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Case Report

Symptomatic Hypercalcemia with Vomiting in a Pediatric Patient with Graves' Disease

Kim GL et al. Symptomatic Hypercalcemia with Graves' Disease

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What is already known on this topic?
• Hypercalcemia may occur in patients with Graves' disease due to increased bone turnover.
• In pediatric populations, hypercalcemia associated with hyperthyroidism is typically mild and asymptomatic.

What this study adds?
• This case highlights that Graves' disease in children can present with symptomatic and marked hypercalcemia requiring acute management.
• It emphasizes the importance of evaluating thyroid function in pediatric patients with persistent nausea, vomiting, and mineral imbalance.

Abstract
Graves' disease (GD) is the leading cause of childhood hyperthyroidism, resulting from excessive thyroid hormone production. In some cases, it can cause alterations in mineral homeostasis, including calcium, phosphorus, and magnesium, which are often overlooked. Hyperthyroidism increases osteoclastic bone resorption, and mild to moderate hypercalcemia occurs in approximately 20-50% of affected patients, typically resolving with appropriate therapy. Although uncommon, symptomatic hypercalcemia in the setting of GD requires immediate evaluation and management. An 8-year-11-month-old girl was brought to the clinic, presenting with recurrent nausea, vomiting, and fatigue. She had multiple hospital admissions over the previous seven months due to drug reaction with eosinophilia and systemic symptoms (DRESS) and acute inflammatory demyelinating polyneuropathy (AIDP). Blood tests showed hyperthyroidism, marked hypercalcemia and hypomagnesemia. She showed tachycardia and weight loss. Based on the Burch-Wartofsky Point Scale, she was diagnosed with impending thyroid storm. Treatment was initiated with intravenous hydration, furosemide, dexamethasone, along with oral methimazole and propranolol. Within a few days, her general condition improved, her heart rate decreased, and gastrointestinal symptoms resolved and serum calcium levels normalized. Follow-up tests showed stable thyroid function and normal calcium levels. This case highlights that symptomatic hypercalcemia associated with GD and suggests that hyperthyroidism should be considered in the differential diagnosis of unexplained persistent nausea and vomiting.
Keywords: Graves' disease, pediatric, hypercalcemia, vomiting

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Introduction
Graves' disease (GD) is the most common cause of hyperthyroidism [1,2]. Its clinical presentation involves a wide range of systemic manifestations, including dysfunction of cardiovascular, gastrointestinal, and bone metabolism. These are commonly expressed as tachycardia, gastrointestinal disturbances, weight loss, and alterations in bone and mineral metabolism [3,4]. Hyperthyroidism may affect mineral homeostasis, but this aspect is often overlooked in clinical practice. The imbalance is primarily caused by increased osteoclast activity, which is promoted by increased thyroid hormone levels, ultimately leading to disorders of bone metabolism and mineral imbalances [5-7]. Previous studies have shown that hypercalcemia occurs in approximately 20–50% of patients with hyperthyroidism; however, severe hypercalcemia has not been observed, with the highest documented level being 12.4 mg/dL [8-10]. Mild hypercalcemia due to hyperthyroidism is usually asymptomatic and often requires no further intervention if the underlying thyroid disease is properly managed [5]. However, although rare, severe hypercalcemia can cause severe nausea and vomiting, and if not treated promptly, can lead to serious clinical problems such as nephrocalcinosis, cardiac dysfunction, osteopenia or osteoporosis [11].

Case Report

An 8-year-11-month-old girl was admitted complaining of recurrent nausea and vomiting that had persisted for more than a month. She had been hospitalized several times over the past seven months. She experienced her first seizure seven months prior to this admission and started on oxcarbazepine for presumed benign Rolandic epilepsy (BRE). After 40 days of oxcarbazepine therapy, the patient developed drug reaction with eosinophilia and systemic symptoms (DRESS), leading to discontinuation of oxcarbazepine and initiation of intravenous corticosteroids, followed by a tapering course of oral steroids. Sixteen days after steroid withdrawal, she developed facial palsy and bilateral lower extremity muscle weakness and was diagnosed with acute inflammatory demyelinating polyneuropathy (AIDP). She received intravenous immunoglobulin (IVIG) and corticosteroids, with gradual improvement in motor strength from 1–2/5 to 3–4/5. Notably, no gastrointestinal symptoms, including nausea or vomiting, were noted during the hospitalization for AIDP.

Four days after the discharge—forty days prior to this admission—she presented to the emergency department with severe nausea and vomiting. Laboratory evaluation revealed a serum calcium level of 12.2 mg/dL. This episode was interpreted as transient hypercalcemia in the context of acute illness and possible dehydration, and she improved with intravenous hydration without requiring hospitalization. However, two days later, she was admitted with persistent nausea and vomiting, and her serum calcium level remained elevated at 12.2 mg/dL. Her symptoms improved with intravenous fluids, and she was discharged after five days. Following discharge, her symptoms recurred and her oral intake progressively declined. Four days later, she returned to the emergency department with dyspnea, postprandial vomiting, and an oxygen saturation of 79%. She was hospitalized with suspected aspiration pneumonia. Although antibiotic therapy was initiated, she developed a rash and required intravenous methylprednisolone. Laboratory tests at that time demonstrated a higher serum calcium level of 13.5 mg/dL. With intravenous hydration and corticosteroid therapy, the calcium level decreased to 11.0 mg/dL by hospital day 3, and subsequently remained within the normal range, allowing discharge. During this period, she did not exhibit typical features of GD (e.g., goiter, exophthalmos, tremor) and her thyroid function tests (TFTs) performed three months earlier were within normal limits; therefore, repeat thyroid testing was not pursued, and the hypercalcemia was attributed to dehydration and acute illness (Table 1).

Two weeks after discharge, gastrointestinal symptoms persisted and weight loss became evident, prompting readmission for further evaluation. Her weight, which was 47 kg at the time of nausea and vomiting, decreased to 41.6 kg at the time of readmission. Initial laboratory tests demonstrated hypercalcemia and hypomagnesemia, with a total calcium level of 13.2 mg/dL (8.8–10.8 mg/dL), ionized calcium level of 1.72 mmol/L (1.05–1.35 mmol/L), magnesium level of 1.39 mg/dL (1.6–2.4 mg/dL), and a suppressed alkaline phosphatase (ALP) level of 116 IU/L (142–335 IU/L). Although paradoxical in the setting of hyperthyroidism, the suppressed ALP level was considered to be influenced by concurrent hypomagnesemia and poor oral intake associated with persistene vomiting. Parathyroid hormone (PTH) was suppressed at 0.84 pg/mL (8-76 pg/mL), which was appropriately suppressed in the setting of hypercalcemia. Levels of calcitonin (1.9 pg/mL; reference 0-10 pg/mL) and 25-hydroxyvitamin D (29.2 ng/mL; reference 20-100 ng/mL) were within normal limits. At that time, serum potassium was 3.4 mmol/L (3.5–5.1 mmol/L), slightly below the reference range but not low enough to suggest hypokalemic paralysis. Her muscle weakness had shown gradual improvement since the admission for AIDP. Considering the marked weight loss, hypercalcemia and persistent gastrointestinal symptoms, TFTs were performed. The results revealed overt hyperthyroidism with total triiodothyronine (T3) 556 ng/dL (reference 93–231 ng/dL), free thyroxine (free T4) 7.23 ng/dL (0.97–1.67 ng/dL), and thyroid-stimulating hormone (TSH) <0.005 μIU/mL (0.60–4.84 μIU/mL). Thyroid autoantibodies were strongly positive, including anti-thyroid peroxidase (anti-TPO) 93.3 IU/mL (0–18 IU/mL), anti-thyroglobulin (anti-Tg) 722 IU/mL (0–37 IU/mL), TSH receptor antibody (TSHRAb) 35.6 IU/L (0–1.75 IU/L), and thyroid-stimulating antibody (TSAb) markedly elevated at 396.5% (<140%). Taken together, these findings were diagnostic of GD. Thyroid ultrasonography demonstrated coarse echogenicity with increased vascularity, and scintigraphy showed diffusely increased uptake, findings consistent with GD (Fig. 1).

The delay of approximately forty days between symptom onset and diagnosis reflected the absence of classic hyperthyroid features during earlier presentations and the reliance on previous normal TFTs. Clinical features consistent with hyperthyroidism and hypercalcemia included nausea and vomiting, weight loss, and tachycardia with a heart rate of 150 beats per minute. Electrocardiographic abnormalities typically associated with hypercalcemia (e.g., QT interval shortening, widened QRS complexes, or Osborn-like waves) were not observed in the patient. According to the Burch–Wartofsky scoring system, the patient scored 35 (25 for tachycardia and 10 for gastrointestinal symptoms), indicating impending thyroid storm [16].

Treatment was initiated with methimazole, a beta-blocker, intravenous hydration, intravenous corticosteroids, and loop diuretics. On the third day, her heart rate decreased to less than 100 beats per minute and gastrointestinal symptoms improved. On the fourth day, serum total calcium, ionized calcium, and magnesium levels improved significantly to 10.2 mg/dL, 1.47 mmol/L, and 1.83 mg/dL, respectively. Methimazole was gradually reduced, and diuretics, steroids, and beta-blockers were discontinued. Muscle weakness due to AIDP, rather than GD, gradually improved. Lower extremity muscle weakness was 3–4/5 at the time of admission for GD and fully recovered during the follow-up period. After discharge, the methimazole dose was adjusted based on the results of follow-up TFT, and calcium and mineral levels were maintained within the normal range (Table 1).

Discussion

We report this case because hypercalcemia associated with GD is rare in the pediatric population and may be easily overlooked. In this context, hypercalcemia is primarily caused by increased bone metabolism induced by thyroid hormones, which increase osteoclast activity and release more calcium into the bloodstream [12]. Such disturbances in mineral metabolism can exacerbate systemic symptoms, and pediatric patients are especially vulnerable to complications such as prolonged disruption of bone remodeling, osteopenia, and increased fracture risk. These complications require careful monitoring and early intervention to prevent long-term skeletal damage [6,7].

In this case, the patient presented with persistent nausea and vomiting. Nausea and vomiting can be symptoms of hypercalcemia, but they are also common and nonspecific symptoms in many other diseases. In the presence of these gastrointestinal symptoms, it may be difficult to consider hyperthyroidism as a differential diagnosis. The absence of typical features of GD (goiter, exophthalmos, tremor) and previously normal TFTs obtained three months earlier further reduced clinical suspicion and contributed to a delay in diagnosis. Although the hypercalcemia episodes occurred during acute illness with vomiting and reduced oral intake, dehydration alone rarely accounts for persistent calcium levels ≥12 mg/dL over 10 days. Our experience underscores that clinicians should not attribute moderate-to-severe hypercalcemia solely to dehydration, but should pursue an appropriate diagnostic workup, even in the absence of typical features of hyperthyroidism. Early diagnosis and appropriate treatment are important not only for the management of acute symptoms but also for preventing secondary complications [5,9].

The patient's history of long-term corticosteroid therapy for DRESS syndrome and AIDP may also have contributed to the delayed recognition of GD. Corticosteroids suppress immune function and may mask or delay the onset of autoimmune thyroid disease, making timely diagnosis difficult. The TFTs performed at the time of AIDP were within the normal range. Although it is difficult to determine the exact time of onset

of hyperthyroidism, it is noteworthy that the patient's serum calcium level was 12.2 mg/dL when she first presented to the emergency department with nausea and vomiting 40 days before being diagnosed with GD, suggesting that hyperthyroidism was present at this time or even earlier.

There have been several reports in which GD and AIDP coexisted, all in female patients in their fifties [17–20]. To our knowledge, this association has not been reported in a pediatric population, and thus this is the first pediatric case in which GD developed sequentially after AIDP. In addition, while previous cases described a simultaneous diagnosis of AIDP and GD, this case is unique in that GD was diagnosed shortly after the onset of AIDP. Although our patient had significant muscle weakness, her serum potassium level was only mildly decreased (3.4 mmol/L; reference 3.5–5.1 mmol/L) and did not reach the range typically associated with thyrotoxic hypokalemic periodic paralysis, making AIDP the more plausible explanation for her neuromuscular symptoms. Regarding the potential immunopathological association between AIDP and GD, some studies have suggested that Th17 cells in AIDP may influence the production of TSHRAb, although the role of Th1 and Th2 cells in the pathogenesis of GD remains controversial and has not been clearly elucidated [18].

Both AIDP-related autoantibodies and antinuclear antibodies (ANA) were negative at the time of diagnosis of AIDP. However, ANA was positive (titer 1:160, speckled pattern) at a recent follow-up visit. Although the temporal relationship does not prove causality, these findings may result from IVIG therapy, or, suggest a predisposition to additional autoimmune diseases, emphasizing the need for continued surveillance.

Another notable finding was the suppressed ALP level. Hyperthyroidism is typically associated with increased bone turnover and often leads to elevated ALP levels [21]. However, in this patient, ALP was paradoxically decreased. The most plausible explanation is the markedly suppressed PTH level due to significant hypercalcemia, leading to a low-turnover bone state that is characteristically associated with reduced ALP activity [22]. Additional factors may also have contributed, including prior corticosteroid therapy that may have suppressed osteoblastic activity [21]. In addition, concomitant hypomagnesemia at admission may have further contributed to decreased ALP activity, as magnesium deficiency has been associated with reduced ALP activity and impaired bone mineralization. Moreover, recent evidence suggests that hypercalcemia itself can independently lower ALP even within the same PTH range [23].

Hypomagnesemia, which was observed in this patient, with a serum magnesium level of 1.39 mg/dL on admission and a nadir of 1.24 mg/dL on the second day of hospitalization, corresponded to mild to moderate hypomagnesemia [24]. This abnormality was thought to have developed due to impaired renal magnesium reabsorption secondary to hypercalcemia and decreased oral intake due to persistent nausea and vomiting [24]. As gastrointestinal symptoms resolved and oral intake improved, serum calcium normalized, and on the fourth day of hospitalization, the magnesium level had also returned to the normal range. Notably, follow-up investigations showed that the serum magnesium level was maintained within the normal range without requiring any supplementation, which supports the interpretation that the hypomagnesemia was transient and caused by reversible hypercalcemia and insufficient intake. Furthermore, hypercalcemia did not recur during the follow-up period with treatment for hyperthyroidism.

In conclusion, this case demonstrates two unusual features: (1) pediatric GD presenting initially with symptomatic hypercalcemia, and (2) GD developing sequentially after AIDP. Furthermore, it emphasizes the need to assess hypercalcemia and thyroid dysfunction in children presenting with persistent, unexplained nausea and vomiting.

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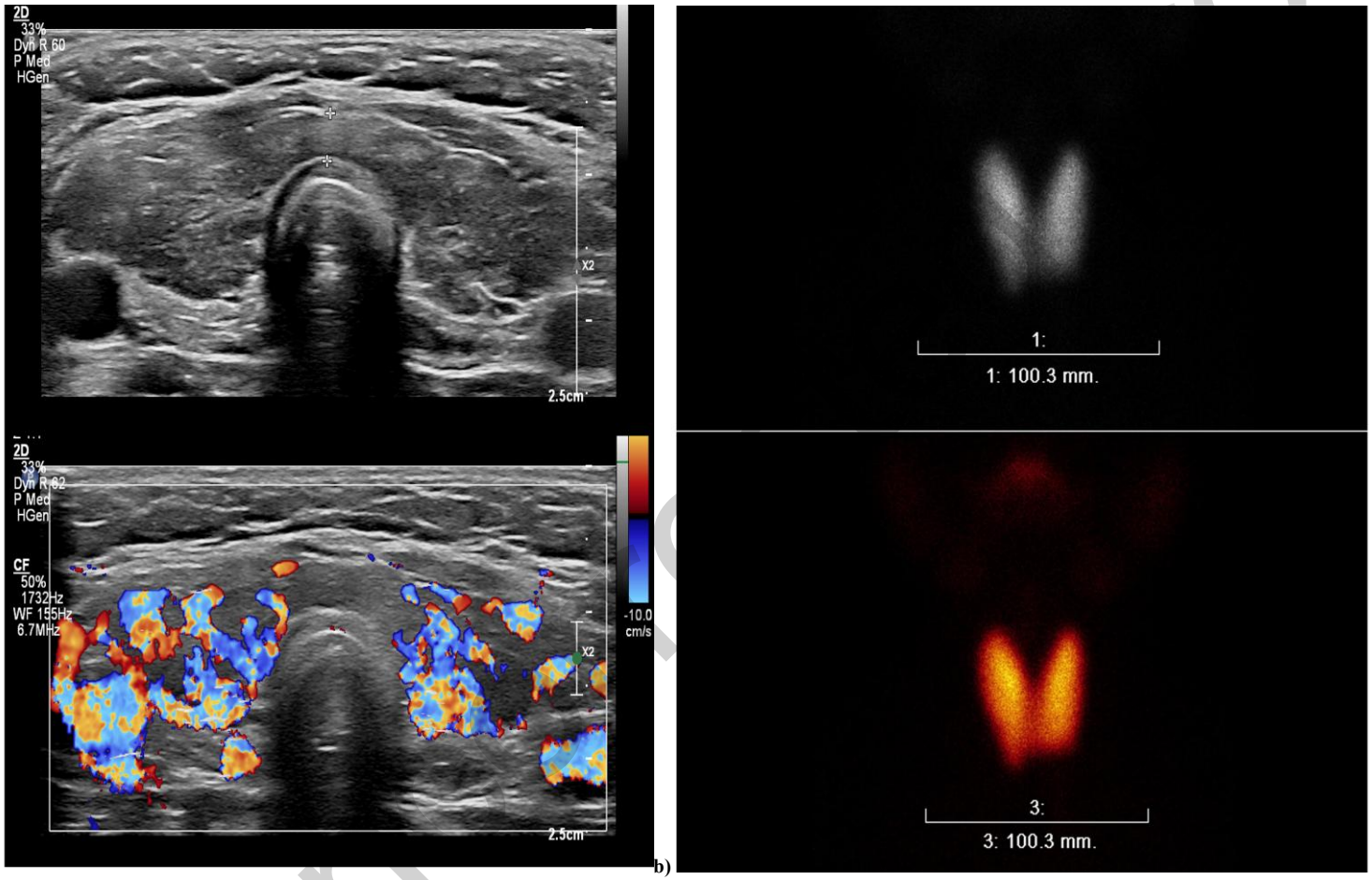

a) b)

Figure 1. Thyroid ultrasonography and scintigraphy of the patient. a) Thyroid ultrasonography shows increased vascularity and coarse echogenicity. b) Thyroid scintigraphy demonstrates diffusely increased radionuclide uptake without evidence of focal lesions

Table 1. Clinical course and laboratory findings during admission and follow-up

	1st visit d/t seizure 7mos PTD*	**Adm for AIDP (26 days) 68 days PTD**	**ER visit for newly developed vomiting 40days PTD**	**Adm for persistent vomiting (5 days) 38 days PTD**	**Adm for persistent vomiting and dyspnea (11 days) 1mos PTD**	**This admission HD1**	**HD2**	**HD3**	**HD4**	**HD10**	**1mos AD‡**	**3mos AD**	**7mos AD**	**11mos AD**
Height, cm [SDS]	145.2 [2.80]	146.5 [2.52]		146.4 [2.41]	146 [2.35]	148 [2.55]					147 [2.32]	147.9 [2.28]	151.9 [2.5]	153.6 [2.49]
Weight, kg [SDS]	53.9 [3.21]	52.3 [2.84]	47 [2.34]	47 [2.34]	43.8 [2.02]	41.6 [1.73]					46.2 [2.15]	46.8 [2.11]	48.4 [2.05]	52.9 [2.30]
BMI, kg/m^2 [SDS]	25.57 [3.03]	24.37 [2.59]		21.93 [1.85]	20.55 [1.40]	18.99 [0.79]					21.38 [1.62]	21.39 [1.57]	20.98 [1.33]	22.42 [1.72]
Laboratory data (Reference range)														
Total Calcium, mg/dL (8.4-10.4)	10.0	10.2	12.2	12.2	13.5	13.2	12.5	11.2	10.2	9.7	9.5	9.4	9.1	9.3
Phosphorus, mg/dL (3.1-5.5)	4.31	5.1	5.5	5.47	4.8	3.83	4.3	4.1	3.2	3.34	5	5.1	5	5.3
Ionized Calcium, mmol/L (1.13-1.32)						1.72	1.72	1.49	1.47	1.21				
Alkaline phosphatase, IU/L (142-335)	399	213	115	114	125	116	102	96	97		297	419	402	398
Magnesium, mg/dL (1.6-2.4)	2.05					1.39	1.24	1.35	1.83	1.68				
T3, ng/dL (91-218)		84.1				556	482			59.1	284	299	197	171
free T4, ng/dL(0.98-1.63)		1.44				7.23	6.42			0.825	1.55	1.52	1.46	1.11
TSH, uIU/mL (0.51-4.30)		1.67				<0.005	<0.005			0.00639	0.00776	<0.005	<0.005	0.327
Anti-TPO, IU/mL (0-18)						93.3				65.5	66.5	114	56.3	31.4
Anti-Tg, IU/mL (0-37)						722				502	746	909	169	70.3
Anti-TSHR, IU/L (0-1.75)						35.6				37.1	>40.0	>40.0	25.9	13.1
TS Ab, % (<140)										396.5		321.4		
25(OH)Vitamin D, ng/mL (30-100)						29.2				20.9		24.2		18.7
1a,25(OH)2 VitD, ng/mL (19.6-54.3)						9.83								100.25
PTH, pg/mL (8-76)						0.84								67.8
Calcitonin, pg/mL (0-10)						1.9								
Urine Ca/Cr, mg/mg (<0.2)						0.65	0.61	0.48	0.5					
ANA (<1:80)		negative											1:160 (speckled pattern)	

*PTD, Prior to diagnosis of GD; †HD, Hospital day; ‡AD, After discharge