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LETTER TO THE EDITORS

Lithium-induced hyperparathyroidism and its potential reversibility in a patient with bipolar affective disorder: case report

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Lithium compounds have been used in clinical practice for nearly eight decades for the treatment of bipolar disorder (BD).[1] They have demonstrated efficacy in both acute and maintenance phases.[2] However, lithium carbonate is associated with various adverse effects, particularly those affecting endocrine-metabolic function[3] – in fact, the association between chronic lithium use and both clinical and subclinical hypothyroidism is well-documented in the literature.[4] In contrast, lithium-induced hyperparathyroidism and subsequent hypercalcemia remain less recognized in clinical practice,[5] with no well-established management guidelines.[6] In this context, we present a case of hyperparathyroidism in a 71-year-old woman with bipolar disorder type II (BD-II) who had been on long-term lithium therapy.

A 71-year-old white woman was diagnosed with osteoporosis in 2011. Initial management included calcium and vitamin D supplementation alongside oral bisphosphonates. Due to adverse effects, oral bisphosphonates were discontinued in 2013. Intravenous zoledronic acid was initiated in 2015, followed by oral risedronate in 2016, with a suboptimal therapeutic response. Denosumab was introduced in 2017, and the patient has since remained on regular treatment, maintaining normocalcemia and adequate serum vitamin D levels.

The patient had a prior diagnosis of major depressive disorder in 1990, later reclassified as bipolar disorder type II in 2018. Lithium carbonate was initiated at a maximum daily dose of 450 mg (controlled-release), titrated to therapeutic serum lithium concentrations (0.6-0.8 mEq/L), in combination with 25 mg of quetiapine at bedtime. The patient remained euthymic under this regimen.

In 2019, during routine laboratory evaluation following the initiation of lithium therapy, hypercalcemia was detected. Investigations conducted as part of the endocrinology protocol for the evaluation of suspected hyperparathyroidism[7] revealed hypocalciuric hypercalcemia, with a 24-hour urinary calcium level of 41 mg (reference range: < 100 mg/24 h), serum calcium of 11.1 mg/dL (reference range: $\leqslant 10.2$ mg/dL), and elevated parathyroid hormone (PTH) levels at 135 pg/mL (reference range: $\leqslant 65$ pg/mL). Repeat testing confirmed these findings. Parathyroid scintigraphy without SPECT-CT performed as part of the workup for primary hyperparathyroidism showed no focal radiotracer uptake, favoring a diagnosis of lithium-associated hyperparathyroidism. With the patient's agreement, lithium therapy was discontinued and lamotrigine was introduced, reaching a maintenance dose of 100 mg/day. The patient has remained euthymic under this new medication regimen.

Despite lithium discontinuation, persistent elevations in serum calcium and PTH levels were observed between 2021 and 2023 during routine monitoring. To reassess for primary hyperparathyroidism, parathyroid scintigraphy with SPECT-CT was performed, which again revealed no evidence of parathyroid adenoma or hyperplasia. Given the absence of structural abnormalities, the patient's asymptomatic status, and relatively limited duration of lithium exposure, the clinical team opted for continued surveillance with serial measurements of serum calcium and PTH. By October 2024, normocalcemia was documented.

Additional factors supporting the diagnostic impression included the absence of clinical comorbidities known to affect calcium metabolism – such as chronic kidney disease, elevated body mass index, or hereditary syndromes – and continued adherence to osteoporosis treatment with sustained vitamin D sufficiency. No structural abnormalities of the parathyroid glands were identified at any point during follow-up. Resolution of biochemical abnormalities following lithium discontinuation further supported the diagnosis. After interdisciplinary discussion and review of clinical and laboratory findings, lithium-induced hyperparathyroidism was suspected.

Lithium-associated hyperparathyroidism remains underrecognized and poorly understood. Hypercalcemia due to hyperparathyroidism, among other potential etiologies, is a clinical entity that is often diagnosed late. When it develops gradually and chronically, patients may tolerate hypercalcemia and remain asymptomatic,[8] as observed in the present case. Conversely, symptomatic presentations can be highly variable and potentially severe; manifestations may include constipation, nephrolithiasis and cholelithiasis, muscle weakness, and renal failure.[8]

In the case reported herein, elevated serum calcium and PTH levels were observed without clinical or radiological evidence of glandular enlargement. Although the precise pathophysiology remains unclear, one proposed mechanism is that lithium acts as an antagonist of the calcium-sensing receptor (CaSR) in the parathyroid glands, inhibiting this signaling pathway and thereby facilitating PTH release despite elevated serum calcium levels.[5] This mechanism may explain the clinical and laboratory findings observed in our case.

Additionally, lithium has been shown to alter the Wnt-β-catenin signaling pathway, promoting parathyroid gland growth and hyperplasia, which is consistent with the increased prevalence of multiglandular disease associated with its chronic use.[9] Notably, in a recent cohort study, a positive association was identified between

bipolar disorder and osteoporosis[10]; however, lithium use was paradoxically linked to a reduced risk of osteoporosis, likely due to its stimulatory effect on bone formation through β-catenin activation. Thus, the overall impact of lithium on calcium metabolism remains a subject of debate.

Another important consideration is the potential reversibility of lithium-associated endocrine dysfunction. In this case, lithium discontinuation did not result in immediate normalization of calcium levels, suggesting that lithium-induced hyperparathyroidism is not solely attributable to its direct pharmacological effects. Moreover, lithium discontinuation has been shown to have more success in patients with shorter exposure to lithium.[5] A longitudinal study conducted in Switzerland investigating the reversibility of lithium-associated hypothyroidism suggested that euthyroidism could be achieved within 3 to 12 months following lithium discontinuation.[4] However, no comparable studies have examined the reversibility of lithium-induced secondary hyperparathyroidism.

For patients in whom normocalcemia is not achieved after lithium discontinuation, the choice between watchful waiting, pharmacotherapy, and surgical intervention remains a clinical challenge.[5] In the present case, given previous fluctuations in calcium levels and the concurrent diagnosis of osteoporosis, the short duration of lithium therapy, and the absence of symptoms, a conservative approach was adopted until the patient achieved normocalcemia and normalization of PTH levels. However, in clinical practice, parathyroidectomy is typically recommended for patients who maintain hypercalcemia after lithium withdrawal or for those who cannot cease lithium therapy.[5] Alternatively, case reports have documented the successful use of cinacalcet hydrochloride, a calcimimetic agent that enhances CaSR sensitivity, in restoring normocalcemia in this setting.[6]

Despite being a relatively early complication of lithium therapy, lithium-induced hyperparathyroidism is often recognized late, which is concerning given the potential deleterious effects of chronic hypercalcemia. The present case underscores the importance of increased awareness of this condition among psychiatrists and other clinicians who manage patients receiving lithium therapy, to ensure timely diagnosis and appropriate intervention.

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Disclosure

The authors declare no conflicts of interest.

Data availability

The data that support this study are available from the authors upon request.

Author contributions

MCMC: Conceptualization, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing.
JSC: Conceptualization, Methodology, Writing – original draft, Writing – review & editing.
GSA: Writing – original draft.
IMSA: Writing – original draft.
ADS: Writing – original draft.
AAL: Conceptualization, Resources, Writing – original draft.
DCL: Investigation, Writing – review & editing.
AMS: Conceptualization, Resources, Writing – review & editing.
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