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CASE REPORT

An Unusual Case of Hypercalcemia Associated with Graves' Disease and Vitamin D Deficiency

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Abstract:

Objective: To present a case of hypercalcemia associated with thyrotoxicosis in a patient with vitamin D deficiency and review biochemical changes during the course of treatment.

Methods: We report a case, describe the changes in serum calcium, phosphorus, parathyroid hormone in Graves' disease and concomitant Vitamin D deficiency. We compare our findings to those reported in literature.

Results: Our patient had hypercalcemia secondary to thyrotoxicosis alone, which was confirmed by low parathyroid hormone level and resolution of hypercalcemia with treatment of thyrotoxicosis. The case was complicated by a concomitant vitamin D deficiency. Serum calcium elevation in patients with thyrotoxicosis occurs secondary to hyperthyroidism alone or due to concurrent hyperparathyroidism. Hypercalcemia from thyrotoxicosis is usually asymptomatic and is related to bone resorption. Vitamin D deficiency can be seen in patients with thyrotoxicosis because of accelerated metabolism, poor intestinal absorption and increased demand during bone restoration phase. Coexistence of hypercalcemia and Vitamin D deficiency in patients with thyrotoxicosis is rare, but possible, and 25-hydroxyvitamin D levels should be checked. The definite treatment for hypercalcemia in thyrotoxicosis is correction of thyroid function.

Conclusion: Hypercalcemia in thyrotoxicosis should be distinguished from concomitant hyperparathyroidism and confirmed by resolution of hypercalcemia with control of thyrotoxicosis. Patients with hypercalcemia and thyrotoxicosis may also have vitamin D deficiency and 25-OH Vitamin D levels should be checked.

Keywords: hypercalcemia, thyrotoxicosis, vitamin D deficiency

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Introduction

Hypercalcemia occurs in association with hyperthyroidism alone or due to concurrent hyperparathyroidism. Asymptomatic serum calcium elevation has been documented in up to 20% of patients with hyperthyroidism and is related to increased bone resorption.[1] We describe a case of hypercalcemia related to thyrotoxicosis and in the presence of vitamin D deficiency.

Case Report

A 34 year old male presented with weight loss of over 35 pounds within 6 months. He also complained of hand tremor, increase in number of bowel movements, and heat intolerance. His family history was significant for hyperthyroidism in two sisters. Physical exam revealed tachycardia, presence of lid lag, warm skin, and increased deep tendon reflexes. His thyroid gland was enlarged and had a bruit. Pertinent laboratory values included a TSH of 0.012 mIU/L (normal, 0.4 to 4.5) with a free T4 of 7.85 ng/dL (normal, 0.8 to 1.8) and a free T3 of over 2000 pg/dL (normal, 230 to 420). Thyroid stimulating immunoglobulins (TSI) and thyroid peroxidase (TPO) antibodies were elevated (TSI-285 (normal $<$ 125% baseline), and TPO antibodies $>$ 1000 IU/mL (normal $<$ 35 IU/mL)). Thyroid uptake and scan revealed diffusely increased homogeneous uptake throughout the thyroid gland, which was calculated to be 41.5% at 24 hours and is consistent with Graves' disease. Patient's serum calcium was 11.4 mg/dL (normal, 8.6–10.2) with a normal albumin and serum phosphorus of 5.7 mg/dL (normal, 2.5–4.5). The iPTH level was 5 pg/mL (normal, 10–65), and the 25-OH vitamin D was 11 ng/dL (normal, $>$30). Serum alkaline phosphatase was 184 U/L (normal, 40–115). His 24-hour urine calcium was 571 mg/24 hrs (normal $<$ 300 mg) with normal creatinine. Patient's blood urea nitrogen was 13 mg/dl (normal, 7–25), serum creatinine was 0.75 mg/dl (normal, 0.79–1.33), and he had a normal estimated glomerular filtration rate of 95 ml/min per 1.73 m^2. Therapy with methimazole and atenolol successfully controlled sympathetic symptoms. Four months later, while off of methimazole, the patient underwent treatment with I–131. When he became euthyroid, the calcium level normalized to 9.9 mg/dL and his phosphorus normalized to 3.5 mg/dL. His Vitamin D was repleted with normalization of serum levels. (Fig. 1).

Discussion

The most common cause of hypercalcemia in thyrotoxicosis is concurrent primary hyperparathyroidism. In 15%–20% of cases however, alterations of calcium metabolism are related to the thyrotoxicosis alone.[1] Our case illustrates hypercalcemia secondary to thyrotoxicosis alone, as supported by low parathyroid hormone (PTH) level and resolution of hypercalcemia with treatment of the thyroid disease. A linear correlation exists between serum calcium levels and parameters of thyroid function, which becomes more pronounced in the age group greater than 60 years.[2] Hypercalcemia in thyrotoxicosis is typically asymptomatic, with calcium levels rarely exceeding 12 mg/dl.[3]

The intestinal absorption of calcium is usually low in thyrotoxicosis. Similarly, renal tubular calcium reabsorption is reduced, leading to hypercalcuria, as seen in this patient.[4] The proposed mechanism of hypercalcemia is enhanced bone resorption, unrelated to the PTH levels.[1,5] High circulating levels of interleukin (IL)-6 seen in hyperthyroidism stimulate bone osteoclastic activity and alter the osteoblast-osteoclast coupling.[6] Triiodothyronine (T3) is known to increase the sensitivity of the bone to IL-6.[3] The hyperadrenergic state of thyrotoxicosis is also implicated in hypercalcemia. Alpha-adrenergic stimulation leads to hypercalciuria and beta-adrenergic stimulation on the bone results in hypercalcemia.[7]

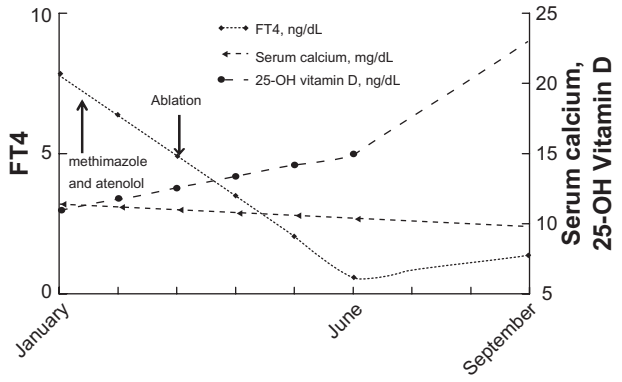

Figure 1. Time course of serum calcium, free thyroxine (FT4) and 25-OH vitamin D levels. The arrows pointing at the free thyroxine curve indicate treatment with methimazole and atenolol and subsequent treatment with I-131.

The PTH levels in hypercalcemia of thyrotoxicosis are either suppressed or low normal. The increased metabolic clearance rates in thyrotoxicosis could also lower the PTH levels.[8] Hyperthyroidism causes hyperphosphatemia by augmenting tubular reabsorption of phosphate regardless of PTH levels.[9,10] A study on 25 untreated hyperthyroid patients by Jastrup et al showed low 1,25-$(OH)_2$ vitamin D levels with normal 25-OH vitamin D. This could be explained by reduced 1-α-hydroxylase activity secondary to hypercalcemia, suppressed PTH and hyperphosphatemia.[5] Our case is unusual because of the presence of hypercalcemia with concomitant vitamin D deficiency.

Undiagnosed vitamin D deficiency is common and 25-OH vitamin D levels are accurate indicators of the vitamin D status. 1,25-$(OH)_2$ vitamin D levels are variable and do not consistently represent vitamin D status. In vitamin D deficiency only about 10% of dietary calcium and 60% of phosphorus is absorbed.[11] With levels less than 30 ng/dl, the intestinal calcium absorption is significantly impaired, which leads to increase in PTH, activation of the conversion of 25-OH vitamin D to 1,25-$(OH)_2$ vitamin D, and the subsequent increase in the intestinal calcium absorption to 30% and phosphorus to 80%.[11,12] In our patient, hypercalcemia from thyrotoxicosis caused suppression of PTH levels, despite coexisting vitamin D deficiency. Patients with secondary hyperparathyroidism from vitamin D deficiency usually have increased renal tubular calcium reabsorption and phosphaturia, leading to low or low-normal serum phosphorus.[13–15] Our patient, on the contrary, presented with hyperphosphatemia, hypercalcemia and hypercalciuria, despite being vitamin D deficient. It is important to check magnesium levels in this situation, because the compensatory increase in PTH does not occur in hypomagnesemia, even when the 25-OH vitamin D levels fall below 20 ng/dl.[16]

Thyrotoxicosis is less commonly recognized as an acquired cause of vitamin D deficiency, which can persist for several months following the treatment of hyperthyroidism. Low 25-(OH) vitamin D levels, less than 30 ng/dl, can be seen in hyperthyroid patients.[14] Vitamin D metabolism is accelerated up to eight times in thyrotoxic patients, when compared to euthyroid controls.[17] Intestinal vitamin D absorption is decreased in a few hyperthyroid patients secondary to rapid transition time of food, malabsorption and diarrhea.[18] In addition, vitamin D deficiency may be induced in some patients with Graves' disease after treatment with anti-thyroid drugs, which is due to the increased demand for vitamin D and calcium during bone restoration.[19]

The definitive treatment for hypercalcemia in thyrotoxicosis is correction of underlying thyroid disease. Beta-blockers may also reduce serum calcium with or without affecting renal calcium metabolism.[7,20] It is important to also monitor the vitamin D levels while treating hyperthyroidism. Treatment of vitamin D deficiency with calcidiol, despite the presence of hypercalcemia, has been shown to be beneficial.[21] It is thus seen from our case that the complex concurrence of thyrotoxicosis, hypercalcemia and vitamin D deficiency is uncommon, but possible.

Conclusion

Hypercalcemia in thyrotoxicosis should be distinguished from concomitant hyperparathyroidism and confirmed by resolution of hypercalcemia with control of thyrotoxicosis. Patients with hypercalcemia may also have vitamin D deficiency and 25-OH vitamin D levels should be checked.

Disclosure

All authors had access to the data and a role in writing the manuscript. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. No financial support was used for this article. The authors confirm that they have permission to reproduce any copyrighted material.

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