Lithium induced hyperparathyroidism in a patient with schizoaffective disorder.

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Background

Lithium is the mainstay of treatment for many patients with Bipolar Affective Disorder given its well established effectiveness as a mood stabilising agent[1]. Its long-term use is reported to be associated with a reduced risk of suicide attempts and suicide deaths in BPAD[2].

While the need for regular monitoring of lithium levels due to a narrow therapeutic index and secondary effects on renal and thyroid function is well established, the effects of long-term lithium use on calcium haemostasis and need for regular monitoring in this patient population is less well defined.

A review of literature suggests that up to 26% of patients on long term lithium therapy have been found to demonstrate elevated calcium levels[3]. Currently no routine monitoring of calcium and parathyroid hormone levels is recommended internationally.

Undiagnosed hypercalcaemia can have long term implications on cardiovascular and bone health and should therefore be monitored more closely in patients who are prescribed lithium.

Case Presentation

A sixty four year old lady with schizoaffective disorder was admitted involuntarily under the Mental Health Act 2001 (Ireland) with a relapse of psychotic symptoms due to medication non-compliance. Pre-admission medications included lithium 600mg nocte, quetiapine XR 400mg nocte and she had been commenced on a paliperidone depot two weeks prior to admission.

She presented with persecutory delusions, believing her husband was going to kill her, that he was selling drugs in their house and was a member of the Irish Republican Army. She described mental and physical abuse from him throughout their forty years of marriage and described a pain in her head whenever she thought of him. There was associated sleep disturbance with the patient sometimes feeling too anxious to sleep for days at a time when her husband was in the house. She denied any depressive or manic symptoms.

Past medical history was significant for hypertension, a stroke twenty years previously (from which the patient had made a full recovery) and hypothyroidism. The patient was admitted and re-commenced on regular medications.

On physical examination she was noted to be constipated with abdominal distension but denied any other physical symptoms

Investigations

Admission bloods:

- Hypercalcaemia - 2.94mmol/L (2.15-2.55 mmol/L)
- Raised corrected calcium - 2.96 mmol/L (2.15- 2.55mmol/L)
- Remaining bloods including TFTs were normal
- Lithium level was 0.84mmol/L (within therapeutic range)

A further review of symptoms revealed constipation and generalised fatigue but she denied other physical symptoms of hypercalacemia including thirst, nausea, loss of appetite, urinary symptoms suggestive of renal calculi and nausea.

Parathyroid hormone level was elevated at 137 pg/mL (15-65 pg/ml) thus pointing towards primary hyperparathyroidism likely secondary to long term lithium use.

A Sestamibi scan was ordered to ascertain if there was a single parathyroid adenoma which could then be surgically removed. The Sestamibi scan was negative for a functioning parathyroid adenoma.

After discussion at the Endocrinology MDT, a Parathyroid CT scan was performed which showed an 8mm x 5mm nodule posterior to the right lobe of thyroid in the tracheoesophageal groove with features suggestive of a parathyroid adenoma.
Daily calcium monitoring showed persistently elevated corrected calcium levels ranging from 2.73 mmol/L to 3.01mmol/L despite adequate oral hydration of 2-3L of water/day

Treatment

Initially the patient was advised to increase her oral hydration in order to reduce calcium levels which were monitored daily. A decision was made by the Psychiatry team, following discussion with Endocrinology to cease Lithium therapy while in hospital due to persistently raised calcium levels despite adequate hydration.

Following cessation of lithium, the patient displayed some hypomanic symptoms on the ward including a reduced need for sleep, reporting to be in love with a fellow male patient on the unit and feeling an increased sexual drive.

She was commenced on sodium valproate with good clinical response. Due to persistently raised calcium and cessation of lithium therapy, the patient was commenced on Cinacalcet, a calcimimetic under the supervision of Endocrinology and referred onto ENT surgeons for consideration of resection of the parathyroid adenoma. Following discussion with the surgical team regarding the potential risks of resection including damage to the recurrent laryngeal nerve and bleeding, the patient opted for medical management.

Authors/ Declarations

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Written informed consent has been obtained by the authors from the patient for publication of this case report.

Discussion

Once an elevated calcium level is found, how should the Psychiatrist proceed?

Firstly, it is important to establish symptoms and determine if the patient needs immediate treatment in the form of IV hydration +/- bisphosphonates[4]. Symptoms of hypercalcaemia include urinary (polyuria and polydipsia), gastrointestinal (nausea, vomiting and constipation), musculoskeletal (bone pain and muscle weakness) and neurological (low mood, lethargy and fatigue).

It is then necessary to establish the underlying cause of hypercalcaemia. Approximately 90% of hypercalcaemia is caused by hyperparathyroidism and malignancy[5]. A repeat serum calcium should be sent along with a parathyroid hormone level.

Under normal physiological conditions, PTH is secreted by the parathyroid gland in response to hypocalcaemia. This response occurs within seconds to minutes. PTH then acts on the skeletal and renal systems to increase serum calcium through various mechanisms. Conversely, the normal physiological response to hypercalcaemia is to suppress parathyroid hormone production. Therefore, an inappropriately normal or raised parathyroid hormone in the context of hypercalcaemia is indicative of hyperparathyroidism.

In the case of lithium induced hypercalcaemia, one would expect to find a raised parathyroid hormone as was the case with this patient. Lithium induced hypercalcaemia is thought to occur due to its mechanism of action on the parathyroid gland. The exact mechanism of this action of lithium is poorly defined, however there are several hypotheses. These include an increased threshold of the calcium sensing receptor within the parathyroid gland and therefore a decreased sensitivity of the parathyroid glands to calcium[6], a decrease of intracellular calcium uptake, increase of PTH, inhibition of action of glycogen synthase kinase 3b and reduction of PTH gene transcription[7].

Once lithium associated hyperparathyroidism is diagnosed, the management is determined based on patient's symptoms. In this case, lithium cessation did not cause a reduction in calcium levels alone as the patient was found to have a functioning parathyroid adenoma driving hypercalcaemia independently of lithium therapy. As such, surgery is considered the definitive cure.

Current Maudsley, NICE and international guidelines do not recommend regular monitoring of calcium levels in patients on long term lithium therapy focusing instead on maintaining therapeutic levels and monitoring for renal and thyroid secondary effects[10, 11].

Learning Points

- Clinicians should consider routine monitoring of calcium levels in patients on long-term lithium therapy
- Hypercalcaemia may go undetected in these patients due to non-specific symptoms and have potential serious long-term sequelae on cardiovascular and bone health.
- Although symptoms can be non-specific, is important to screen for symptoms of hypercalcaemia in patients on long term lithium therapy, to include reduced appetite, nausea, constipation, increased thirst, fatigue and weakness.
- This case and review of the literature indicates that there is a role for including guidelines for monitoring Calcium and Parathyroid hormone among patients on lithium. This is likely to result in the earlier identification and reduced morbidity from longstanding undetected hypercalcaemia.

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