CASE REPORT

Lithium-induced parkinsonism associated with vocal cord paralysis: an atypical presentation

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ABSTRACT

Drug-induced parkinsonism has been commonly studied and discussed regarding antipsychotic agents, but lithium-induced parkinsonism should also be considered when patients present with parkinsonian symptoms and chronic lithium use. There are several reports of parkinsonism arising during lithium administration and regressing following its reduction or discontinuation. Our case is, to date, the first case in the literature in which vocal cord paralysis occurred as the first symptom of lithium-induced parkinsonism, contributing to confuse doctors and patients and to delay diagnosis and treatment. In our clinical case prompt withdrawal of lithium and its reintroduction at lower doses led to complete resolution of this disabling clinical presentation. This report emphasizes the importance of careful monitoring of lithium levels, especially in elderly subjects, and the need to consider lithium-induced parkinsonism even when unusual motor symptoms appear in chronic lithium users.

KEYWORDS: bipolar disorder; lithium neutotoxicity; Drug-Induced Parkinsonism; Lithium-Induced Parkinsonism; iatrogenic parkinsonism; extrapyramidal symptoms

INTRODUCTION

Although drug-induced parkinsonism (DIP) is commonly attributed to domapinergic receptor antagonist agents, there are several reports of lithium-induced parkinsonism (LIP) [1-10]. The literature in this regard is small and controversial, however this entity should be considered when evaluating patients with parkinsonian symptoms and a history of chronic lithium use [2].

Lithium is the gold standard in the treatment and prevention of manic and depressive episodes in bipolar disorders, but one problem with its use is its neurotoxicity. Although adverse reactions are not always related to serum lithium levels and can occur within the plasma range, its neurotoxicity is usually identified clinically and confirmed by lithium levels above 1.0 mmol/L [11]. Several types of neurological side effects have been reported with long-term lithium treatment [12]. Previous cases of LIP without signs of lithium toxicity have been reported, such as ours, in which all motor symptoms were reduced after lithium tapering or discontinuation [5]. To our knowledge, however, to date, there have been no reports of vocal cord paralysis associated with iatrogenic Parkinsonism in patients chronically taking lithium. However, cases of vocal cord paralysis associated with idiopathic Parkinson's disease (IPD) have been reported [13].

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We describe the rare case of a patient with elevated serum lithium levels and disabling LIP associated with vocal cord paralysis leading to severe hoarseness, with no other signs of lithium toxicity, resolving with decreased serum lithium levels. The aim of this work is to increase the consideration of this clinical entity to help clinicians achieve an early diagnosis of LIP in order to allow rapid management.

CASE REPORT

A 65-year-old man had a manic episode at age 29, followed by a major depressive episode and was successfully treated for thirty-five years with maintenance therapy of lithium carbonate 600 mg/day and clomipramine 75 mg/day.

Family history was negative for idiopathic parkinsonism and any other movement disorders. Over the years, apart from a slight tremor in the distal extremities of his upper limbs, he had not developed any motor impairments. Six months before seeing him he manifested an insidious and progressive loss of voice, for this reason he promptly contacted an otolaryngologist who diagnosed him with idiopathic paralysis of the vocal cords. In the following months, the clinical picture progressively became more complicated with marked slowing down of movements. Neurological examination revealed severe parkinsonism with tremor, cogwheel rigidity, bradykinesia, muscle weakness, and difficulty walking. Cognitive examination was normal and unchanged. The neurologist who examined him subjected the patient to EEG and SPECT DaTSCAN exams.

EEG was within normal limits and SPECT DaTSCAN did not show idiopathic Parkinson's disease, so an iatrogenic cause was postulated and the case came to our attention.

At the time of admission to our department, his home therapy was as follows: Lithium Carbonate 600 mg/day, Clomipramine 75 mg/day and Ramipril 5 mg in combination with Hydrochlorothiazide 25 mg for the recent onset of essential hypertension.

On mental status examination, the patient appeared intact in consciousness, lucid, well oriented, and euthymic. He had no thought or perception disorders, nor did he complain of anxiety or insomnia. His psychomotricity was seriously compromised: the physical examination highlighted both a marked rigidity of the postural muscles and the presence of the "toothed trochlea" phenomenon in passive movements, especially of the upper limbs. His voice was almost completely absent and he reported swallowing problems.

Routine blood tests and measurements of serum lithium levels were promptly performed. The renal, thyroid and hepatic functions showed no abnormalities, the electrolyte profile was also within the limits, while the serum lithium levels were elevated (1.36 mmol/L). Therefore, lithium was promptly discontinued and her hypertension treatment was modified to discontinuation of hydrochlorothiazide and maintenance of Ramipril 5mg, with adequate blood pressure control, on the advice of a specialist nephrologist who we have contacted. In the following weeks, the clinical picture gradually improved with a progressive reduction of parkinsonian signs and symptoms. The patient gradually recovered autonomy in the common activities of daily life and, albeit more slowly, the hoarseness secondary to the paralysis of the right vocal cord also resolved.

When the patient was discharged, lithium therapy was carefully restructured to 450 mg/day, with a serum lithium level of 0.53 mmol/L, clomipramine was maintained at 75 mg/day with good illness. Evaluated at one month, three months and six months after discharge, the patient's mood remained stable even at the lowest serum lithium levels.

DISCUSSION

IPD and DIP are the two most frequent manifestations of a bradykinetic rigid extrapyramidal syndrome [14]. Both disorders are mainly caused by a lack of dopamine levels in the basal ganglia [15]. In IPD, dopamine deficiency is secondary to dopaminergic neuronal loss in the substantia nigra pars compacta (pcSN) of the midbrain. In DIP, on the other hand, the reduction of the effects of dopamine is secondary to the action of different types of drugs (eg neuroleptics, antiemetics, antihypertensives).

Despite several hypotheses, the pathophysiological mechanism underlying LIP is unclear. The literature suggests that the most significant risk factors for LIP appear to be patient age, serum lithium levels, and long-term treatment [16]. However, adverse reactions are not always related to serum lithium levels and can occur within the plasma range [17,18]. As some authors have argued, it is likely that advancing age or an underlying subclinical encephalopathy, such as latent parkinsonism, may play a role in the patient's "hypersensitivity" to the neurotoxic effects of lithium [19]. For example, some authors suggest that patients with lithium-induced movement disorders often suffered from a previous insult to the basal ganglia [20,21]. It has also been suggested that older patients have a more permeable blood-brain barrier, so serum lithium levels may appear therapeutic, but in reality, brain lithium levels may be much higher [10,22]. Further hypotheses suggest that lithium reduces the number of dopamine receptors in the striatum or may induce an increase in central cholinergic activity [5,23]. Other authors suggest that there may be a genetic predisposition to store lithium within neurons [17,24].

The present case shows a clear temporal relationship between the reduction of serum lithium levels and resolution of the signs and symptoms of drug-induced parkinsonism. The reasons why this patient has developed high serum lithium levels in recent months are due to the fact that the patient had started taking, about ten months earlier, a new drug for the treatment of arterial hypertension (Hydrochlorothiazide + ramipril) which it notoriously reduces the renal elimination of lithium, increasing its serum levels. Since his serum lithium levels (1.36 mmol/L) were above the normal range, it could be argued that his symptoms were a manifestation of lithium neurotoxicity. However, it should be noted that no other signs indicative of toxicity (e.g. disorientation, dysarthria, nausea, vomiting, diarrhea, delirium, polyuria, polydipsia, oliguria, EEG slowing, electrolyte disturbances) were present and that following the reduction of serum lithium levels there was a gradual resolution of parkinsonian symptoms. These latter results suggest that this patient did indeed have LIP that became clinically manifest and disabling at higher serum levels.

As our case report clearly shows, lithium toxicity can occur in patients treated long-term, particularly in cases of dehydration, supervening renal function decline, or when a new drug is introduced due to numerous interactions with lithium. Lithium levels can be increased by diuretics and NSAIDs, but reports suggest that ACE inhibitors, ARBs, antidepressants, antipsychotics, and antiepileptics may also play a role. Thiazide diuretics, in particular, have a significant ability to increase serum lithium levels by interacting with renal function.

This case suggests that patients on lithium salt treatment who develop parkinsonism should reduce the lithium dose to rule out that it is not a side effect of lithium. In these clinical pictures, the reduction of the lithium dose can alleviate or resolve this disabling side effect, contributing to improve the patient's quality of life and at the same time can maintain its efficacy in preventing relapses of the affective disorder. It is vital to keep in mind that the side effects of lithium can be varied and polymorphic, therefore the differential diagnosis of a patient on lithium therapy presenting with neurological and/or motor symptoms should always include lithium toxicity. In most cases, lithium toxicity is preventable. Proper education and monitoring will certainly reduce the number of toxic episodes in patients treated with lithium. Further studies should be done to analyze the clear relationship between lithium and parkinsonism.

CONCLUSION

In conclusion, we present a rare case of lithium-induced extrapyramidal syndrome characterized by parkinsonian-like motor symptoms to which vocal cord paralysis with loss of voice is added to make the case unique. Fortunately for this patient it was sufficient to discontinue the lithium therapy and restore it at a reduced dose to completely resolve the motor picture and prevent relapses of bipolar

disorder. Bipolar patients with a history of chronic lithium intake should be regularly evaluated for the occurrence of long-term side effects, the most known of which, to date, are represented by renal function alterations and thyroid and parathyroid abnormalities.

We believe that motor disturbances should also be properly considered as lithium-induced side effects and investigated through careful physical examination. In cases of diagnostic uncertainty, as in our case, the use of DatScan can help. Although we cannot exclude that a picture of LIP may not resolve despite the reduction or suspension of lithium, our experience and the various reports in the literature lead us to conclude that in the management of such a clinical picture, the first therapeutic action should be that of reducing lithium therapy or eventually suspending it and considering the therapeutic alternatives available for mood stabilization.

Conflict of interest

The author(s) declare that they have no competing interests.

Consent for publication

Written informed consent from the patient has been taken and is available for review by Editor in chief of the journal.

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