, which revealed no definite evidence of a perfusion defect in the bilateral basal ganglion, indicating that she had secondary Parkinsonism other than idiopathic Parkinson's disease. Suspecting that her secondary Parkinsonism was related to lithium intoxication, we tapered the dose of lithium while continuing the use of Madopar. After this adjustment, her gastrointestinal symptoms subsided, and her mobilization gradually improved with rehabilitation and nutritional supplementation. After 2 weeks, she was discharged in an improved condition. The patient's condition has been stable for 8 months since her discharge.

3. Discussion

The toxic effects of lithium mainly affect the kidneys, liver, heart, and glands but are usually mild and reversible. A lithium serum level of > 1.0 mmol/L may cause neurological symptoms, and prolonged lithium intoxication can lead to permanent brain damage.[7] Lithium intoxication can occur acutely or chronically. Acute lithium intoxication usually results from an episode of substantial ingestion. Because lithium is readily absorbed through the gastrointestinal tract, the primary symptom is typically gastrointestinal distress. Acute neurotoxicity can manifest even when the lithium level is normal, but its symptoms are usually reversible, although the recovery process may require several months.[7,12] Chronic lithium intoxication is typically related to mechanisms that reduce renal lithium excretion, such as dehydration, infection, or drug interactions. Adverse reactions unrelated to serum lithium level can occur within the normal plasma range.[7,8] Symptoms of mild lithium intoxication include nausea, vomiting, diarrhea, blurred vision, polyuria, lightheadedness, fine resting tremor, muscular weakness, and drowsiness. Symptoms of moderate lithium intoxication include increasing confusion, blackouts, and fasciculation; increased deep tendon reflexes, myoclonic twitches, and jerks; choreoathetosis; urinary or fecal incontinence; increasing restlessness followed by stupor; mood changes; memory impairment; executive dysfunction; and hypernatremia. Finally, symptoms of severe lithium intoxication include coma, convulsions, cerebellar signs, cardiac dysrhythmias (including sinoatrial block, sinus and junctional bradycardia, and first-degree heart block), hypotension or (rarely) hypertension, circulatory collapse, and renal failure. Neurotoxicity is usually identified clinically. Cerebellar symptoms, dementia, Parkinsonism, choreoathetosis, and brainstem syndromes may persist even after lithium treatment is halted.[10] Lithium toxicity and its related permanent neurological sequelae can occur even when the serum lithium level is not elevated.[12] In patients undergoing maintenance therapy, the mortality rate due to lithium intoxication is 9%; this rate increases to 10% for those with permanent neurological damage.[13] Lithium-associated movement disorders include Parkinsonism, dyskinesia, myoclonus, dystonia, akathisia, rest-

less legs syndrome, cerebellar syndrome, and guttering. Lithium may affect dopamine, norepinephrine, gamma-aminobutyric acid, serotonin, and glutamate neurotransmission through receptor expression, receptor affinity, neurotransmitter release and reuptake, neurotransmitter metabolism, and cellular response. Lithium may also cause damage to the basal ganglia, iron accumulation in the substantia nigra, cerebellar degeneration, and reduced inhibition in the motor cortex. Factors such as genetics, underlying diseases, inherent vulnerability, drug interactions, dehydration, and renal failure can predispose individuals to the adverse effects.[14] Parkinsonism is the most commonly reported lithium-associated movement disorder. The mean age of affected individuals was found to be approximately 55 years, indicating that Parkinsonism is more likely than is Parkinson's disease to be lithium-induced. Compared with use of other antidepressants, chronic lithium use is associated with higher dopaminergic drug use.[6]

Four hypotheses for the pathogenesis of lithium-induced Parkinsonism have been proposed. First, lithium may reduce dopamine in the synaptic cleft of the striatum and limbic system, an effect that has been demonstrated in rat models. Second, the anticholinesterase activity of lithium increases the bioavailability of acetylcholine and causes an imbalance in the dopamine/acetylcholine ratio in the basal ganglia.[7,14] Third, autopsy studies have revealed damage in the brain that was probably related to lithium, leading to the hypothesis that lithium-induced Parkinsonism is caused by direct neuronal damage in dopaminergic neurons.[14] Finally, reports investigating similar populations have highlighted the role of genetic predisposition.[14] In an older population, underlying subclinical latent Parkinsonism may play a role in a patient's hypersensitivity to the neurotoxic effects of lithium. A study also suggested that because older patients have a more permeable blood–brain barrier than younger patients do, their serum lithium level may appear to be at a therapeutic level, but their brain lithium level may be considerably higher.[7] In a case report on an older man with lithium intoxication–related reversible Parkinsonism, his lithium level was reported to be at the upper limit of normal (1.34 mEq/L). Dopamine transporter SPECT imaging can help distinguish Parkinson's disease from drug-induced Parkinsonism.[7,14] Lithium-induced Parkinsonism has the poorest prognosis among movement disorders, with only one out of three individuals fully recovering after clinical management.[14]

In addition to causing movement disorders, the long-term administration of lithium has been reported to potentially impair cognitive functions, including learning, vigilance, alertness, short-term memory, and psychomotor speed.[4]

4. Conclusion

Older adults have lower lithium tolerability than do younger adults, and neurotoxicity can occur in older adults at concentrations regarded as therapeutic for the general adult population. Serum concentrations of lithium must be reduced for older adults, particularly those who are extremely old or exhibit frailty. For older patients, controlling therapies and minimizing various risks (including mortality risk) are crucial because these patients are highly prone to iatrogenesis. Educating patients and their family about the adverse effects of treatments and prodromal symptoms of lithium intoxication is essential. The risks and benefits of prescribing lithium to older adults must be thoroughly weighed. Clinicians must ensure that patients are aware of the features of lithium toxicity, and such awareness is particularly crucial for the older population because they have an increased risk of experiencing adverse effects related to lithium therapy and may experience difficulties understanding and remembering essential information.

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