Lithium Intoxication-induced Acute Parkinsonism Complicated with Hyperparathyroidism and Nephrogenic Diabetes Insipidus: Report of A Case

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Abstract-

Objective: To describe a patient with lithium intoxication presenting as acute parkinsonism, adverse metabolic effects and nephrogenic diabetes insipidus (DI).

Case report: We report a case of a 67-year-old woman with a bipolar affective disorder who was treated with lithium for 10 years. Under concomitant renal insufficiency and urinary tract infarction, she experienced progressive hand tremor, bradykinesia, and unsteady gait. Laboratory results revealed hypercalcemia and hypermagnesiemia. A high serum lithium level (3.6 mEq/L) was found; thus lithium was discontinued. She was found to have a high serum level of intact parathyroid hormone: 135.0 pg/ml and a suspicious parathyroid adenoma. Polyuria with hypernatremia was also noted. A water deprivation test confirmed nephrogenic diabetes insipitces.

After correction of electrolyte imbalance and reduction of lithium level, her consciousness recovered. Her parkinsonian features were responsive to levodopa 400 mg/day in 2 divided doses. One month later, apart from the residual extrapyramidal symptoms and mania, her condition was otherwise stationary.

Conclusions: Tremor is the most frequent movement disorder associated with lithium therapy, while severe parkinsonism has been rarely reported. It should be kept in mind in differential diagnosis of acute parkinsonism especially in elder patients who receive a chronic lithium carbonate therapy.

Key Words: Lithium, Parkinsonism, Nephrogenic DI

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INTRODUCTION

Lithium, which is extensively used in bipolar affective disorders, has a narrow therapeutic index and can be poisonous. There are three types of lithium intoxication: acute, acute on chronic, and chronic. Acute lithium intoxication from accidental ingestion usually has mild symptoms even at potentially lethal levels (3.5 mEq/L).

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Chronic lithium intoxication can cause more severe symptoms, including gastrointestinal effects, cardiovascular effects, renal side effects, metabolic adverse effects such as notably hypothyroidism, hyperparathyroidism, nephrogenic diabetes insipidus (DI), and neurologic effects e.g. lethargy, coarse hand tremor, dysarthria, nystagmus, ataxia, myoclonic twitch, seizure, and parkinsonism[1,2].

Tremor is the most frequent movement disorder associated with lithium therapy, while severe parkinsonism has been rarely reported in previous studies and approximately 5% to 20% patients who receive lithium therapy develop nephrogenic DI[3].

Herein, we report a patient with a bipolar disorder who suddenly developed disabling parkinsonism, and adverse metabolic effects, including nephrogenic DI simultaneously.

CASE REPORT

A 67-year-old woman without other remarkable medical histories received lithium carbonate 400 mg/day and clonazepam 1 mg/day for a 10-year history of bipolar affective disorder. This regimen had kept her disorder under control. One week prior to this admission, her appetite began to progressively deteriorate. She then experienced hand tremor, psychomotor slowness, and difficulty walking.

Upon arrival in emergent room, she presented psychic slowness with significant cognitive impairment, masked face, severe bradykinesia, severe rigidity of four limbs, and postural tremor in all limbs. Results of blood chemistry analysis showed mild leukocytosis (white blood cell: 11610/cumm), renal function deterioration (blood urea nitrogen/creatinine: 28/2.3 mg/dL), and electrolyte imbalance (sodium: 143 mmol/L, potassium: 5.0 mmol/L, calcium: 11.6 mg/dL, and magnesium: 3.5 mg/dL (ref.: 1.6-2.3 mg/dL). Urine analysis showed pyuria (WBC>100/mm^3, nitrate: 3+). Brain computed tomography showed no abnormal finding.

A high serum lithium level 3.6 mEq/L (ref.: 0.6-1.2 mEq/L) was detected ; thus we discontinued the medication. We also found a high intact parathyroid hormone (PTH): 135.0 pg/mL (ref.: 15.0-76.0 pg/mL). Sonography revealed an enlarged superior parathyroid (about 0.6×0.5 cm in size), suggesting an enlarged parathyroid adenoma. The other endocrine functions (thyroid and adrenal) were normal.

Polyuria (exceeding 8000cc/day) was found on hospital day 4. Blood chemistry showed hypernatremia (Na: 180 mg/dL). Serum osmolality had increased to 362 mosm/L, and urine osmolality to 198 mosm/L. A water deprivation test was done and confirmed to have nephrogenic DI secondary to lithium intoxication. Forced hydration was initiated. In addition to fluid hydration, the patient was given moduretics (amiloride HCl 5 mg and hydrochlorothiazide 50 mg divided in 2 doses) as well as naproxen 250 mg divided in 2 doses to control her DI. The amount of urine gradually decreased.

Despite an improvement in consciousness, followed by electrolyte imbalance corrected and lithium level lowered down (0.7 mEq/L), signs of parkinsonism remained. Thus we prescribed levodopa 400 mg/day to ameliorate her extrapyramidal symptoms. Levodopa was tapered after one month. At this time, the patient experienced a return of manic symptoms due to her bipolar disorder, for which she was prescribed valproic acid 700 mg/day. Apart from the residual extrapyramidal symptoms and mania, her condition was otherwise stationary.

DISCUSSION

It has been reported that an advanced age and high lithium levels are predisposing factors to lithium intoxication. Lithium intoxication may be increased by fever, infections, high sodium diet, vomiting, diarrhea, renal insufficiency and other drugs, such as neuroleptics, diuretics, calcium antagonists, and tricyclic antidepressants[4]. In our case, the predisposing events maybe old age, renal insufficiency and urinary tract infection.

The pathophysiological mechanism underlying parkinsonism in lithium intoxication is not completely understood. Some authors suggest that lithium may induce a decrease of dopamine in the striatum or limbic system. Others speculate that lithium acts as an anticholinesterase and is able to increase central cholinergic activity[5]. There may also be a genetic predisposition to storing lithium inside neuron[6]. Another hypothesis is that patients with movement disorders induced by lithi-

um have often experienced preexisting insults to the basal ganglia[7].

Usually, via discontinuing lithium and introducing biperidene and levodopa±carbidopa[5,8], approximately 40-74% of cases were observed regression of symptoms. However, 15% of cases persist after drug withdrawal, leading to a diagnosis of underlying idiopathic Parkinson's disease. In our case, her parkinsonian features were responsive well to levodopa 400 mg/day.

Another issue to consider is how lithium can cause nephrogenic DI. Often the cause of nephrogenic DI is the kidney's resistance to antidiuretic hormone. Lithium appears to act by accumulating in the collecting tubule cells. There it inhibits the ability of ADH to increase water permeability. The treatment of nephrogenic DI induced by lithium includes discontinuing lithium, putting the patient on a low-sodium diet, and prescribing amiloride, thiazide diuretics (to diminish distal water delivery) and a nonsteroidal anti-inflammatory drug (to decrease the synthesis of prostaglandins)[9]. Initially our patient responded poorly to fluid hydration therapy, after moduretic and naproxen were prescribed, her condition began to improve dramatically.

A third point to consider is how lithium treatment can give rise to hypercalcemia and primary hyperparathyroidism. One previous study had associated lithium-induced hypercalcemia/hyperparathyroidism with a normal serum phosphorus level and an elevated serum Mg level[9]. These irregularities might be resulted from lithium linking with the calcium receptor on the parathyroid and then stimulating PTH secretion[10]. It has been reported that there is a high incidence of parathyroid adenomas versus four-gland hyperplasia in those undergoing prolonged lithium therapy. It is best treated with excision of the adenoma rather than subtotal parathyroidectomy[11]. In our patient, parathyroid adenoma was suspected via sonography, and followed up closely by our endocrinologist.

CONCLUSION

This is a rare case who suffered from lithium-induced parkinsonism associated with nephrogenic DI and other adverse metabolic effects simultaneously. Though rare, it should be kept in mind in differential diagnosis of acute parkinsonism especially in the elder patients who receive a chronic lithium carbonate therapy. Lithium intoxication can be avoided by conservative prescribing, care in combining drug therapies, and educating the patient and caregivers to recognize early signs of the condition.

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