

## Case Report

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# Tetany Due to Refeeding Syndrome in A Recently Diagnosed Child with Celiac Disease

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## Abstract

Celiac disease (CD) occurs in genetically predisposed individuals, and usually presents with gastrointestinal symptoms. Hypocalcemia with associated tetany has rarely been reported as the presenting symptom of CD. A 4-year-old girl presented to us with bilateral painful carpopedal spasm. The patient was diagnosed with CD one month ago, and although adherent with her gluten-free diet, she consumed large amounts of gluten-free foods due to exceptional voracious appetite. Low serum calcium, phosphorus and vitamin D were found on admission and were corrected with appropriate parenteral and oral administration. Symptomatic hypocalcemia can occur in the context of celiac crisis and/or refeeding syndrome, a disorder characterized by the sudden shift in fluids and electrolytes that occurs in malnourished patients, who are refed without restrictions. Newly diagnosed malnourished patients with CD should be advised to increase their oral intake gradually, and to closely monitor their serum electrolytes.

**Keywords:** Celiac disease; Celiac crisis; Carpopedal spasm; Hypocalcemia; Hypophosphatemia; Refeeding syndrome; Tetany

## 1. Background

Celiac disease (CD) also known as gluten enteropathy is an autoimmune disorder that occurs in genetically predisposed individuals [1]. Genetically susceptible persons react to gluten, a group of proteins found in wheat and in other grains, and most present with gastrointestinal symptoms like abdominal distention, diarrhea, malabsorption

and failure to thrive. Diagnosis is typically made by a combination of serological studies and intestinal biopsies [1]. The genetic susceptibility to CD is associated with well-identified haplotypes in the human leukocyte antigen class II region, as such haplotypes are expressed on the antigen-presenting cells of the intestinal mucosa. The only known effective treatment is strict life-long avoidance of gluten.

Hypocalcemia with associated tetany has rarely been reported as the presenting symptom of CD [2,3]. We present a 4-year-old girl with recently diagnosed CD, who two weeks after starting gluten-free diet presented with bilateral painful carpopedal spasm due to severe hypocalcemia. In addition, she had hypophosphatemia, hypomagnesemia, low serum 25-hydroxyvitamin D and increased serum parathyroid hormone. The constellation of her electrolyte abnormalities was consistent with refeeding syndrome (RFS) that was triggered by the abrupt and unrestricted refeeding with large amounts of gluten-free foods.

## **2. Case Presentation**

A 4-year-old girl presented to the emergency room of our hospital with generalized numbness, bilateral painful carpopedal spasm and lower extremity hypertony that developed over the last six hours. The patient was recently diagnosed with CD, when one month ago she presented to us with a three-week history of diarrhea along with prominent abdominal distention and 7% weight loss. At that time, she had severe hypokalemia (serum potassium 2.8 mEq/L) that was corrected with intravenous (IV) supplementation of potassium chloride, and asymptomatic hypocalcemia (serum calcium 7 mg/dL). The patient was referred to another hospital for intestinal biopsy that along with the serological studies, i.e., high titer of IgA antibodies against tissue transglutaminase confirmed the suspected diagnosis of CD. The patient was started on a gluten-free diet and instructed to gradually increase her oral intake. At discharge from the second hospital, the serum calcium had almost normalized (8.5 mg/dl), and she was advised to return as an outpatient in three weeks. Two weeks later, she presented to us with tetany, as described above. According to her parents, she was compliant with the prescribed gluten-free diet, and she had normal bowel movements daily. However, she had an unprecedented voracious appetite, constantly asking and consuming large quantities of natural gluten free foods (potatoes, corn, bananas, etc.), as well as gluten-free baked products such as bread crumbs and toasted bread.

On admission, she weighted 14.5 kg, height 101 cm, body mass index (BMI) 14.2 kg/m<sup>2</sup> (15<sup>th</sup> percentile for age and sex). The serum calcium was 5.7 mg/dL (normal 8.5-10.5), ionized calcium 2.68 mg/dL (4.4-5.4), phosphate 2.7 mg/dL (normal 4.3-5.4), magnesium 1.57 mEq/L (1.8-2.5), sodium 142 mEq/L (135-145), potassium 4.8 mEq/L (3.5-5.1), albumin 3.5 g/dL (3.5-5.5), and alkaline phosphatase 121 U/L (120-502). Additionally, she had extremely low serum 25-hydroxyvitamin D (3 ng/mL, normal >20), elevated serum intact parathyroid hormone (241 pg/mL, normal <65) and iron deficiency anemia [hemoglobin 9.5 g/dL (normal >11), serum ferritin 2.9 ng/mL (normal >12)], for which she received 200 mg of IV iron sucrose as a slow infusion. Tetany was corrected within hours with continuous infusion of calcium gluconate under continuous cardiac monitoring, but asymptomatic hypocalcemia required daily supplementation of oral calcium carbonate 1g/day and oral vitamin D3 drops 1,600 IU/day, until it

was fully corrected on the 8<sup>th</sup> hospital day. Hypophosphatemia and hypomagnesemia were fully-corrected earlier, i.e., on the 5<sup>th</sup> hospital day.

Her hospitalization was complicated by development of edema that required fluid restriction and administration of furosemide and left lower lobe pneumonia treated with IV ceftriaxone. After 16 days of hospitalization, she was sent home in excellent clinical condition with oral supplements of calcium, vitamin D3 and multi-vitamins containing thiamine. The oral supplements of calcium carbonate and multi-vitamins were discontinued one month after discharge, while supplemental vitamin D was discontinued approximately two months later, when the serum concentrations of 25-hydroxyvitamin D were steadily >30 ng/mL. Currently the patient is asymptomatic, with a normal physical examination, serum electrolytes, vitamin D3 and parathyroid hormone.

### **3. Discussion**

Clinical presentation of CD with tetany is extremely uncommon [2, 3]. Despite that, the serum calcium of patients with untreated CD appears to be lower than in normal subjects, as shown by a screening study in United Kingdom that found serum calcium to be on average 0.02 mmol/L lower in asymptomatic CD patients than the general population [4]. Kavak et al studied various markers of bone mineral density and bone mineral content in 34 children with untreated CD at diagnosis, and in 28 CD patients on a gluten-free diet for one year. Hypocalcemia, albeit mild was detected in 17.6% of the newly diagnosed patients with CD and in only 3.6% of the treated patients, while serum calcium levels were significantly lower in untreated patients. Moreover, the intact parathormone concentrations were significantly higher in patients with newly diagnosed CD ( $66.69 \pm 37.92$  pg/mL versus  $45.16 \pm 24.02$  pg/mL, respectively;  $P=0.017$ ) [5]. Shaker et al described 15 adult patients, 11 of whom were >60 years of age, who were examined for skeletal disease, hypocalcemia or both and in whom the diagnosis of CD was subsequently made [6]. Most patients had no or mild gastrointestinal symptoms indicating that patients with CD, hypocalcemia and skeletal complaints may be seen by other specialists for years before the correct diagnosis is made.

Hypocalcemia in CD is thought to occur due to loss of villous surface area along with decreased vitamin D, with unabsorbed dietary calcium binding to excess fatty acids in the intestinal lumen as a result of prominent fat malabsorption [6]. Impairment of the active intestinal calcium transport has also been described due to depletion of calbindin from the enterocytes [7]. Calcium malabsorption causes secondary hyperparathyroidism, as seen in our case. It has also been shown that hypocalcemia leads to insufficient endogenous cholecystokinin release by the duodenal mucosa during meals. This fails to stimulate normal gallbladder contraction and pancreatic enzyme secretion and leads to worsening steatorrhea and a vicious circle, with fatty acids in the intestinal lumen binding dietary calcium, preventing its absorption, and further aggravating the underlying hypocalcemia [8].

Although hypocalcemia in CD results mainly from intestinal malabsorption of calcium, insufficient calcium supply in strict gluten free diets may also play a role [9]. Thus, patients with CD should be advised to consume natural, calcium-rich gluten free products or buy baked calcium-fortified gluten-free foods that have the potential of

increasing the calcium content in their diet. In our patient, we were unable to find accurate information regarding the calcium and phosphate content of the baked gluten-free products she consumed, because no such information was available on the product labels.

The dramatic presentation of our patient with painful carpedal spasm can be part of a constellation of symptoms referred to as celiac crisis or more likely be a symptom of what is known as RFS. More specifically, celiac crisis is a life-threatening syndrome of patients with CD, who have profuse diarrhea and severe metabolic disturbances including hypokalemia, hypocalcemia, hypernatremia or hyponatremia and hypomagnesemia [10]. On the other hand, RFS is characterized by the sudden shift in fluids and electrolytes that occurs in malnourished patients, who are suddenly refeed without restrictions [11]. It shares many of the metabolic disturbances of celiac crisis but is not associated with diarrhea (our child had normal bowel movements), while its hallmark electrolyte disturbance is hypophosphatemia. Table 1 summarizes risk factors for RFS that have been used in adults [12]. Despite the paucity of reports on RFS in children with CD, the pathophysiology of the syndrome is considered well-established. Abrupt refeeding with gluten-free foods of a malnourished child with CD leads to increased insulin and decreased glucagon secretion, as part of the body's anabolic adaptation. As an anabolic hormone, insulin promotes the biosynthesis of protein and fat for which an adequate mineral supply is required but is unavailable due to the chronic malnutrition. In addition, insulin promotes the intracellular transport of potassium, which is followed by intracellular carriage of phosphorus and magnesium, leading to the characteristic triad of electrolyte abnormalities of the syndrome, i.e., hypokalemia, hypophosphatemia, and hypomagnesemia. RFS is also associated with vitamin deficiency, mainly of thiamine, an essential coenzyme in carbohydrate metabolism, and this was the reason we prescribed multi-vitamins with thiamine in our patient [13].

Although our child did not have the classic risk factors of RFS summarized in Table 1, the fact that she was liberally refeed at home against medical advice with gluten-free foods after the diagnosis of CD was established likely triggered the severe hypocalcemia in the context of already borderline serum calcium (8.5 mg/dL) and uncorrected vitamin D deficiency. Agarwal et al described 35 patients with CD, five of whom (3 boys, median age 6.5 years, range 2.2-10) were identified as having RFS. All five children had hypocalcemia, hypophosphatemia, hypokalemia, hypoalbuminemia and anemia. Despite their clinical features fulfilled the criteria for celiac crisis, their symptoms worsened after the introduction of a gluten-free diet, a similar situation with that of our patient. All were successfully managed with gradual feeding and correction of the electrolyte abnormalities, and non-received corticosteroids, the classical treatment of celiac crisis [14].

Unintentional weight loss $\geq$ 10-15% of body weight over the last 6 months.
Little or no nutritional intake for the last 10 days.
BMI $<$ 18.5 kg/m <sup>2</sup> .
Hypophosphatemia, hypokalemia, hypomagnesemia prior to feeding.

**Table 1:** Risk factors for RFS (modified from reference 12).

#### 4. Conclusion

In conclusion, although hypocalcemia is a relatively common finding in CD, it is usually asymptomatic and presentation of CD with hypocalcemic carpopedal spasms is exceptional. The unrestricted refeeding of malnourished CD patients with gluten-free foods can precipitate the appearance of hypophosphatemia, hypocalcemia, and symptomatic tetany. Hence, newly diagnosed malnourished patients with CD should be advised to increase their oral intake gradually, and to closely monitor their serum electrolytes.

#### Conflict of Interest

None.

#### Ethics Statement/Confirmation of Patient Permission

Ethics approval not required. Patient's family permission for publication was obtained.

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