CLINICAL VIGNETTE

Bipolar Patient Presenting with Lithium-Induced Hyperparathyroidism Following Years of Lithium-Induced Hypothyroidism

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Case Presentation

A 39-year-old female with history of Bipolar disorder type 1, initially presented to endocrinology 9-years ago with sub-clinical hypothyroidism thought to be lithium-induced. She was referred by her psychiatrist who was concerned her thyroid function was fluctuating over time from normal to slightly elevated TSH 5.0-8.0 U/ml (normal range 0.5-4.5 U/ml). On initial exam, she appears calm, with stable vitals. She had an enlarged thyroid gland without palpable nodules, a bilateral hand tremor pronounced when holding a pen, but otherwise had a normal physical exam. Her psychiatrist had started her on levothyroxine 25mcg daily with concern that she was going to develop overt hypothyroidism, as well as to see if it would help her depression she was having between manic episodes. She did well on low dose levothyroxine 25mcg daily over the course of the first 5 years of follow-up, until her TSH suddenly became suppressed below <0.5 U/ml. She was re-hospitalized for a manic episode, and at that time her levothyroxine was discontinued due to concerns that continued use would lead to more episodes of uncontrolled mania. She was monitored twice a year for possible recurrence of her lithium-induced thyroiditis. Her TSH continued to remain in the normal range from 1.5-4.0 U/ml without thyroid replacement. Repeated checks show absence of antithyroid antibodies.

Her lithium dose was maintained at 600mg twice daily the entire 9-years and she was able to function between manic episodes, including working and going to school part-time. However approximately 1-year ago, her labs showed elevated calcium levels of 10.4-10.8 mg/dl. Patient denied taking calcium supplements or antacids. Work up for multiple myeloma was negative with normal expected values for SPEP and UPEP. Her PTH-rp level was undetectable. Vitamin D25 OH levels were normal at 29 ng/dl and her magnesium level was 2.1 mg/dl. An intact PTH showed elevated parathyroid hormone level of 92 pg/ml and on repeat 71 pg/ml (normal 15-65 pg/ml). She had normal kidney function.

The conclusion was she had hyperparathyroidism, with a question of if it was spontaneous primary hyperparathyroidism or lithium-induced. Twenty-four hour urine calcium collection was 180.0 mg/24 hours which is in the normal range (100-300 mg/24 hours) which ruled Familial hypocalciuric hypercalcemia (FHH). Her DEXA showed normal bone density. Clinic ultrasound did show a parathyroid adenoma, and the thyroid gland was enlarged to 1.5 times normal size heterogeneous without distinct thyroid nodules. Given the large size of the thyroid gland which can make identifying para-thyroid adenomas difficult, I forgoed the traditional nuclear medicine sestamibi scan in favor of the more sensitive 4D-CT parathyroid scan that we do at UCLA. The CT parathyroid scan did not show any candidate parathyroid adenomas.

The patient denies abdominal pain, chest pain or palpitations. She noted more polyuria than the past and more muscle and joint pains in the past year. Kidney ultrasound was negative for renal calculi and she had no nephrogenic diabetes insipidus or lithium associated nephropathy. Her psychiatrist had briefly lowered her lithium dose over the years but she had developed more manic episodes and he wanted to keep her on the current dose.

Patient is followed every 2-3 months and continues to have mildly elevated calcium levels no higher than 10.8 mg/dl but can be as low as 9.0 mg/dl at times. She asked to be monitored but is open to future surgery if necessary.

Discussion

Lithium is commonly used for bipolar disorder and is thought to be the "gold standard" for treatment. Due to the toxicities associated with it, prescription rates have been recently decreasing in favor of less toxic alternatives.[1] The most common side effects are polyuria, polydipsia, tremor, weight gain, and cognitive impairment. With long-term use of lithium, nephropathy, hypothyroidism or thyroiditis, and hyperparathyroidism can occur. This patient, initially showed the hypothyroidism and goiter followed by the hyperparathyroidism and hypercalcemia, but has not developed nephropathy.

Lithium-induced hypothyroidism is a common side effect. The mechanism is thought to be due to inhibition of thyroid hormone release from the thyroid, as well as decreased iodine trapping in the gland and inhibition of the synthesis of thyroid hormone.[2] Goiters can form just as they form for other causes of hypothyroidism. The thyroid grows to compensate for the reduction of thyroid synthesis and release. Overt hypothyroidism has estimated prevalence of 8-19% of patients on lithium, while up to 23% can have subclinical hypothyroidism.[3]

Our patient never had a TSH >10 U/ml, and was thus categorized in the subclinical hypothyroid phase. Treatment of subclinical hypothyroidism is recommended in patients with refractory depression, which would justify treatment.[3] Patients with subclinical hypothyroidism can also be monitored if they are asymptomatic. This patient was tried on low dose levothyroxine but became hyperthyroid on the low levothyroxine dose. Usually patients who stop lithium have resolution or improvement of their lithium-induced hypothyroidism. However it is a general rule to not stop lithium treatment if it is effective in treating the bipolar disorder and to monitor and/or treat the hypothyroidism.

A less common side-effect from long term lithium is hyperparathyroidism. In our patient, the subclinical hypothyroidism improved over time, but she later developed hypercalcemia which increased her polyuria with muscle and joint pains. Lithium causes a shift in the inhibitory set point for PTH secretion to a higher calcium concentration, by antagonizing the calcium sensing receptor, thus resulting in a higher than normal calcium level to suppress serum PTH.[4]

Unlike lithium-induced hypothyroidism, in which discontinuation of lithium often leads to improvement of the hypothyroidism, patients with lithium-induced hyperparathyroidism may have persistent hypercalcemia, months and even years after the lithium has been discontinued.[4] Some but not all patients develop hypercalcemia from lithium, and some association factors that may include prior thyroid disease, longer duration of use of lithium, and higher dose.[5] If hypercalcemia becomes severe, leading to cardiac, kidney, and bone effects, surgery with parathyroidectomy is recommended. Discontinuation or reduction of lithium dose may not be feasible in patients who have stable bipolar disorder on lithium. In general, patients with lithium-induced hyperparathyroidism have a higher prevalence of mutli-gland involvement or 4-gland hyperplasia than those with sporadic hyperparathyroidism.[4] Subtotal parathyroidectomy in which 2 or more parathyroids are removed may be necessary to prevent recurrence especially if patient is to continue on lithium treatment.[6] Some patients who want to avoid surgery but must continue lithium treatment, may be candidates for cinacalcet medical therapy.[7] Cinacalcet is a calcimimetic which lowers the threshold for activation of the calcium-sensing receptor by extracellular calcium, thus leading to decreased PTH secretion by the parathyroid glands. It is not widely used for hyperparathyroidism caused by lithium, since symptomatic patient are recommended for surgery, but it is an interesting option that we also use for non-surgical patients who have spontaneous primary hyperparathyroidism.

Educational points in this case include that long-term use of lithium often leads to toxicities that can affect kidneys, thyroid, and parathyroid glands. Thyroid disease is very common, and the resulting overt hypothyroidism or symptomatic subclinical hypothyroidism can be treated with levothyroxine replacement while allowing the patient to continue lithium treatment. There is no urgency to treat patients with subclinical hypothyroidism, and testing thyroid function in 3-month intervals is reasonable and may be a safer alternative than risking hyperthyroidism by prescribing levothyroxine to patients prone to manic episodes. The parathyroid disease from lithium-induced hyperparathyroidism can lead to enlarged parathyroid adenoma or adenomas as in spontaneous primary hyperparathyroidism. The hypercalcemia caused by lithium-induced hyperparathyroidism may not resolve with discontinuation of lithium or reduction of lithium dose. It may be necessary to pursue parathyroidectomy, frequently subtotal rather than removal of just 1 parathyroid to avoid recurrence as many patients need to stay on lithium for life. The dilemma is that not every patient on lithium develops the same toxicities, to the same degree, and thus there is no single treatment and each case must be considered carefully.

REFERENCES

1. **Gitlin M.** Lithium side effects and toxicity: prevalence and management strategies. *Int J Bipolar Disord.* 2016 Dec;4 (1):27. Epub 2016 Dec 17. Review. PubMed PMID: 27900734; PubMed Central PMCID: PMC5164879.
2. **Lazarus JH.** Lithium and thyroid. *Best Pract Res Clin Endocrinol Metab.* 2009 Dec;23(6):723-33. doi: 10.1016/j.beem.2009.06.002. Review. PubMed PMID: 19942149.
3. **Kleiner J, Altshuler L, Hendrick V, Hershman JM.** Lithium-induced subclinical hypothyroidism: review of the literature and guidelines for treatment. *J Clin Psychiatry.* 1999 Apr;60(4):249-55. Review. PubMed PMID: 10221287.
4. **Szalat A, Mazeh H, Freund HR.** Lithium-associated hyperparathyroidism: report of four cases and review of the literature. *Eur J Endocrinol.* 2009 Feb;160(2):317-23. doi: 10.1530/EJE-08-0620. Epub 2008 Nov 10. Review. Pub Med PMID: 19001061.
5. **Meehan AD, Udumyan R, Kardell M, Landén M, Järhult J, Wallin G.** Lithium-Associated Hypercalcemia: Pathophysiology, Prevalence, Management. *World J Surg.* 2018 Feb;42(2):415-424. doi: 10.1007/s00268-017-4328-5. PubMed PMID: 29260296; PubMed Central PMCID: PMC5762804.
6. **Hundley JC, Woodrum DT, Saunders BD, Doherty GM, Gauger PG.** Revisiting lithium-associated hyperparathyroidism in the era of intraoperative parathyroid hormone monitoring. *Surgery.* 2005 Dec; 138(6): 1027-31; discussion 1031-2. PubMed PMID: 16360387.
7. **Sloand JA, Shelly MA.** Normalization of lithium-induced hypercalcemia and hyperparathyroidism with cinacalcet hydrochloride. *Am J Kidney Dis.* 2006 Nov;48(5):832-7. PubMed PMID: 17060004.

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