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 hypermagnesemia. 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 insipidus.

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

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).
Chronic lithium intoxication can cause more severe symp-
toms, including gastrointestinal effects, cardiovascular
effects, renal side effects, metabolic adverse effects such
as notably hypothyroidism, hyperparathyroidism, nephro-
genic 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 parkinson-
ism 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 bipo-
lar 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 psy-
chic 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 elec-
trolyte 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/mm³, 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 medica-
tion. 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 hospi-
tal 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
depprivation test was done and confirmed to have nephe-
genic 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 experi-
enced a return of manic symptoms due to her bipolar dis-
order, for which she was prescribed valproic acid 700
mg/day. Apart from the residual extrapyramidal symp-
toms 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 intoxi-
cation. 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 antidepres-
sants(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 anti-
cholinesterase 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\textsuperscript{e} 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)\textsuperscript{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\textsuperscript{9}. These irregularities might be resulted from lithium linking with the calcium receptor on the parathyroid and then stimulating PTH secretion\textsuperscript{30}. 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\textsuperscript{8}. 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.

**REFERENCES**