Hypocalcemia Following Treatment with Radioiodine in a Child with Graves' Disease

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Background: Hypocalcemia is a rarely recognized complication of ¹³¹I therapy that has been previously reported in only one child with Graves' disease treated with radioiodine (RAI). Here we report a second child with this occurrence.

Patient Findings: A 12-year-old African American girl with hyperthyroidism due to Graves' disease and moderate persistent asthma, requiring oral prednisone, was treated with 11.1 mCi of RAI. While normocalcemic initially, the patient developed symptomatic hypocalcemia (6.6 mg/dL), within 3 months postablation. Concomitant findings included hyperphosphatemia, an inappropriately normal parathyroid hormone (PTH) level, vitamin D deficiency, and normal axial bone mineral density. After 2 weeks of treatment with calcium and calcitriol the symptoms of hypocalcemia resolved, and the calcium level returned to normal. PTH levels remained within the reference range throughout.

Summary: In this child with Graves' disease, who was normocalcemic on presentation, RAI treatment was followed by compromised function of the parathyroid glands which was sufficient to produce symptomatic hypocalcemia. It is noteworthy and likely pertinent that the patient had a background of vitamin D deficiency and was receiving prednisone for asthma.

Conclusion: Patients scheduled to receive ¹³¹I should be evaluated for risk factors for hypocalcemia in order to minimize the likelihood of this potentially serious complication.

Introduction

HYPOCALCEMIA DUE TO HYPOPARATHYROIDISM following thyroidectomy for various etiologies, including Graves' disease, goiter, and thyroid cancer, is well described in the literature with a prevalence of up to 7.6% (1). On the other hand, hypocalcemia, either transient or permanent, following radioiodine (RAI) for Graves' disease or thyroid cancer (2–11) has been rarely described in case reports of adults and in only one report in 1952 of a teenage boy following RAI for Graves' disease (2). Vitamin D is essential for the absorption of dietary calcium and phosphorus in the gastrointestinal tract to maintain bone health and other functions. Vitamin D deficiency in children is receiving increased attention (12), and is a recognized predisposing factor for hypocalcemia following thyroidectomy in adults (13). The case presented here illustrates the importance of evaluation of vitamin D status in at-risk patients, especially children, who are scheduled to receive RAI.

Patient

A 12-year-old African American girl was found to have a goiter during an evaluation for asthma. Her total thyroxine

(T4) level was elevated at 23.4 mcg/dL (301 nmol/L) with a normal range 4.5–12.0 mcg/dL, and she was referred for an endocrine evaluation. She had asthma diagnosed at age 10 years, with frequent exacerbations requiring repeated courses of oral steroids. She had an aunt with Graves' disease. She presented with classic symptoms of hyperthyroidism of 4 month's duration, including nervousness, poor concentration, tremors, headaches, and heat intolerance, diarrhea, and weight loss of 10 lbs with increased appetite. She weighed 40 kg (25th percentile) and was 152 cm tall (50th percentile) and had a sexual maturity rating of Tanner 3. The heart rate was 150/min, blood pressure was 110/56 mmHg and respirations were 24/min. She had a symmetrical, firm, nontender diffuse goiter of ~40 g, with a bruit. There was mild left eye proptosis without diplopia. The deep tendon reflexes were exaggerated. The laboratory evaluation confirmed hyperthyroidism due to Graves' disease: free T4 was 7.77 ng/dL (normal range 0.93–1.6 ng/dL), total triiodothyronine (total T3) was 651 ng/dL (71–180 ng/dL), thyroid-stimulating hormone (TSH) was 0.005 U/L (0.5–3.5 U/L), thyroid stimulating immunoglobulin activity was 237% (0%–139%), thyroid peroxidase (TPO) antibodies were 7 IU/mL (0–20 IU/mL), and

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TABLE 1. LABORATORY RESULTS IN A 12-YEAR-OLD AFRICAN AMERICAN GIRL

Therapy results	At initial evaluation	3 weeks after RAI	3 months after RAI	8 weeks after treatment with calcium and calcitriol	8 months after RAI patient missed calcitriol for 6 days
1. Free T4	7.77	2.62	2.15	1.98	1.35
2. Total T3	651	228	176		157
3. TSH	0.005			0.009	0.005
4. Ca	8.9		6.6	8.9	7.6
5. Ca ⁺⁺			3.12	4.5	
6. PTH			21	19	18
7. BAP			94.3	74.4	71.2
8. CPK			403	170	238
9. Mg			1.6		
10. Phos			9.0	7.0	7.6
11. D25			10.4	45.9	27.2
12. D1,25			75	117.6	93.8
13. Alk phos	310				217

Normal ranges: 1. free T4 (0.93–1.6 ng/dL), 2. total T3 (71–180 ng/dL), 3. TSH (0.5–3.5 U/L), 4. calcium (8.9–10.4 mg/dL), 5. ionized calcium (4.5–5.6 mg/dL), 6. intact parathyroid hormone (15–65 pg/mL), 7. bone specific alkaline phosphatase by ICMA (0–21.3 mcg/dL), 8. total creatine kinase (24–173 U/L), 9. magnesium (1.6–2.6 mg/dL), 10. phosphorus (4.6–5.5 mg/dL), 11. 25-hydroxy vitamin D (32–100 ng/mL), 12. vitamin D 1,25-dihydroxy (10–75 pg/mL), 13. alkaline phosphatase (70–490 IU/L).

PTH, parathyroid hormone; RAI, radioiodine; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone.

the thyrotropin receptor antibody binding inhibition index was 39.96 IU/L (0–1.75 IU/L) by electrochemiluminescence immunoassay. Serum electrolytes were normal as were the levels of calcium and alkaline phosphatase (Table 1).

She was treated with prednisone and atenolol to control symptoms of thyrotoxicosis and to prevent status asthmaticus. The 24 hour radiiodine uptake was 100% and the scan revealed a homogeneous pattern of activity. In consultation with the family, RAI treatment was chosen (because of its fairly rapid response, complicating asthma, and concerns of compliance). Asthma and tachycardia stabilized with atenolol 25 mg and prednisone 10 mg daily, and after 2 weeks she received a RAI dose of 11.1 mCi, based on the RAI uptake and the estimated gland weight. She was observed monthly following RAI treatment, and remained hyperthyroid but comfortable while continuing atenolol and alternate day prednisone (5 mg/day). Three months after RAI she complained of shortness of breath, pain, and paresthesias in her extremities. She was restless with frequent muscle spasms, bone pains, generalized weakness, dysphagia, and diarrhea. Her family admitted that she did not like dairy products and did not spend much time outdoors. Retrospectively, her sister reported that she had experienced frequent muscle spasms at night, and worsening bronchospasms beginning approximately one month after RAI. The heart rate was 80/min, and there was mild tremor of the fingertips; mild Graves' ophthalmopathy remained unchanged. Chvostek and Trousseau signs were absent. The free T4 level had fallen to 1.84 ng/dL (normal range 0.93–1.6 ng/dL).

Blood samples were sent to a reference laboratory (Lab-Corp) according to their specimen preparation and shipment protocols. The calcium level was decreased at 6.6 mg/dL (8.9–10.4 mg/dL), phosphorus was increased to 9.0 mg/dL (4.6–5.5 mg/dL), and the parathyroid hormone (PTH) level was 21 pg/mL (15–65 pg/mL), in the range consistent with hypoparathyroidism. The 25-OH vitamin D level was markedly reduced at 10.4 ng/mL (32–100 ng/mL) and the 1,25-dihydroxy vitamin D level was 75 pg/mL (10–75 pg/mL). An electrocardiogram revealed sinus rhythm with a heart rate of

73/min; the QT interval was 408 milliseconds, which is normal for her age. A DEXA scan indicated lumbar spine bone mineral density (BMD) of 0.878 g/cm² with a Z-score of –1.0, and total body BMD of 0.911 g/cm² with a Z-score of –1.5 (DEXA scan Lunar Prodigy; GE Healthcare). After one week of treatment with 1,25-dihydroxycholecalciferol (calcitriol) 0.5 mcg twice/day, elemental calcium (calcium carbonate) 1000 mg/day, and prednisone 10 mg daily, her shortness of breath, bone pains, and muscle spasms improved, and her calcium level increased. Once the vitamin D levels identifying the deficiency were available, she was treated with a combination of calcitriol, ergocalciferol (50,000 U twice weekly), and calcium supplements for 12 weeks. Ergocalciferol replacement was then discontinued when it became evident that vitamin D levels had normalized. Prednisone was tapered over 8 weeks, and the total/ionized calcium remained stable. When the patient stopped calcitriol treatment for 6 days, 8 months following RAI treatment, the serum calcium level decreased to 7.6 mg/dL (Table 1). Calcitriol was restarted and she remained symptom-free and normocalcemic on calcitriol 0.5 mcg twice/day and calcium carbonate 1000 mg/day.

Discussion

We identified at least 10 case reports since the 1950s that documented the development of hypocalcemia in patients with no prior history of parathyroid disease who received RAI treatment, including one 14-year-old boy (Table 2). The time of onset of symptomatic hypocalcemia following RAI was variable, and ranged from 5 days to 10 months, and the majority of patients required treatment with calcium and vitamin D for more than one year. PTH levels were rarely reported before 1980. In cases thereafter, PTH was low or immeasurable, implying hypoparathyroidism, but assays used were less sensitive and specific than are currently available. Multiple factors predisposed to hypocalcemia in our patient, including radioactive iodine therapy, vitamin D deficiency, and treatment with glucocorticoids.

TABLE 2. PUBLISHED CASES OF SYMPTOMATIC HYPOCALCEMIA FOLLOWING RADIOIODINE, PRESENTED BY YEAR OF PUBLICATION

Age (years)/ gender (ref)	Total RAI dose (mCi)	Time to onset of symptoms	Symptoms	Duration of treatment for hypocalcemia	At time of symptoms	
					PTH (pg/mL)	Calcium (mg/dL)
14/M (2)	4	72 days	Tetany	6 months	n/a	n/a
36/F (3)	5	2 months	Carpopedal spasm	More than 1 year ^a	1	6.4
45/F (4)	14	9 months	Seizures	10 year	n/a	6.5
57/M (5)	40	10 months	Carpopedal spasm, perioral paresthesias	n/a ^a	n/a	5
38/F (6)	150	1 month	Carpopedal spasm, perioral paresthesias	More than 1 year ^a	n/a	5.7
52/M (7) ^b	10	4 months	Paresthesias myoclonus	More than 1 year ^a	n/a	n/a
46/F (8)	5	6 months	Muscle spasms	2 years	Undetectable	5
22/F (9) ^c	4	10 months	Paresthesias of extremities	12 years	0.26	7.1
58/M (10)	15.7	5 months	Lethargy, tetany	More than 1 year ^a	n/a	4.5
58/F (14)	3.5	5 days	Neck pain, fever, QT prolongation	n/a ^a	n/a	7.7
12/F (our case)	11.1	1 month	Muscle spasms, bronchospasm	More than 6 months ^a	21	6.6

The indication for RAI treatment was hyperthyroidism except when indicated. Patient did not receive calcium or vitamin D supplements before RAI unless noted below:

^aTime, elapsed from the RAI administration to the date of publication, was either not defined or approximated by authors, but patient was requiring calcium and vitamin D supplementation at the time of publication.

^bPatients were treated with RAI for thyroid cancer (6) and angina (7).

^cPatient was hypercalcemic before RAI administration.

Experiments using mice showed that RAI can damage parathyroid tissue and cause hypocalcemia if administered in large doses (15) since β particles emitted by ^{131}I can penetrate up to 2.5 mm into surrounding tissues (16). Intrathyroidal parathyroid glands, present in about 4% of adults (17), may be at increased risk for destruction. The elevated phosphorus and inappropriately low serum PTH level in our case imply the inability of the post-RAI parathyroid glands to appropriately respond to hypocalcemia. Noteworthy in this respect is the report of a series of patients with sustained hypocalcemia and normal PTH levels post-thyroidectomy, who evidently never recovered an adequate parathyroid response to low serum calcium levels (18). The administered dose of RAI of 11.1 mCi was calculated by the consulted radiologist and appeared to be slightly higher than the recommended dose for children (19) of 150–200 μCi (5.5–7.4 MBq) sodium iodine-131 per gram of thyroid mass (40 g) corrected for the 24-hour ^{123}I uptake (100%).

Parathyroid function after RAI treatment was examined in at least two clinical studies, including serial measurements of serum calcium and PTH, in patients treated with RAI for hyperthyroidism or thyroid cancer remnant ablation (20,21). Both studies demonstrated diminished parathyroid reserve and low serum calcium levels although patients were noted to be asymptomatic (20). Adams and Chalmers (21) evaluated 60 patients who had received RAI treatment over a variable time period, and found that 10% had persistent hypocalcemia after an intravenous calcium deprivation test, with no relationship between the serum calcium level and the time since receiving the ^{131}I dose. The calcium deprivation test is preformed by an infusion of disodium hydrogen ethylene diaminetetracetic acid (EDTA), followed by calcium measurements before and 2, 6, 12, and 24 hours after. The chelate EDTA is known to bind calcium in the blood with normal response being restoration

of serum calcium levels to at least 90% of pre-EDTA levels by 12 hours. Guven *et al.* (20) evaluated 19 patients following treatment with RAI (100–150 mCi) for thyroid cancer remnant ablation. All patients were hypothyroid, and all had normal serum calcium levels before RAI administration. Six months after RAI, the serum calcium level was less than 8.4 mg/dL in 7 of 19 patients, with inappropriately normal PTH levels. Notably, none of the patients in that study had symptoms of hypocalcemia.

Our patient had hyperthyroidism, a condition known to alter the function of the parathyroid axis. The hyperthyroid state accelerates bone turnover, favoring bone resorption by osteoclasts with relative osteoblast inhibition and shortening of the bone remodeling cycle (22).

Hyperthyroidism sometimes causes hypercalciuria and may cause hypercalcemia with suppression of PTH secretion (23) although rarely in children (24). PTH levels increase and calcium excretion declines when normocalcemic hyperthyroid patients are treated with antithyroid drugs (22). Resolution of bone resorption may have contributed to the fall in serum calcium in our patient when T4 levels decreased following RAI.

Another key factor that contributed to hypocalcemia in our patient was compromised vitamin D status. Vitamin D deficiency is common in children and adults, with 9% of the pediatric population in the United States estimated to be vitamin D deficient, and 61% of children insufficient (12). Risk factors for vitamin D deficiency include ethnicity, limited sun exposure and low dietary intake of foods fortified with vitamin D, with an increased risk in children who are non-Hispanic blacks, Mexican Americans, female, older, obese, and adolescent (12).

Glucocorticoid therapy for asthma also presumably contributed to hypocalcemia in our patient. Glucocorticoids

decrease calcium absorption by inhibiting vitamin D-mediated transcellular calcium transport in the small intestine (25), decreasing the synthesis of calcium binding protein (26,27), increasing the rate of degradation of 1,25-dihydroxy vitamin D (27) and increasing the urinary excretion of calcium by stimulating the mineralocorticoid receptor in the distal tubule (14).

When the level of 25(OH) D levels fall below 40 nmol/L (16 ng/mL) maintenance of adequate intestinal calcium absorption depends on a rise in PTH synthesis (28). The majority of patients with vitamin D deficiency are not hypocalcemic because there is a compensatory rise in PTH secretion and increased production of 1,25-dihydroxy vitamin D. Patients with a relatively short duration of vitamin D deficiency can have low 25-hydroxy vitamin D levels, but normal 1,25-dihydroxy vitamin D levels. In patients with hyperthyroidism the serum 1,25-dihydroxy vitamin D concentrations appear to be lower than in hypothyroid patients or euthyroid individuals (29). It is possible that for calcium homeostasis our patient had low 25-hydroxy vitamin D, elevated PTH, and 1,25-dihydroxy vitamin D levels before RAI administration. Post-RAI when PTH synthesis declined and oral prednisone was administered (for acute exacerbation of asthma) levels of 1,25-dihydroxy vitamin D appeared spuriously normal.

It is possible, but unlikely, that our patient also has autoimmune hypoparathyroidism. There was no prior history or symptoms of hypocalcemia, and her baseline serum calcium level was normal. There was no family history of a calcium disorder or phenotypic malformations, suggestive of a cytogenetic abnormality (DiGeorge syndrome) or a metabolic myopathy (Kearns-Sayre syndrome). The patient had no history of mucocutaneous candidiasis, alopecia, visual problems (keratitis) or symptoms of fat malabsorption (suggestive of pancreatic insufficiency), or Addison's disease. Her initial evaluation included normal electrolytes, and no evidence for pernicious anemia, hepatitis, or diabetes, so we did not evaluate her for autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. Sporadic idiopathic hypoparathyroidism, associated with calcium-sensing receptor autoantibodies, can be accompanied by autoimmune thyroid disease (elevated TSH and positive TPO antibodies) (30), but occurs very rarely in patients with Graves' disease and mostly in the Asian population (31).

We hypothesize that this child developed hypocalcemia following RAI treatment and the combination of resolving hyperthyroidism; vitamin D deficiency and concomitant short-term high dose glucocorticoid treatment complicated her hormonal profile. It is unclear to what extent vitamin D deficiency or use of systemic steroids predisposed this child to hypocalcemia but in a study of adults who had thyroidectomy primarily for compressive goiter, vitamin D levels less than 15 ng/mL increased the risk for postoperative hypoparathyroidism 28-fold (32). Eight months after treatment with RAI, following correction of vitamin D deficiency with ergocalciferol, our patient still required calcium and calcitriol supplementation to maintain normocalcemia, suggesting permanent hypoparathyroidism. Based on our experience with this child, we propose that hypocalcemia following ¹³¹I therapy may be more common than presently anticipated. We recommend careful follow-up of patients with multiple preexisting risk factors for hypocalcemia. Optimization of calcium and vitamin D status before RAI therapy or thyroidectomy and close monitoring of calcium and PTH status after RAI administra-

tion in individuals with risk factors for hypocalcemia seems amply justified.

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Disclosure Statement

Both authors disclose no potential conflicts of interest.

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