Case Report

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2023.50.007986

A Case of Lithium Induced Hyperparathyroidism

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ARTICLE INFO

Received: May 03, 2023

Published: May 25, 2023

Citation: T Patrick Jensen, Eleanor P Iodice and Ana P V Glass. A Case of Lithium Induced Hyperparathyroidism. Biomed J Sci & Tech Res 50(4)-2023. BJSTR. MS.ID.007986.

ABSTRACT

A 76-year-old white female with a history of bipolar illness, chronically managed on lithium, presented with altered mental status in the context of normal pressure hydrocephalus. She exhibited signs of catatonia with autonomic instability including uncontrolled hypertension and isolated episodes of tachycardia. Bush Francis catatonic rating scale score was 21, which was highly suggestive of catatonia; however, she did not respond to Ativan challenge which suggested an encephalopathy, not classical catatonia. Labs revealed apparent primary hyperparathyroidism with associated hypercalcemia and elevated PTH in the setting of longterm lithium use. Lithium was discontinued on the day of her first psychiatry consultation, and tthereafter, her serum calcium began to normalize. The patient was discharged on lamotrigine instead of lithium. This case presents a unique opportunity for the psychiatric and the greater medical community to gain awareness about lithium induced primary hyperparathyroidism. It demonstrates a need for the American Psychiatric Association to develop lithium monitoring guidelines similar to the NICE guidelines where lithium prescribing providers regularly monitor for renal disturbances and endocrinopathies, including calcium regulation (ionized calcium and intact PTH). In doing so, providers can avoid unnecessary investigation and identify lithium induced hyperparathyroidism early so as to avoid advanced hypercalcemia and its resultant medical and psychiatric sequelae.

Case Presentation

A 76-year-old white female with a history of bipolar illness, chronically managed on lithium, presented with altered mental status in the context of normal pressure hydrocephalus. This patient had a complicated hospital course. She was a poor historian and could not answer any screening questions due to apparent catatonia. She groaned during the course of the interview and did not respond to commands or painful stimuli. She exhibited signs of catatonia with autonomic instability including uncontrolled hypertension and isolated episodes of tachycardia. Bush Francis catatonic rating scale score was 21, which was highly suggestive of catatonia; however, she did not respond to Ativan challenge which suggested an encephalopathy, not classical catatonia. She required an NG tube because she stopped eating altogether. She manifested classical symptoms of normal pressure hydrocephalus, including the classic triad of altered mental status, ataxia, and urinary incontinence. She did undergo a large volume lumbar puncture without any improvement of mental status. The patient had subsequent complications during the course of her hospitalization. It was discovered she had a Klebsiella and Proteus UTI.

This was treated with Rocephin and Clindamycin. Neurology closely followed the patient and performed head imaging which was consistent with corticobasal degeneration however, those changes did not adequately explain her acute mental status change which occurred over one week. Chest x-ray revealed opacities which may have been secondary to atelectasis. She was also followed by Nephrology for progressive hypernatremia and hypercalcemia. Her sodium continued to rise as high as 154. Labs revealed apparent primary hyperparathyroidism with associated hypercalcemia and elevated PTH in the setting of longterm lithium use. Oncology was

consulted and they ruled out multiple myeloma and PTHrp secreting tumors. We discontinued lithium on the day of her first psychiatry consultation, and thereafter saw a decrease in her serum calcium levels. She was discharged on lamotrigine as an alternative to lithium therapy. As the patient was a poor historian, her husband provided the history of present of illness.

He reported her having altered mental status for 3-4 days prior to her hospital presentation with continued progressive decline since admission. She used to say a few words to him, but mostly stopped talking and eating over the past week prior to her admission. She was intermittent with following commands and mostly laid in bed all day. Her husband recalled a similar episode of altered mental status during a hospitalization several months prior. She had been treated inpatient after a hip surgery. At that time, doctors discontinued her lithium and ziprasidone with improvement in her mental status, and she was discharged home. Soon thereafter, her outpatient psychiatrist resumed lithium and ziprasidone. Her husband reported progressive decline and intermittent periods of confusion, ultimately leading up to her current hospitalization. The patient's husband reported a longstanding history of manic episodes with associated symptoms of elevated energy, decreased need for sleep, grandiosity, flight of ideas, pressure speech, goal-directed activity, and distractibility. He also reported recurrent depressive episodes dating back to 20 or 30 years ago. She was well-managed on lithium for the last 20 years. Although a rare side effect, it appears the patient developed parathyroid hyperplasia and hypercalcemia as a result of long-term lithium use.

Physical Exam

Vitals and Measurements

a) T : 37 °C (Oral) HR : 82 RR : 18 BP : 107/69 SpO2 : 96%

b) HT: 163 cm WT: 80.6 kg IBW: 55.1 BMI: 30.3

c) General: Chronically ill-appearing white female, lying in bed no distress

d) Head: Normocephalic and atraumatic

e) Eyes: Open, pupils are reactive

f) Cardiac: Regular rhythm, intermittently tachycardic, no murmur

g) Abdomen: Soft and nontender, bowel sounds hypoactive

h) Extremities: No edema

i) Lungs: No respiratory distress, lungs are clear, on room air

j) Neuro: Pupils are equal round and reactive, she is awake, cannot follow commands, she does

k) Withdraw to painful stimuli.

Mental Status Exam

a) Appearance: Disheveled

b) Behavior/Motor Activity: Psychomotor retardation

c) Musculoskeletal: Observed muscle strength/tone within normal limits

d) Gait/Station: Not observed

e) Speech: The patient only groans on occasion

f) Mood: Unknown

g) Affect: Blank stare

h) Thought Process/Associations: Unknown

i) Thought Content: Unknown

j) Cognition/Attention/Memory/Concentration: Inattentive during the interview and requires redirection

k) Insight: Impaired

l) Judgment: Impaired

m) Language: Largely mute

n) Fund of Knowledge: Unknown

Home Medications

Aspirin (81 mg oral delayed release tablet) = 1 tab, Oral, Daily

Bacillus coagulans-inulin (Probiotic Formula oral capsule), 1 cap, Oral, Daily

Ergocalciferol (50 mcg (2000 intl units) oral capsule), 100 mcg= 2 cap, Oral, Daily

Levothyroxine (75 mcg oral tablet), 1 tab, Oral, Daily, 1 refills

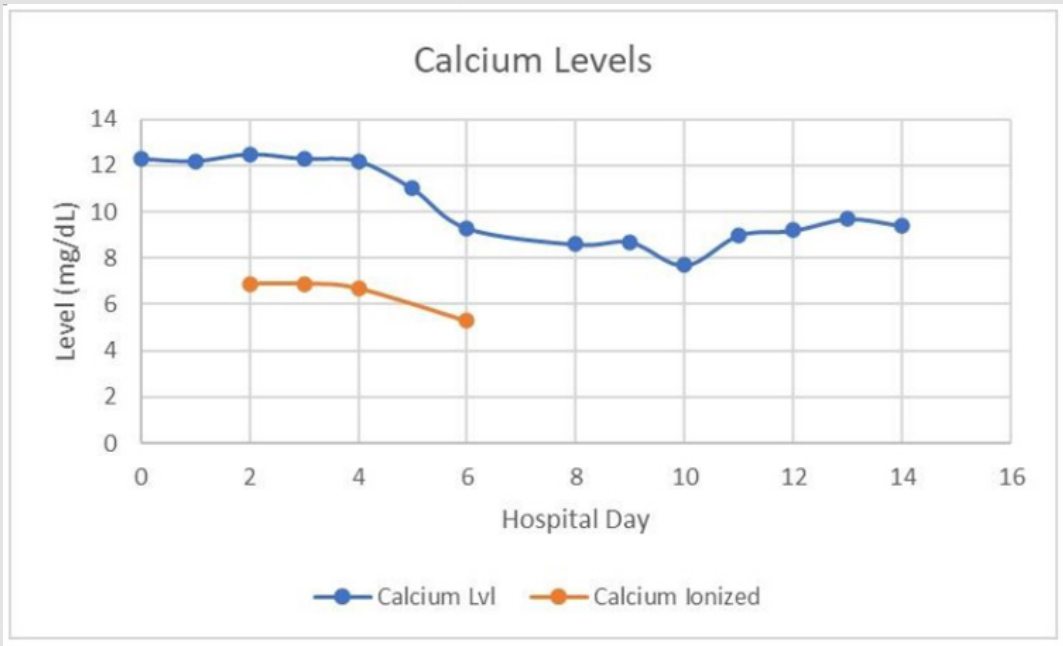
Lithium (300 mg oral capsule), 300 mg= 1 cap, Oral, BID

Simvastatin (40 mg oral tablet), 1 tab, Oral, QPM, 3 refills

Ziprasidone (80 mg oral capsule), 80 mg= 1 cap, Oral, HS

Labs

The patient's initial CBC was significant for high MCHC, low RDW, and low lymphocyte percentage. See Table 1 below for more information. The patient's CMP was significant for increased BUN, and creatinine as well as an increased calcium level of 12.3 mg/dL. The ionized calcium and PTH level were also collected and found to both be increased initially at 6.9 mg/dL and 111.1 pg/mL respectively. See Table 2 for more information. The patient's lithium was discontinued upon admission which corresponds to hospital day 0. As can be seen in the graph below, Graph 1, both calcium and ionized calcium levels significantly dropped into the normal range following lithium discontinuation.



Graph 1: Calcium Levels vs. Hospital Days.

Table 1: Patient's Initial CBC.

CBC and Diff	3
WBC (/uL)	1.08E+04
RBC (/uL)	4.69E+06
Hgb (g/dL)	12.9
Hct (%)	39.7
MCV (fL)	84.8
MCH (pg)	28
MCHC (g/dL)	32
RDW (%)	16
Platelets (/uL)	1.54E+05
MPV (fL)	8.7
Neutrophil % Auto	74.4
Lymphocyte % Auto	14.3
CBC and Diff	3
Monocyte % Auto	10
Calcium Ionized (mg/dL)	10
Eosinophil % Auto	1.1
Basophil % Auto	0.2
Absolute Neuts (/uL)	8.00E+03
Absolute Lymphs (/uL)	1.50E+03
Absolute Monos (/uL)	1.10E+03
Absolute Eos (/uL)	1.00E+02
Absolute Basos (/uL)	0

Table 2: Patient's Initial CMP with Ionized Calcium and PTH.

Routine Chemistry	
Sodium Lvl (mmol/L)	141
Potassium Lvl (mmol/L)	3.9
Chloride Lvl (mmol/L)	107
CO_2 (mmol/L)	25
Glucose Lvl (mg/dL)	95
BUN (mg/dL)	26
Creatinine Lvl (mg/dL)	1.03
Calcium Lvl (mg/dL)	12.3
Protein Lvl (g/dL)	6.9
Albumin Lvl (g/dL)	4.1
Bilirubin Total (mg/dL)	0.3
AST (unit/L)	15
ALT (unit/L)	12
Alkaline Phos (unit/L)	98
Calcium Ionized (mg/dL)	6.9
Parathyroid Hormone Lvl (pg/mL)	111.1

Discussion

Lithium therapy is a well-know and utilized treatment for bipolar disorder. It remains indicated for maintenance treatment along with acute use for its anti-manic characteristics. Although it has

been widely used since 1949, the mechanism of action as a mood stabilizer remains quite elusive. And although lithium is efficacious as a mood stabilizer, it can also produce many endocrinopathies, some of which are underappreciated. For example, lithium is known to cause Diabetes Insipidus and Hypothyroidism, but also can case Hyperparathyroidism. In a Swedish epidemiological cross-sectional study of patients who had received lithium for 15 years or more, the prevalence rate was 3.6% for persistent hypercalcemia, 2.7% for surgically verified hyperparathyroidism and 6.3% for incidence of hyperparathyroidism [1]. We should not that our case study, the patient had been taking maintenance lithium therapy for over 20 years. Calcium homeostasis is an intricate association between gut, kidneys, and bone remodeling.

Calcitriol (1, 25-dihidroxyvitamin D3) acts to enhance absorption of calcium in the small intestine and PTH induces calcium secretion from the bone and resorption from the kidneys. Calcitonin, on the other hand, normalizes hypercalcemia by inhibiting osteoclast activity and calcium resorption from the kidneys [2]. The etiology of lithium's mechanism to dysregulate calcium and hyperparathyroidism remains quite elusive. It is thought that lithium may disrupt the calcium regulating thermostat of the parathyroid gland. That is, the point at which PTH is secreted from the gland for calcium homeostasis becomes altered. More specifically, it is possible that lithium antagonizes the calcium sensor on the PTH gland itself and thus diminishes the suppression of PTH that would normally occur in the presence of serum hypercalcemia [3]. It should be also be noted that calcium homeostasis and the parathyroid glands are not directly regulated by the pituitary. That is, the gland itself is the regulator, responding to blood concentrations of calcium as its thermostat. Others have speculated that lithium may directly stimulate PTH release and in vitro studies have confirmed that lithium has stimulated PTH release from normal or hyperplastic PTH gland cells but not in adenomatous tissue [4].

It is also suggested that lithium may antagonize the calcium-sensing receptor via the inositol monophosphate pathway which results in a higher calcium level being required to suppress the parathyroid hormone release from the parathyroid gland [5]. Other mechanisms of action include lithium's proposed affect to increase calcium resorption on the renal tubules by inhibiting PTH-sensitive adenylate cyclase which may explain elevated calcium even in the context of a normal intact PTH [6]. Thus, it behooves mental health providers to include calcium level screens prior to and during lithium therapy. The National Institute for Health and Care Excellence (NICE) guidelines recommend calcium monitoring every six months for patients taking lithium in addition to renal and electrolyte monitoring [7]. If there is an elevation of calcium, an intact PTH can be subsequently drawn.

If calcium is only mildly elevated and the patient is asymptomatic with normal intact PTH, one could either discontinue lithium for an alternative mood stabilizer or re-check calcium and intact PTH in 2-6 weeks [4]. One should also screen for nephrolithiasis, osteoporosis, osteopenia, dehydration, renal impairment, and dyspepsia if hypercalcemia persists as these are common adverse effects of persistent hypercalcemia. Acute hypercalcemia can present with the classic multisystem illness known as "stones, bones, moans, and psychiatric groans." Our patient presented with altered mental status and appeared catatonic at times. Differential diagnosis of hyperparathyroidism include malignancy, sarcoidosis, milk alkali syndrome, vitamin D deficiency, increase calcium intake, lithium use, diuretic therapy, adrenal insufficiency, and thyrotoxicosis. Other tumors can also cause PTH dysregulation and include ovarian tumors, thymomas, and small cell lung cancers. One should ensure that the patient is not taking lithium or a thiazide diuretic when obtaining diagnostic studies such as serum calcium and intact PTH [8].

Treatment of lithium Induced Hypercalcemia (LIH) other than mere cessation from lithium include the calcimimetic cinacalcet. Cinacalcet acts as an allosteric agonist of the calcium sensing receptor. In the PTH glad, this acts to lower the threshold of where the gland responds to serum calcium, thus making it more sensitive to calcium and subsequently lowering PTH secretion [9]. Michael Dixon and others report on a case of LIH which was subsequently corrected with cinacalcet and unfortunately the patient continued to relapse. The decision was made to resume lithium nearly a year later subsequent to parathyroidectomy. Thus, there is some precedent for re-trial of lithium in treatment resistant cases after measures have been performed to normalize calcium [10]. In another case by Rizwan Szalat and others, lithium was continued after two gland parathyroidectomy and calcium along with PTH remained within normal limits [8]. The decision for parathyroidectomy in the setting of LIH remains somewhat controversial as the etiology of LIH is inconclusive.

There are some cases where LIH patients did undergo parathyroidectomy and some had post-surgical adenomas while others had hyperplasia with later pathological examination [11]. This has resulted in some theorizing that lithium itself can transform the parathyroid gland into a PTH-secreting adenoma. Pre-operative ultrasound followed by a sestamibi scan can assist the surgeon in determining whether the patient is a viable candidate for surgery and if the surgery ought to involve multiple PTH glands [4]. Otherwise, one could wait to see if PTH levels normalize in subsequent weeks to months after lithium discontinuation as LIH is typically reversible. Rifai and others report a case where lithium induced hyperparathyroidism took several months for the PTH levels to normalize [12]. In conclusion, our case study did present with a lithium induced hyperparathyroidism resolved with discontinuation of lithium.

Her delirium resolved and she was discharged on Lamictal as an alternative mood stabilizer. She did receive calcitonin to relieve her hypercalcemia but did not require a parathyroidectomy. Thus, for excellent patient care, I would recommend the American Psychiatric Association would develop lithium monitoring guidelines similar to the NICE guidelines where lithium prescribing providers regularly monitor for renal disturbances and endocrinopathies, including calcium regulation (ionized calcium and intact PTH). In doing so, providers can avoid unnecessary investigation and catch lithium induced hyperparathyroidism early so as to avoid advanced hypercalcemia and its medical and psychiatric complications.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2023.50.007986

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