CLINICAL VIGNETTE

Familial Hypocalciuric Hypercalcemia

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Case Report

A 38-year-old male with history of Vitamin D deficiency and hypertension, presented with concerns about vitamin D and parathyroid hormone levels. The patient had seen an outside provider 2 years prior and was diagnosed with severe vitamin D deficiency. He was also told that his parathyroid hormone level was elevated. He was started on Vitamin D supplementation and did not follow up until he presented to our office. The patient was taking losartan 100 mg daily for blood pressure control and Vitamin D3 5000 International Units daily. Physical exam was normal as were vital signs. Initial labs revealed a Vitamin D level of 33 and Calcium 9.1. Intact Parathyroid Hormone (iPTH) level was slightly elevated at 57 pg/ml (normal 11-51 pg/ml). Labs were repeated on subsequent visit and iPTH was still elevated at 58, with Vitamin D level of 26 and Calcium of 10.0.

The patient was referred to endocrinology. Repeat iPTH level was elevated at 65, along with Vitamin D level of 35 and Calcium level of 10.0. PTH related hormone was normal at 14 pg/ml. A 24 hour urine revealed normal Calcium excretion of 201 mg/24 hours (normal 0-300 mg/24 hours).

Discussion

Familial hypocalciuric hypercalcemia (FHH) is a benign cause of hypercalcemia that involves inactivating mutations of calcium sensing receptor.[1] It has an autosomal dominant inheritance pattern with high penetrance.[2] These mutations lead to fewer normal calcium-sensing receptors on the parathyroid or renal cell. As a result, the kidneys increase the tubular reabsorption of calcium and magnesium, and the parathyroid glands become less sensitive to calcium and requires higher level of calcium concentration to decrease PTH release.[3] This leads to hypercalcemia, hypocalciuria, and high normal or elevated magnesium levels.

In patients with FHH, hypercalcemia is typically mild and serum parathyroid hormone (PTH) concentration is typically inappropriately normal or mildly elevated. They typically do not exhibit signs and symptoms of hypercalcemia such as acute kidney injury, constipation, polyuria, confusion, nausea, abdominal pain, and bone pain. However, possible associations with pancreatitis, chondrocalcinosis and gallstones have been reported.[2,4]

Given most cases of FHH are benign and do not need parathyroidectomy, as in the cases of primary hyperparathyroidism, it is important to distinguish FHH from primary hyperparathyroidism. In general, urinary calcium excretion is typically less than 200 mg/day (or calcium/creatinine clearance ratio < 0.02) in patients with FHH and higher than 200 mg/day (or calcium/creatinine clearance ratio > 0.02) in patients with primary hyperparathyroidism. Around 80 percent of patients with FHH, the calcium/creatinine clearance ratio is less than 0.01.[5] During evaluation of patients with hypocalciuria where FHH is suspected, it is important to consider other conditions that can cause hypocalciuria, such as mild renal insufficiency, vitamin D deficiency, low calcium intake, and certain medication use such as thiazides or lithium.

Despite these differences, sometimes differentiating FHH and primary hyperparathyroidism can be difficult when they present in an atypical way. Approximately 10 percent of patients with primary hyperparathyroidism can have hypercalcemia with upper normal serum PTH concentration.[6] Some patients with primary hyperparathyroidism can also have calcium/ creatinine clearance ratio of < 0.01, especially if they have concurrent vitamin D deficiency.[7] In these atypical cases, especially in patients with urinary calcium/creatinine clearance ratio between 0.01 and 0.02, mutational analysis of calcium sensing receptor can be helpful, although it is by no means perfect due to different possible mutations.[5] Some clues that can be helpful in identifying patients with FHH include family history of hypercalcemia with hypocalciuria, and family members with hypercalcemia who underwent unsuccessful parathyroid surgery. It is also worthwhile to test the serum and urinary calcium in several first degree relatives.

Patients with FHH should be counseled on the benign nature of the disorder and to avoid invasive interventions such as parathyroid surgery. Effort should also made to identify the affected family members and counsel them as well.[8] Sometimes calcimimetics such as cinacalcet have been used to reduce the serum calcium concentration in FHH patients with possible symptoms of hypercalcemia and or serum calcium level > 1 mg/dL than the upper limit of normal.[9]

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