

Hypocalcemic seizure in an adolescent with Down syndrome: a manifestation of unrecognized celiac disease

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SUMMARY: Korkmaz HA, Dizdärer C, Ecevit ÇÖ. Hypocalcemic seizure in an adolescent with Down syndrome: a manifestation of unrecognized celiac disease. Turk J Pediatr 2013; 55: 536-538.

Celiac disease (CD) affects up to 1% of the general population. Classically, it manifests with intestinal symptoms (diarrhea, steatorrhea, abdominal pain or discomfort) associated with weight loss and anemia. Seizure is a rare form of presentation of CD. A 13-year-old female patient with Down syndrome was admitted to the pediatric emergency department with generalized tonic-clonic seizure in addition to numbness around the mouth, paresthesias, and muscular cramping for seven days. Investigations revealed severe hypocalcemia and vitamin D deficiency, which were a consequence of malabsorption secondary to histopathologically confirmed CD. Physicians should be aware that unrecognized CD can cause severe hypocalcemia.

Key words: hypocalcemia, seizure, celiac disease, Down syndrome, vitamin D deficiency.

Celiac disease (CD) is an immune-mediated enteropathy triggered by ingestion of wheat gluten and recognized to involve all the ethnic groups, with a worldwide prevalence of 1–2%¹. Many studies originating from different centers have reported a prevalence of CD in Down syndrome (DS) ranging from 4.6%-13%²⁻⁴. It is estimated that 6.3% of children with DS in Turkey have CD⁵. CD was reported in 1% of 100 DS patients in Turkey in another study⁶. Originally considered a rare malabsorption syndrome of childhood, CD is now recognized as a common condition that may be diagnosed at any age and that affects many organ systems¹. CD might present in an atypical manner with a predominance of extra-intestinal manifestations such as anemia, short stature, recurrent stomatitis, infertility, Graves' disease, type 1 diabetes mellitus, and various musculoskeletal signs and symptoms¹. Hypocalcemia in CD was reported in 17.6% of the newly diagnosed patients and in 3.6% of the patients receiving treatment⁷. Untreated patients had significantly lower serum calcium and significantly higher intact parathormone levels than did treated patients⁷.

Here, we report a 13-year-old female patient with DS and Hashimoto's thyroiditis who presented to the pediatric emergency department

with generalized tonic-clonic seizure. The case demonstrates a rare pattern of clinical presentation of undiagnosed CD in a child and emphasizes the need to consider CD.

Case Report

A 13-year-old female patient with DS was admitted to our hospital with a generalized tonic-clonic seizure with preceding numbness around the mouth, paresthesias, and muscular cramping for seven days. She also had weight loss (14 kg) and chronic diarrhea for six months. She had no events that might have caused seizure such as trauma, infections, fever, poisoning, or administered drugs. Her medical history revealed an uneventful birth history, no other seizure, normal cardiac function, and L-thyroxine treatment for Hashimoto's thyroiditis since the age of five years. Her parents were not relatives and the remaining family members were healthy. Her vital signs were as follows: blood pressure, 90/60 mmHg; heart rate, 122 beats per minute; oxygen saturation, 94%; and body temperature, 36.4°C. The physical examination revealed confusion, weight 38 kg (25th percentile), height 138 cm (25th-50th percentile), positive Chvostek's sign and Trousseau's sign, DS stigmata, and pubertal stage Tanner 5. The remaining systemic

evaluation was normal.

Laboratory analysis showed the following: total calcium 1.3 $\mu\text{mol/L}$ (normal: 2.2-2.7), ionized calcium 0.84 $\mu\text{mol/L}$ (normal: 1.13-1.18), phosphate 1.13 mmol/L (normal: 0.95-1.5), mild iron deficiency anemia (hemoglobin 9.2 g/dl , ferritin 5.6 ng/ml , red blood cells [RBCs] $3.16 \times 10^6/\mu\text{L}$, mean corpuscular volume [MCV] 72 fL) with normal white blood cell count. Corrected QT interval was consistent with hypocalcemia: 0.46 seconds (normal: 0.32-0.44). Seizure stopped with intravenous calcium gluconate (2 cc/kg) and diazepam. She showed normal serum free T4 (fT4), free T3 (fT3), and thyroid-stimulating hormone (TSH) levels, as 1.38 ng/dl (normal: 0.92-1.99), 2.54 pg/ml (normal: 2.15-5.83), and 2.82 $\mu\text{U/ml}$ (normal: 0.73-8.35), respectively. Parathyroid hormone level was 182.9 pg/ml (normal: 15-65), magnesium 0.62 mmol/L (normal: 0.66-0.95), 25-OH vitamin D <2.5 ng/ml (normal: 15-50), and 1-25-OH vitamin D 10 pg/ml (normal: 15-90). Weight loss of 10 kg and chronic diarrhea for six months necessitated investigations for CD. Immunoglobulin (Ig)A and IgG antigliadin, IgA transglutaminase, and antiendomysial antibodies were found to be positive. Duodenal biopsy showed focal villous blunting and atrophy with mildly expanded lamina propria with lymphocytes and plasma cells, consistent with CD. Her symptoms resolved with intravenous administration of calcium gluconate for two days and intramuscular administration of vitamin D (a single dose of 300,000 IU). She was treated with oral iron supplements (ferrous sulfate 200 mg two times a day) for iron deficiency anemia. She was discharged with oral calcium lactate (50 mg/kg/day) and a gluten-free diet.

The clinical response to the gluten-free diet was excellent. Evaluation after 18 months revealed a content and alert child with a weight gain of 14.2 kg (weight 52.2 kg, 50th-75th percentile; height 139.8 cm, 10th-25th percentile), resolution of diarrhea, and normal levels of calcium, phosphorus, alkaline phosphatase, 25-OH vitamin D, and parathormone. She presented normal blood counts and serum biochemical analyses within two months after discharge. Additionally, there were no further episodes of tetany or diarrhea over the 18 months of follow-up.

Discussion

After a first unexplained non-febrile seizure, laboratory testing should be considered particularly in patients with suggestive clinical findings such as seizure, weight loss, chronic diarrhea, paresthesias, and muscular cramping, as in our patient. The work-up should include electrolyte levels, including sodium, potassium, calcium, magnesium, and phosphorus. Once hypocalcemia is found, major causes of hypocalcemia in children and adolescents should be investigated by obtaining a basic metabolic panel, liver function tests, PTH, 25-OH vitamin D, and 1,25-(OH)₂ vitamin D⁸. A work-up for malabsorption should be undertaken if it is suggested by the history or initial laboratory results, such as in our patient. The diagnosis of secondary vitamin D deficiency due to CD was made in our case upon detection of antigliadin antibodies. Vitamin D deficiency can be mistaken for pseudohypoparathyroidism (PHP) in some cases⁹ because children with PHP present with hypocalcemia and normal or elevated serum phosphorus concentrations despite elevated serum PTH levels.

The mechanism of hypocalcemia in CD is complex. Calcium malabsorption in CD is due to villous atrophy in the proximal intestine. Villous atrophy causes a reduction in active absorption of calcium and an increase in unbound intraluminal fatty acids that bind intraluminal calcium. Calcium malabsorption causes secondary hyperparathyroidism, and the latter results in an enhanced metabolic breakdown of vitamin D metabolites^{10,11}. Of the untreated patients with CD, 29.4% had high intact parathormone concentrations⁷. Additionally, vitamin D receptor resistance in the intestinal wall has been suggested, and the amount of vitamin D-dependent calcium-binding proteins in the intestinal wall appears to be reduced in active disease¹¹.

Patients with DS are at higher risk for developing autoimmune diseases than the general population¹²⁻¹⁴. Autoimmune diseases like Hashimoto's thyroiditis, Graves' disease, diabetes mellitus type I, CD, autoimmune chronic active hepatitis, alopecia, vitiligo, and hypoparathyroidism are recognized associations with DS¹²⁻¹⁵. The risk of CD is increased in children with DS^{2-4,12}. George et al.¹² reported the prevalence of CD in children with DS as

7%. The reason for the high prevalence of CD in DS patients is not completely known. This has been associated with the role of histocompatibility antigens HLA DR3 and HLA DQA*0101¹²⁻¹⁴. The first hypothesis is that chromosome 21 bears many immune regulatory genes like ICOS-Ligand and the autoimmune regulator gene, which can trigger autoimmunity in the presence of an extra copy of chromosome 21. Another hypothesis is that presence of nonspecific mucosal anomalies in DS can cause increased gluten permeability, leading to CD and other food allergies¹²⁻¹⁴.

In summary, this case illustrates that pediatricians should consider CD in patients with hypocalcemia when they present with seizure, weight loss, chronic diarrhea, paresthesias, and muscular cramping. An excellent response can be achieved with appropriate treatment. The case demonstrates a rare pattern of clinical presentation of undiagnosed CD in a child and emphasizes the need to consider CD.

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