Refractory Hypoparathyroidism in a Child with Celiac Disease

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Hypoparathyroidism occurring spontaneously in children after the first few years of life is uncommon and is most often due to an autoimmune condition, such as autoimmune polyglandular syndrome type 1. Other etiologies include familial hypocalcemia with hypercalciuria and DiGeorge syndrome [1].

Hypomagnesemia is a well-established cause of secondary hypocalcemia, though its effect on parathyroid hormone (PTH) levels is variable. Numerous mechanisms have been suggested for the hypocalcemia, including end-organ unresponsiveness to parathyroid hormone, impaired synthesis and/or release of PTH, and impaired formation of 25-dihydroxyvitamin D3 [2]. We present a case of hypomagnesemia secondary to celiac disease (CD) that resulted in refractory hypoparathyroidism, and describe the effect of a gluten-free diet.

PATIENT DESCRIPTION

A previously healthy 12 year old female presented with a 1 day history of fever, headache, vomiting and spasms of her hands and feet. Her family history included six sisters diagnosed with asthma, one of whom was also diagnosed with CD. No family members were known to have suffered from hypoparathyroidism or hypocalcemia.

In the emergency room she was not in acute distress. Her weight was 36 kg, height 149 cm (both in the 10th percentile) and body mass index 16.2. Physical examination was notable for carpopedal spasm and positive Chvostek sign. Breast Tanner stage was II. No dysmorphic features were noted. The rest of the physical examination was normal.

Laboratory studies on admission revealed mild microcytic anemia, hypocalcemia, hyperphosphatemia and hypomagnesemia [Table 1]. Glucose, blood urea nitrogen, creatinine, uric acid, sodium, potassium, chloride and albumin were normal. Urine biochemistry analysis revealed a calcium level of 46 mg/dl, with calcium-creatinine ratio of 0.5 (normal < 0.2); urine fractional excretion of Mg^{+2} was 4.5% (normal in hypomagnesemic state < 2%).

The patient was treated with intravenous fluids, calcium and magnesium, as well as oral calcitriol and aluminum hydroxide as a phosphate binder. After the vomiting ceased, calcium and magnesium were begun orally. The clinical signs of hypocalcemia resolved, and the patient was discharged on oral therapy, including thiazide diuretics for treatment of hypercalciuria, to ambulatory follow-up and completion of diagnostic workup.

Intact PTH (iPTH) was measured in plasma with the ADVIA Centaur assay (Siemens, Erlangen, Germany), a two-site sandwich immunoassay using direct chemiluminometric technology. Plasma PTH was 14.6 pg/ml (normal > 12). Vitamin D 25-OH was 8 ng/ml (normal 20–45). An endocrine workup, including thyroid-stimulating hormone and free thyroxine, ACTH test and fasting blood glucose levels, were normal. The familial history of CD prompted a celiac workup: IgA anti-tissue transglutaminase (tTG) antibody test was highly positive at 110 U/ml, as was anti-endomysial antibody (EmA). Small bowel biopsy demonstrated moderate villous atrophy, while gastric biopsy showed chronic follicular gastritis as well as the presence of *Helicobacter pylori*. A gluten-free diet and triple therapy for *H. pylori* eradication were introduced.

During the initial 6 months of therapy, calcium and magnesium levels were persistently low and phosphorus levels persistently high despite appropriate therapy. EmA at that time became negative, though tTG was still positive. The patient suffered repeated tetanic episodes and required several hospitalizations due to symptomatic hypocalcemia. When supervised drug administration during hospitalization failed to normalize levels despite increasing doses, oral therapy was replaced by prolonged parenteral therapy, resulting in only a partial improvement – even with maximal doses. Serum PTH levels, which were initially low to normal, became subsequently undetectable on two consecutive tests performed 3 months apart [Table 1].

Nine months after the initial diagnosis, calcium levels became normal. Hemoglobin levels began to rise, magnesium levels gradually rose, and phosphorus levels progressively normalized as well. PTH returned to normal levels after 1 year of therapy. Drug doses were gradually reduced. Twenty-two months after the initial diagnosis the patient discontinued all drug therapy, with hemoglobin, calcium,

Table 1. Laboratory values at admission and during follow-up

Blood value (normal range)	Admission	3 months	6 months	14 months	22 months
Hemoglobin (12–16 g/dl)	10.8	10.8	10.6	10.2	14.8
MCV (78–102 fl)	70.4	73.9	73.4	81.1	81.0
Albumin (3.5–5 g/dl)	4.0	4.6	4.1	4.1	4.4
Calcium (8.4–10.4 mg/dl)	5.1	6.5	7.6	8.7	9.6
Phosphorus (2.7–4.5 mg/dl)	7.4	10.2	8.6	5.8	4.7
Magnesium (1.7–2.55 mg/dl)	1.47	1.49	1.25	1.45	1.97
PTH (12–35 pg/ml)	14.6	13.8	‹ 3 (two consecutive tests)	23.8	
Vitamin D 25-OH (20–45 ng/ml)		8	14		
tTG (0–30 u/ml)	110		50	22	Negative
EmA	Positive		Negative	Negative	Negative
Urine value					
Calcium (5–36 mg/dl)	18.3	7.9	8.3	10.9	
Creatinine (90–300 mg/dl)	35.6	43.3	38.9	23.4	
Ca2+/Creatinine ratio (mg/mg)	0.51	0.18	0.21	0.47	
Fractional excretion of magnesium (%)	4.5%				

MCV = mean corpuscular volume, PTH = parathyroid hormone, tTG = anti-tissue transglutaminase, EmA = anti-endomysial antibody

phosphorus and magnesium levels remaining normal until the end of follow-up 7 years later. Fractional excretion of Mg^{+2} normalized and continues to be normal.

COMMENT

Our patient presented with hypocalcemia and hyperphosphatemia, a combination strongly suggestive of hypoparathyroidism. Interestingly, PTH levels were initially at the low end of the normal range (though inappropriately low for a patient with hypocalcemia), and only later did they drop to undetectable levels. Magnesium levels, as well as calcium, phosphorus and PTH levels, ultimately normalized in response to a gluten-free diet.

Two possible mechanisms could have contributed to the patient's clinical presentation: malabsorption causing hypomagnesemia and vitamin D deficiency, and an autoimmune mechanism. Inhibition of PTH release secondary to hypomagnesemia would plausibly explain the low PTH levels in our patient. A similar course was previously described in an adult patient with hypomagnesemia and low normal PTH level who responded to calcium therapy with a decrease in PTH to undetectable levels [3]. Although hypomagnesemia-related hypoparathyroidism generally involves magnesium levels < 1 mEq, serum magnesium levels may not accurately reflect intracellular magnesium status. Additional mechanisms may include skeletal resistance to PTH due to chronic magnesium depletion as well as vitamin D deficiency. Our patient's hypomagnesemia was likely due to malabsorption resulting from CD. Magnesium levels, as well as calcium, phosphorus and PTH levels, ultimately normalized in response to a gluten-free diet.

We did consider an autoimmune etiology such as the AIRE-mutation-related autoimmune polyglandular syndrome type 1 (APS-1), but a focused search in our patient found evidence of hypoparathyroidism alone without chronic mucocutaneous candidiasis or adrenal insufficiency. At least two of the three must be present in order to define the disorder. Nonetheless, endocrine autoimmunity appears to be a spectrum because some patients with AIRE mutations may initially have only one manifestation.

The association of CD with idiopathic hypoparathyroidism has been described in a handful of patients [4]. A small number of adult patients have been described whose hypocalcemia and hyperphosphatemia were poorly controlled by calcium and vitamin D therapy but ultimately responded to a gluten-free diet [4]. While hypomagnesemia is not a feature of either of the above entities, low PTH levels can interfere with renal magnesium absorption. An alternative autoimmune mechanism might involve the role of the calcium-sensing receptor (CaSR). There has been accumulating evidence that the presence of CaSR antibodies as in APS-1 can lead to hypoparathyroidism. Similarly, previously described cross-reactivity of anti-endomysial antibodies with parathyroid tissue could elegantly explain her clinical picture. However, since we did not test cross-reactivity in vitro, this must remain speculative for our patient.

Since primary hypoparathyroidism is not likely to explain our patient's hypomagnesemia, we believe that her hypomagnesemia contributed to the other clinical manifestations, including low calcium, high phosphorus and low PTH levels. CD seems to have been the cause of the hypomagnesemia and, therefore, treatment of CD with a gluten-free diet was the key to resolving her hypoparathyroid state. Initially elevated fractional excretion of Mg^{+2} was likely due to intravenous magnesium administration.

To the best of our knowledge we have presented the first case of complete clinical and laboratory resolution of refractory hypoparathyroidism resulting from a gluten-free diet in a young celiac disease patient. The case emphasizes the myriad manifestations of celiac disease and the potential extra-intestinal implications of prompt diagnosis of celiac disease and the resultant treatment [5].

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