Hyperparathyroidism Resulting From Lithium Treatment Remains Underrecognized

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Until recently, I never paid much attention to the possibility that abnormalities of the parathyroid glands could be relevant to patients in my practice. But I decided to learn more about this issue when one of my patients with bipolar disorder who had been treated with lithium told me that she had been given a diagnosis of a parathyroid adenoma after her primary care physician noted hypercalcemia on routine testing.

Since undergoing successful surgery to remove the adenoma, she is feeling much sharper mentally and more energetic.

Lithium continues to be the gold standard for the treatment of bipolar disorder. It is also helpful for related diagnoses, such as schizoaffective disorder and cyclic major depression. In addition to watching out for the well-known complications of lithium treatment—hypothyroidism and decreased renal function—health care providers should be aware of hyperparathyroidism.

Development of Hyperparathyroidism
The parathyroid glands are 4 small structures located on the posterior surface of the thyroid gland, which monitor calcium levels in the blood and release parathyroid hormone (PTH). PTH is a peptide that acts to increase the concentration of calcium in the blood by enhancing the release of calcium from bones. In addition, PTH acts on the kidneys to increase active reabsorption of calcium from distal tubules as well as to increase the excretion of phosphate, also leading to more free calcium in circulation. Finally, PTH raises calcium levels by increasing the production of activated vitamin D, which enhances absorption of calcium by the intestine.

Primary hyperparathyroidism usually results from an adenoma in a single gland, although other causes may be double adenoma or hyperplasia in multiple glands. Previous exposure to radiation in the facial or neck area and certain medications, including thiazide diuretics, may cause primary hyperparathyroidism. In some families, the disease may be inherited. Parathyroid cancer is an extremely rare cause of primary hyperparathyroidism.

Secondary hyperparathyroidism results from any medical condition that causes low calcium levels. This is most often due to kidney failure and the consequent rise in phosphate levels. Vitamin D deficiency is another possible cause.

The lithium connection. It turns out that lithium, a mainstay in the treatment of bipolar disorder, is associated with an increased incidence of hyperparathyroidism. Approximately 15% to 20% of patients receiving long-term lithium treatment show elevated calcium levels, although only a few of these patients also have significant elevations of PTH levels and clinical symptoms of hyperparathyroidism. Interestingly, lithium-associated clinical hyperparathyroidism is almost always caused by a single parathyroid adenoma rather than 4-gland hyperplasia.1

The first case of lithium-associated hyperparathyroidism (LAH) was reported in 1973,2 and many additional reports followed. It appears that longer duration of treatment is associated with an increased incidence of LAH.3 Curiously, about 75% of patients receiving lithium in whom LAH develops are women, which is consistent with the overall higher prevalence of hyperparathyroidism in women and unlike the gender-neutral ratio typical of bipolar disorder and lithium use.4 Rather than considering the cessation of lithium treatment when LAH is discovered, which may or may not reverse the calcium and other abnormalities, the usual procedure is to surgically intervene and remove the offending parathyroid glands.

Effects of Hyperparathyroidism
When a parathyroid gland enlarges and produces too much PTH, the blood calcium level becomes high, bones may lose calcium, and kidneys may excrete too much calcium. These changes may give rise to symptoms and signs such as polyuria, thirst, fractures, and kidney stones. Neuropsychiatric symptoms associated with primary hyperparathyroidism include anxiety as well as cognitive and psychotic presentations. However, the most common presentation is depression with associated apathy. In a prospective study of 34 patients with hyperparathyroidism, Velasco and colleagues found that approximately one-third of participants had no psychiatric symptoms, one-third had affective symptoms (with or without paranoia), and one-third had cognitive impairment. Affective symptoms were most common in patients with modest elevations in electrolyte levels, while cognitive deficits were more often related to higher calcium concentrations. **Hypercalcemia.** The severity of psychiatric symptoms in patients with hyperparathyroidism often correlates with the increase in serum calcium levels. Calcium performs a crucial role in nerve conduction. Consequently, it is no surprise to find out that some common symptoms of parathyroid hyperactivity and high calcium levels are related to the nervous system. Other symptoms have to do with the muscular system, which uses changes in intracellular calcium concentration to initiate and transmit the command to contract muscle fibers. Improper regulation of calcium levels may result in muscle cramps and weakness. The heart is a muscle, and therefore its conduction system is also vulnerable, with possible shortening of the QT interval, rhythm disturbances, and even cardiac death. The skeletal system not only functions as the reservoir of calcium for the body, but calcium phosphate is an essential ingredient of bone tissue. Consequently, a hyperactive parathyroid system contributes to osteoporosis and vulnerability to bone fractures. When hypercalcemia is present, it is important not only to screen for hyperparathyroidism but also to rule out other possible underlying conditions, such as malignancy and drug-induced elevations in calcium levels. **Case Note**

Already, early in the process of screening for elevated calcium levels in my many patients who are receiving lithium, I have identified a patient with hypercalcemia and a markedly elevated PTH level, which may indicate hyperparathyroidism. She is a 50-year-old woman with schizoaffective disorder who has been receiving long-standing lithium therapy and is undergoing further evaluation by an endocrinologist. All of us are hopeful that her recent cognitive decline and mental apathy will prove to be reversible.

**References:**

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