

# Case Report

## Lithium-induced Symptomatic Hypercalcemia and Hyperparathyroidism in a Patient with Bipolar Affective Disorder: A Case Report and Review of Literature

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### ABSTRACT

Lithium induced primary hyperparathyroidism is an uncommon endocrine side effect of long term lithium therapy. We studied the case of a 67-year-old female patient on long term lithium therapy for bipolar affective disorder, who developed resistant hypercalcaemia and parathyroid adenoma which required parathyroidectomy. Furthermore, the effect of chronic lithium therapy on parathyroid glands and serum calcium levels, its pathogenesis, and management were reviewed. Periodic monitoring of serum calcium levels in patients on long term lithium therapy should be practiced. Surgical removal of the affected parathyroid gland is an effective treatment modality in selected patients with resistant hypercalcaemia and parathyroid adenoma and/or hyperplasia. However, regular post-operative follow up is needed for early identification of recurrence in such patients.

**Key words:** *Hyperparathyroidism, lithium-induced hypercalcemia, parathyroidectomy*

### INTRODUCTION

Lithium remains the first-line therapy for patients with psychiatric disorders such as acute mania and bipolar affective disorder.<sup>[1]</sup> Although thyroid dysfunction is the most common endocrine side effect of lithium, hypercalcemia and primary hyperparathyroidism are also reported.<sup>[2]</sup> A high degree of clinical suspicion is necessary to recognize these less common side effects. We report a patient, who developed resistant

hypercalcemia and parathyroid adenoma which required parathyroidectomy, whilst receiving long-term lithium therapy.


### CASE REPORT

A 67-year-old female was diagnosed to have bipolar affective disorder in 1976 and received 500 mg of

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lithium carbonate daily since then. She had no other comorbidities such as type 2 diabetes or hypertension. She presented with a history of weight loss, polyuria, polydipsia and generalized weakness for a duration of 6 months. Physical and mental state examination did not reveal any abnormalities including bone tenderness. Body mass index was 21.2 kg/m<sup>2</sup>. Investigations revealed a serum-corrected calcium level of 2.78 mmol/l (1.12–1.33 mmol/l) on repeated assessment and serum phosphate was 2.6 mg/dl (2.7–4.5 mg/dl). Serum intact parathyroid hormone (PTH) level was 86.4 pg/ml (normal range - 14–72 pg/ml). Serum alkaline phosphatase was 124.9 IU/l (<90 IU/l) and bone mineral density studies showed evidence of osteoporosis. Thyroid function assay was normal with free T4 level of 1.2 ng/dl (0.94–1.71 ng/dl) and thyroid-stimulating hormone level of 1.55  $\mu$ IU/ml (0.45–4.51  $\mu$ IU/ml). The 24-h urinary calcium excretion was 148.6 mg/24 h (100–300 mg/24 h). Serum 25-hydroxyvitamin D level was low at 14.26 nmol/l (25–125 nmol/l). Serum albumin and serum creatinine were normal.

Lithium was discontinued as the symptoms and biochemical features were suggestive of lithium-induced hyperparathyroidism. The clinical features and biochemical parameters did not normalize 3 months after cessation of lithium treatment (serum calcium was 2.48 mmol/l and PTH was 84 pg/ml). The 99m Tc-sestamibi dual-phase scintigraphy showed significant tracer retention in delayed images in the left inferior parathyroid gland, which is suggestive of hyperfunctioning. Therefore, surgical resection of the hyperfunctioning gland was planned. The patient underwent bilateral neck exploration. Left inferior parathyroid gland was enlarged and firm in consistency, with an approximate size of 1.8 cm  $\times$  1.5 cm. There was no operative evidence of malignancy. Other three parathyroid glands and thyroid gland looked normal. The enlarged parathyroid gland was removed. There were no operative complications and the postoperative recovery was uneventful.

Macroscopically, the excised tissue showed a well-encapsulated tumor measuring 20 mm  $\times$  12 mm  $\times$  7 mm in size and weighing 2.9 g. Microscopy revealed diffuse sheets of polygonal cells separated by thin fibrovascular septae. Cells were round or oval with abundant eosinophilic cytoplasm and nuclei with chromatin. The findings were in favor of parathyroid adenoma.

She is being followed up regularly and remains asymptomatic. Postoperatively, serum ionized calcium and PTH levels returned to normal levels.

## DISCUSSION

Lithium has been used in clinical practice as an effective treatment for bipolar affective disorder. It is known to interfere with thyroxin synthesis and PTH metabolism at multiple levels.<sup>[3,4]</sup> The first reported case of hypercalcemia following lithium treatment was in 1973.<sup>[5]</sup> Studies have shown that the incidence of hyperparathyroidism among patients on long-term lithium therapy is four- to six-fold higher compared to the general population.<sup>[6]</sup>

Several mechanisms have been postulated to explain the biochemical changes in lithium-induced hyperparathyroidism. It is associated with the elevated serum levels of calcium, magnesium, and PTH, and decreased 24-hour urinary calcium excretion and cyclic adenosine monophosphate levels. These findings are similar to familial hypocalciuric hypercalcemia. However, in primary hyperparathyroidism, urinary calcium excretion is increased.<sup>[7]</sup>

Calcium sensing receptors (CSRs) are present in parathyroid glands, renal tubules, and bone tissue. CSR plays an important role in calcium/inorganic phosphate homeostasis, cation transport, urine concentration, and renin release.<sup>[8]</sup> Lithium is known to act on CSR in parathyroid cells, thereby shifting the set points, resulting in excessive release of PTH.<sup>[9]</sup> This is by competitively antagonizing CSRs and thereby raising the threshold of serum calcium necessary to inhibit PTH secretion, resulting in an increase in PTH synthesis, cellular proliferation, and secretion.

Although lithium causes a systemic effect, most series have shown that solitary parathyroid adenoma is more common than multiglandular parathyroid hyperplasia. Several studies showed an incidence of solitary parathyroid adenoma among this group of patients to be between 72.5% and 93%.<sup>[6,9-11]</sup> However, a higher incidence (83%) of multiglandular hyperplasia has also been reported.<sup>[10,11]</sup> The main drawback of these studies is the relatively low patient numbers.

In most patients receiving short-term lithium therapy, calcium and PTH levels tend to normalize within 1–2 months after discontinuation of lithium.<sup>[12]</sup> However, discontinuation of lithium has a lower success rate in patients receiving long-term lithium therapy (>10 years).<sup>[12]</sup>

Recently, calcimimetics have been used in the treatment with or without discontinuation of lithium.<sup>[13]</sup> They activate CSRs which have been antagonized by lithium, resulting in a decrease in PTH secretion and preventing

hyperplasia of parathyroid gland. However, in patients with resistant parathyroidism and moderate-to-severe hypercalcemia, parathyroidectomy is the mainstay of treatment,<sup>[12]</sup> which has a higher success rate. Surgery results in biochemical remission in the immediate postoperative period with normalization of calcium and PTH levels. Furthermore, parathyroidectomy was shown to improve psychosomatic symptoms in 90%–97% of patients with lithium-induced hyperparathyroidism. However, recurrence of symptoms of hyperparathyroidism (8%–42%) following parathyroidectomy was also reported in the literature.<sup>[6,7]</sup>

The use of preoperative localization studies including sestamibi scans and computed tomography and subsequent focused neck exploration is controversial, although incorporated routinely in the management.<sup>[7]</sup> However, data supporting preoperative localization in these patients are limited,<sup>[7]</sup> and studies have shown poor sensitivity and limited utility in planning surgical approaches.<sup>[14]</sup> Nevertheless, sestamibi scans may help to detect mediastinal parathyroid adenoma.<sup>[15]</sup> Due to the poor sensitivity of imaging, bilateral neck exploration is advised before parathyroidectomy to exclude multiglandular involvement.

## CONCLUSION

Periodic monitoring of serum calcium level in patients on long-term lithium therapy should be incorporated by clinicians. A high index of clinical suspicion needs to be maintained to detect hypercalcemia in these patients who present with vague symptoms such as generalized body weakness. Parathyroidectomy is an effective treatment modality in patients with resistant hypercalcemia and parathyroid adenoma and/or hyperplasia. However, patients should be regularly monitored after surgery to detect recurrence of disease.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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### Conflicts of interest

There are no conflicts of interest.

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