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AAACE Clinical Case Reports

journal homepage: www.aaaceclinicalcasereports.com



Case Report

Lithium-Associated Hyperparathyroidism Followed by Catatonia

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ARTICLE INFO

Article history:

Received 8 December 2020

Accepted 12 December 2020

Available online 19 December 2020

Key words:

catatonia

hypercalcemia

hyperparathyroidism

lithium

ABSTRACT

Objective: To familiarize the medical community with the less common adverse effects of lithium on parathyroid function, we present a case of lithium-associated hyperparathyroidism followed by the development of new-onset catatonia in a patient with schizoaffective disorder.

Methods: To allow for the safe resumption of lithium, the patient received laboratory screening of serum lithium, blood urea nitrogen, serum creatinine, calcium, and thyroid-stimulating hormone levels. The hypercalcemia was evaluated by measuring parathyroid hormone (PTH), ionized calcium, and 25-hydroxy vitamin D levels.

Results: A 58-year-old man with longstanding schizoaffective disorder was admitted for worsening psychotic symptoms following noncompliance with his risperidone and lithium regimen. Exploratory laboratory tests (hospital day 5) showed an elevated PTH level of 72 (reference, 15–65) pg/mL, ionized calcium level of 1.4 (reference, 1.03–1.23) mmol/mL, and a serum calcium level of 11.3 (reference, 8.4–10.5) mg/dL. After the discontinuation of lithium (day 6), anergia (day 7), mutism, and posturing (day 10) developed. Worsening catatonic symptoms of negativism and poor oral intake necessitated dehydration management with intravenous isotonic saline (day 24). The hypercalcemia persisted for 6 weeks. Treatment with cinacalcet (day 43) rapidly normalized the serum calcium levels (day 44). The catatonia, depression, and psychosis began resolving when clozapine (day 50) and electroconvulsive therapy (day 59) were initiated. PTH levels did not normalize until day 82.

Conclusion: This report describes a case of prolonged hyperparathyroidism and hypercalcemia following treatment with lithium. Catatonia is unusual in patients with lithium-associated hyperparathyroidism but this report suggests that in settings yet to be determined, it is related to hypercalcemia of this syndrome.

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Introduction

Lithium remains a gold standard treatment for bipolar disorder.¹ Although lithium is known to cause a wide range of adverse reactions, an often overlooked side effect is lithium-induced hyperparathyroidism.^{2,3} The prevalence of primary hyperparathyroidism is 0.2% in women and 0.08% in men.⁴ However, hyperparathyroidism in lithium-treated patients ranges from 8.6% to 26%.^{5,6} The most

common neuropsychiatric symptoms of primary hyperparathyroidism are fatigability, lassitude, memory difficulties, anxiety, and depression.^{7,8} In extremely rare instances, hyperparathyroidism is associated with a catatonic syndrome. To date, only 2 case reports have reported an association between catatonia and hyperparathyroidism.^{9,10} We present a clinical case report of a patient with treatment-resistant schizoaffective disorder who initially developed hyperparathyroidism associated with lithium treatment followed by a catatonic syndrome, which prolonged the course of the illness.

Case Report

A 58-year-old man with a psychiatric history of schizoaffective disorder, hypertension, and hypothyroidism was admitted to the

Abbreviations: PTH, parathyroid hormone; ECT, electroconvulsive therapy.

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psychiatric unit following the development of a long series of episodes of worsening psychosis. Two weeks prior to admission, he left his group home without permission. Since that time he had been non-compliant with risperidone and lithium regimen. On examination of his mental status, the patient was observed talking and laughing to himself and displayed disorganized behavior, delayed responses, excessive staring, increased psychomotor activity, poor self-care, and urinary incontinence. On some previous hospitalizations, the patient had experienced mania as a component of his schizoaffective disorder. The complete blood count, thyroid panel, and computed tomography scan of head were reported normal. Albumin and renal function were within the normal range during the hospital course.

On hospital day 1, the patient was restarted on lithium 900 mg/d and risperidone 2 mg/d. The patient reported taking lithium prior to leaving his boarding home; however, the treatment team was unable to ascertain the duration of lithium use as a result of a lack of reliable collateral information. Prior to resuming the lithium treatment, he was screened with laboratory assessment of serum lithium, blood urea nitrogen, serum creatinine, calcium, and thyroid-stimulating hormone levels and an electrocardiogram. The electrocardiogram revealed a prolonged QTc interval of 500 ms, which normalized upon the discontinuation of risperidone. The screening labs were remarkable for mildly elevated calcium at 10.7 (reference, 8.4–10.5) mg/dL and repeat calcium on day 5 showed 11.3 mg/dL. To further evaluate the hypercalcemia, parathyroid hormone (PTH) levels, ionized calcium, and 25-hydroxy vitamin D levels were measured. Laboratory results on hospital day 5 showed the following values: PTH 72 (reference, 15–65) g/mL, ionized calcium (reference, 1.03–1.23) mmol/mL, and 25-hydroxy vitamin D 21.1 (reference, 30–80) ng/mL. Given that the patient was taking lithium prior to the current admission, it was determined that the elevated PTH levels were induced by lithium, and hence, lithium was discontinued on hospital day 6. The endocrinology team recommended addressing the hypercalcemia conservatively by monitoring the calcium levels and maintaining adequate oral fluid intake. The PTH and calcium levels remained elevated for the next 5 weeks, with serum and ionized calcium levels fluctuating between 10.7 to 11.5 mg/dL and 1.32 to 1.43 mmol/L, respectively. To address the patient's psychosis, aripiprazole was initiated on hospital day 7 and titrated up to 20 mg. Because of the long history of treatment resistance and based on previous successes, olanzapine was also initiated on hospital day 7 and was titrated up to 25 mg/d over the next few weeks. However, by day 10, the patient began flipping from psychomotor agitation into an anergic, depressed state. Sadness, crying, and psychomotor retardation was intermingled with intermittent mild catatonic symptoms in the form of mutism and posturing. Despite the addition and escalation of escitalopram to 20 mg daily, by day 14, the treatment team noted worsening catatonic symptoms. The patient displayed vacant fixed stares, waxy flexibility, posturing, negativism, withdrawn behavior, and prominent mutism. Of note, despite a protracted psychiatric illness with multiple hospitalizations, this patient had no previous history of catatonia. On day 14, the Bush Francis Catatonia Rating Scale scored between 10 and 23 (mild-moderate catatonia); intramuscular lorazepam 1 mg three times a day was started and further titrated to 1.5 mg three times a day by day 18. For brief intervals, the patient became communicative while on lorazepam and verbalized profound depressive ideation. The worsening catatonia led to restricted oral intake and subsequent dehydration, requiring treatment with intravenous saline for 24 hours (day 24). Upon the resolution of dehydration, bitemporal electroconvulsive therapy (ECT) three times a week was initiated. The patient developed severe confusion after 4 ECT treatments, and hence ECT was stopped on day 32. The patient was switched from escitalopram to

venlafaxine and titrated up to 112.5mg/d on hospital day 40. On day 40, the calcium level was 11.5 (8.4–10.5) mg/dL, PTH level was 67.41 (15–65) g/mL, ionized calcium level was 1.43 (1.03–1.23) mmol/mL, and 25-hydroxy vitamin D level was 27 (30–80) ng/mL. On the account of persistently elevated ionized serum calcium levels and the failure in the improvement of patient's neuropsychiatric status, the patient was started on cinacalcet (an agonist of parathyroid calcium-sensing receptors) at 30 mg twice a day on hospital day 43. The patient's calcium levels dropped to 10.1 mg/dL and PTH level remained at 67 pg/dL on hospital day 44. On day 50, aripiprazole and olanzapine combination were discontinued as a failed treatment trial, and clozapine was gradually titrated to 400 mg daily. The patient was also restarted on a course of bifrontal ECT on day 59, which he tolerated well with no development of confusion on this second attempt. In the weeks following the initiation of clozapine and ECT, the patient's active hallucinations, catatonia, psychomotor agitation, and behavioral organization improved and he became more communicative. The elevated PTH level normalized on hospital day 82. The calcium and PTH levels were stabilized by a starting dose of cinacalcet 30 mg twice a day, with no need for dosage escalation. The patient's psychiatric status stabilized on a combination of clozapine 400 mg HS and haloperidol 5 mg twice a day. The patient was advised to continue cinacalcet after discharge until his follow-up appointment with the endocrine service.

Discussion

We present a case of lithium-induced hyperparathyroidism followed by a first episode of catatonia in a patient with long-standing treatment-resistant schizoaffective disorder. This report is consistent with the literature that hypercalcemia and hyperparathyroidism are serious medication side-effects that occur in the context of lithium treatment and that can complicate the course of a psychiatric illness. Hypercalcemia can also occur independent of hyperparathyroidism following lithium treatment. During the initial 4 weeks of lithium carbonate administration, serum calcium and immunoreactive PTH levels increase within the normal range in 80% of patients, but may rise above normal in 10% of patients after long-term therapy.¹¹ A case-control cross-sectional prevalence study of 112 bipolar patients showed lithium treatment can cause hypercalcemia in up to 24% and hyperparathyroidism in 8.6% of cases.⁵ A recent meta-analysis of 60 publications showed an absolute risk for hypercalcemia and hyperparathyroidism of approximately 10% in 730 lithium-treated patients when compared with 730 unexposed individuals.¹² Because of the absence of population-based data, the true prevalence of lithium-induced hypercalcemia and hyperparathyroidism is unknown.¹³ Lithium causes hypercalcemia through several mechanisms. It increases the renal calcium reabsorption in the loop of Henle and can also independently stimulate PTH release. Lithium alters the set point for PTH secretion to a higher serum calcium concentration by antagonizing calcium-sensing receptors. This alteration in receptor sensitivity raises the threshold of calcium required to suppress PTH output by the parathyroid gland. Hence, the parathyroid cells react as if the extracellular concentration of calcium has decreased, resulting in excessive PTH secretion.^{6,14} In the index case, stopping the lithium and encouraging oral fluids did not lower the elevated calcium and PTH levels even 5 weeks after stopping lithium.¹⁵ Lithium alters the parathyroid gland activity and structure through chronic stimulation or by "unmasking" the underlying subclinical pathology.^{16,17} Following the initiation of lithium, calcium and PTH levels may increase within days or weeks or much later in the course of the treatment.¹⁶ Patients on chronic lithium for >3 years can exhibit 3-fold increases in parathyroid mass³ compared with patients on lithium for <6 months.^{15,16} Once these hyperplastic changes

develop in the parathyroid gland, the clinical presentation might resemble primary hyperparathyroidism and the phenomenon has been referred to as lithium-associated primary hyperparathyroidism.^{3,11,14–16}

Cinacalcet is the mainstay of treatment when a patient is not suitable for surgery, which may be appropriate in severe refractory cases.¹⁸ The index case showed the complete resolution of laboratory measures on cinacalcet 30 mg twice a day. These relatively lower cinacalcet dosages are typically prescribed for managing secondary hyperparathyroidism as compared to primary hyperparathyroidism. It is highly likely that our patient's hyperparathyroidism/hypercalcemia was secondary to lithium treatment. We cannot definitively determine whether or not lithium unmasked a preexisting subclinical hyperparathyroidism.

Of note, the patient was unable to complete an initial course of bitemporal ECT because of delirium. However he was able to tolerate and benefit from a second course of bifrontal ECT later in the hospital course. We concluded that the correction of hypercalcemia along with switching to bifrontal ECT explained the different tolerance levels of the ECT treatment.

Catatonia was another challenging aspect in the patient's clinical course. A meta-analysis of 73 studies showed the overall pooled prevalence of catatonia to be 9.0% among 110 774 individuals and was 20.6% in the presence of medical and neurologic comorbidities. The majority (55 studies) included psychiatric inpatients.¹⁹ In psychiatric patients, catatonia is equally prevalent in mood disorder and schizophrenia.²⁰ However, catatonia is more prevalent in bipolar affective disorder compared with schizophrenia or unipolar major depressive disorder.^{19,21} Hyperparathyroidism can, on extremely rare occasions, present with catatonia as the chief presenting symptom. There have been 2 rare cases reported of hyperparathyroidism presenting as catatonic stupor.^{9,10} It is our opinion that our patient had a catatonia-predisposing bipolar affective component to his psychiatric history but did not develop catatonia until he developed lithium-associated hyperparathyroidism. Moreover, while highly confounded by other factors, the resolution of catatonia and the normalization of calcium levels were closely associated in time, while the PTH remained elevated long after the patient began to improve. The elevated PTH is a marker of excessive activity of the parathyroid gland and exerts its effect through an alteration of the calcium levels but did not appear to directly affect the mental status.

Conclusion

Hyperparathyroidism and hypercalcemia are well documented but under-recognized complications of lithium therapy. This report describes a case of prolonged hyperparathyroidism and hypercalcemia following treatment with lithium to help heighten the awareness of this medication effect. Catatonia is rare in patients with lithium-associated hyperparathyroidism but this report

suggests that in settings yet to be determined, it is related to the hypercalcemia of this syndrome.

Disclosure

The authors have no multiplicity of interest to disclose.

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