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The prevalence of celiac disease in children with iron-deficiency anemia

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Background/aims: *Celiac disease is an immune-mediated enteropathy caused by a permanent sensitivity to gluten in genetically susceptible individuals. Iron-deficiency anemia is the most commonly encountered anemia in humans. Iron-deficiency anemia also is a common extraintestinal manifestation of celiac disease. To determine the celiac disease prevalence in children with iron-deficiency anemia and to compare the hematologic parameters in iron-deficiency anemia patients with and without celiac disease.* ***Materials and Methods:*** *A total of 61 patients aged 2-16 years who presented with iron-deficiency anemia were included in this study. Hemoglobin, red cell indices (mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red cell distribution width), serum iron, and serum ferritin were determined. Venous blood samples for anti-tissue transglutaminase antibody immunoglobuline A were obtained from these patients. Upper gastrointestinal endoscopy was recommended to patients who had positive serology.* ***Results:*** *Of 61 patients with iron-deficiency anemia, 13 (21,3%) had positive serology for celiac disease. The small intestine biopsy of all patients with positive serology showed villous atrophy (Marsh 3). The mean hemoglobin level was significantly lower in iron-deficiency anemia patients with celiac disease when compared to those without celiac disease (7,8±2,6 vs. 11,3±0,9 g/dL, p<0,05). There was a statistically significant negative correlation of tissue transglutaminase titers with hemoglobin, red cell indices, serum iron, and serum ferritin levels.* ***Conclusions:*** *Screening of celiac disease by anti-tissue transglutaminase antibody should be done as a routine investigation in children with iron-deficiency anemia. Biopsy should be recommended in patients with iron-deficiency anemia who have positive celiac disease serology.*

Key words: Celiac disease, prevalence, iron-deficiency anemia, child

Demir eksikliği anemisi olan çocuklarda çölyak hastalığı

Giriş ve Amaç: *Çölyak hastalığı genetik olarak yatkın kişilerde glutene karşı kalıcı hassasiyetle ortaya çıkan immün aracılı bir enteropatidir. Demir eksikliği anemisi insanlarda en çok görülen anemidir. Demir eksikliği anemisi aynı zamanda çölyak hastalığının en yaygın görülen ekstraintestinal bulgularından biridir. Bu çalışmada amacımız demir eksikliği anemisi olan çocuklarda çölyak hastalığı prevalansını belirlemek ve bu hastalardaki hematolojik parametreleri çölyak hastalığı olmayan demir eksikliği anemisi olan hastalarınkiyle karşılaştırmaktı.* ***Gereç ve Yöntem:*** *2-16 yaşları arası demir eksikliği anemisi olan 61 hasta çalışmaya alındı. Hastaların hemoglobin, eritrosit indeksleri (ortalama eritrosit hacmi, ortalama eritrosit hemoglobini, ortalama eritrosit hemoglobin konsantrasyonu, eritrosit dağılım genişliği), serum demir ve ferritin düzeyleri değerlendirildi. Hastalardan anti-transglutaminaz immunglobulin A çalışmak için venöz kan örnekleri alındı. Çölyak hastalığı serolojisi pozitif olan hastalara üst gastrointestinal sistem endoskopisi önerildi.* ***Bulgular:*** *Demir eksikliği anemili 61 hastanın 13'ünde (%21,3) çölyak hastalığı serolojisi pozitifti. Bu hastaların ince barsak biyopsisi villöz atrofi (Marsh 3) ile uyumluydu. Çölyak hastalarının ortalama hemoglobin seviyeleri çölyak hastalığı olmayan demir eksikliği anemili hastalarınkinden anlamlı derecede düşüktü (7,8±2,6 vs 11,3±0,9 g/dl) (p <0,05). Doku transglutaminaz antikoru titreleri ile hemoglobin, eritrosit indeksleri, serum demir ve ferritin seviyeleri arasında istatistiksel olarak anlamlı negatif bir korelasyon vardı.* ***Sonuç:*** *Anti-doku transglutaminaz antikoru ile çölyak hastalığı taraması demir eksikliği anemisi olan çocuklarda rutin olarak yapılmalıdır. Çölyak hastalığı serolojisi pozitif olan demir eksikliği anemili hastalara biyopsi yapılması önerilmektedir.*

Anahtar kelimeler: Çölyak hastalığı, prevalans, demir eksikliği anemisi, çocuk

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INTRODUCTION

Celiac disease (CD) is an immune-mediated enteropathy caused by a permanent sensitivity to gluten by taking nutrients such as wheat, barley, and rye in genetically susceptible individuals (1-4). It is characterized by the presence of chronic inflammation of the small bowel's mucosa and submucosa that results in malabsorption of nutrients (5-7). CD is one of the most commonly known genetic disease, with a prevalence ranging from 1:85 to 1:500 in different populations (2,6,8,9).

The presentation of CD has been described as two clinical subtypes. Classic presenting features of CD include chronic diarrhea, failure to thrive, abdominal distention, and weight loss (10). Most individuals with CD have the silent or atypical (subclinical) form, and the condition may present insidiously, for example with iron-deficiency anemia (IDA), osteoporosis, cryptogenic hypertransaminasemia, or neurological symptoms (4). CD is a common cause of various hematologic disorders, the most common of which is anemia. The anemia of CD is usually due to malabsorption of micronutrients such as iron, folic acid, and vitamin B12 (9).

IDA is the most commonly encountered anemia in humans and is usually due to either increased iron loss or impaired absorption of iron (9). IDA resistant to oral iron supplementation is a common extraintestinal manifestation of CD and has been described as the sole manifestation of the disease without overt malabsorption (1-5,8,9,11).

The absorption of dietary iron occurs in the proximal small intestine and depends upon several factors, including an intact mucosal surface and intestinal acidity (5,9,10). The iron deficiency in CD is primarily attributed to the enteropathy characterized by mucosal damage of the small intestine that results in impaired absorption of iron, but there may also be occult blood loss in the gastrointestinal tract (9,12).

The prevalence of CD in adult patients presenting with IDA varies from 0 to 14,6% (2,7,11,13-15). The first prevalence study in children with IDA has reported a prevalence rate of 4,4 % for CD (3).

Our aim in this study was to determine the CD prevalence in children with IDA and to compare the hematologic parameters in IDA patients with and without CD.

MATERIALS and METHODS

A total of 61 patients aged 2-16 years who presented with IDA were included in this prospective study. Mean weight and height were 21 kg and 111 cm in CD patients and 19 kg and 106 cm in non-CD patients, respectively. According to body weight and height, there was no statistically significant difference between CD and non-CD patients. Patients with chronic disease, hemorrhagic diathesis, or any other blood disease were excluded. None of the patients had gastrointestinal tract findings of CD, such as chronic diarrhea, abdominal distension or vomiting, and failure to thrive. Some of the patients had fatigue and pallor due to anemia. Their hemoglobin (Hb), red cell indices [mean corpuscular volume-(MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW)], serum iron, and serum ferritin were below the acceptable level for age (16).

None of the patients had Hemoccult-positive stools. Giardia lamblia was not detected in any of the stools and biopsy specimens. Total IgA levels were determined in all subjects; IgA deficiency was not found in any patient.

Venous blood samples for tissue transglutaminase antibody (tTG) were obtained from all patients. Samples were tested for tTG antibodies using a commercially available enzyme-linked immunosorbent assay (AESKU 7503, Germany). 13 patients with IDA had positive serology for CD; the mean tTG IgA value was 152±101 IU/mL. Upper gastrointestinal endoscopy (UGIE) was recommended to patients who had positive serology. The histopathological findings of CD were classified according to the Marsh criteria (17). The study was approved by the Ataturk University Ethics Review Committee of the Faculty of Medicine, and informed consent was obtained from the parents.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) software.

RESULTS

Of 61 children with IDA, 36 (59%) were female and 25 (41%) were male. The mean age of the patients who were enrolled in this study was 5,3±4,3 years (range: 2-16 years). Of 61 patients with IDA, 13 (21,3%) had positive serology for CD. Of 61 children with IDA, 25 (40,9%) were resistant to Fe therapy. These patients had received Fe therapy before being admitted to our hospital. Seven of 25 (28%) patients with refractory IDA had CD.

The small intestine biopsy of all patients with positive serology showed villous atrophy (Marsh 3c). The prevalence of biopsy-proven CD in patients with IDA was 21,3%.

In Table 1, the mean levels of Hb, Hct, MCV, MCH, RDW, serum iron, and serum ferritin in IDA patients with CD are compared with the levels in IDA patients without CD.

The mean Hb level was significantly lower in IDA patients with CD than in those without CD (7,8±2.6 vs. 11,3±0,9 g/dL, p<0,05).

There was a statistically significant negative correlation of tTG titers with Hb, red cell indices, serum iron, and serum ferritin levels (p<0,01).

DISCUSSION

IDA can be found in CD patients even in the absence of diarrhea or steatorrhea. The loss of iron in the sloughing intestinal enterocytes, malabsorption of dietary iron, and rarely gastrointestinal bleeding can contribute to the pathogenesis of IDA in CD (18). We found that the prevalence of CD in children with IDA was 21,3% in our study. Various rates of prevalence of CD in IDA patients have been reported among different studies (2,3,7,13-15). One of this studies was performed on children, and CD prevalence had been determined to be 4.4% in children with IDA (3). Between 5% and 8,5% of adults with unexplained IDA have CD (7). In another study, CD was found as the cause of IDA of obscure origin in a significant proportion (14.6%) of patients (2). In a small, uncontrolled study of patients with IDA attending a hematology clinic, five of 85 patients (5.8%) were found to have previously undiagnosed CD and were unresponsive to oral iron supplementation (14). In a screening study of anemic blood donors, 22 of 483 cases (4.5%) were shown to have biopsy-proven gluten enteropathy (15). Grisolano et al. (11) reported that 8,7% of patients presenting with IDA were diagnosed with CD. In one prospective study of 100 patients with IDA, which included esophagogastroduodenoscopy and colonoscopy in the workup of anemia, no patient was found to have CD (13).

In the present study, we determined the highest prevalence rate of CD in children with IDA in comparison to other literatures. In the first CD prevalence study in our county, the serological and biopsy-proven prevalence of CD in children were as high as 1:115 and 1:158, respectively (6). The Turkish Celiac Disease Study Group reported that the biopsy-proven prevalence of CD was 1:212 (0,47%) in healthy Turkish school children. On the other hand, the estimated prevalence of CD (biopsy-proven CD patients plus previously diagnosed CD subjects plus children with high tTG and EMA positivity without biopsy) was 1:58 (1,74%) in this study (19). This high prevalence of CD in Turkey may explain why the prevalence rate of CD in children with IDA is the highest one (21,3%).

Physicians should be aware of the significant relation existing between IDA and subclinical CD even if gastrointestinal symptoms are absent or nonspecific (2,3). Similarly, none of our patients had gastrointestinal symptoms and signs of CD. In particular, higher celiac rates have been reported in celiac screenings of patients resistant to iron therapies (3). Carroccio et al. (14) found that the celiac prevalence in adults with IDA was 5,8%, whereas the same rate was 20% in the refractory anemia subgroup. In our study, 25 patients (40,9%) were resistant to iron supplementation. However, 7 of 25 (28%) patients had CD.

In one study, the Hb level in CD patients was inversely correlated with the severity of the histolo-

Table 1. Comparison of hematological parameters in IDA patients with and without CD

	CD patients	Non-CD patients	p-value
Hb (g/dL)	7,8±2,6	11,3±0,9	<0,05
Hct (%)	27,5±9,2	33,9±4,2	<0,05
MCV (fL)	57,3±4,5	74,4±3,3	>0,05
MCH (pg/mL)	37,3±2,1	24,6±2,2	<0,05
RDW	18,7±3,7	16,2±1,3	<0,05
Serum iron (µmol/L)	19,1±10,9	25,7±9,4	>0,05
Ferritin (ng/mL)	6,4±5,3	16,3±5,7	>0,05

gical injury. Patients with Marsh 3 lesions had the most severe anemia, consistent with the role of impaired intestinal absorption in the pathogenesis of IDA (2). In another study on adult celiac patients presenting with unexplained IDA, 90% of patients had Marsh 3 lesion in histological examination. In all these patients, antiendomysial (EMA) and/or tTG antibodies were present (4).

Antibody titer appears important, as most false-positive results occur at the lowest titer. High EMA titers are therefore highly reliable in identifying CD. However, in clinical practice, EMA sensitivity is disappointing. tTG antibodies replace EMA in the last few years. Also, the high sensitivity of tTG antibodies of 95% is impressive (8).

In our study, IDA patients with CD had lower Hb levels than those without CD. Biopsy in patients who had undergone endoscopy revealed Marsh 3 lesions. Subclinical CD patients presenting with IDA, if they have lower Hb levels, may have severe histologic injury. Moreover, we found that Hb levels of CD patients negatively correlated with tTG titers. Different studies have demonstrated that IDA may be the only presenting symptom in CD (4). Therefore, CD should be considered in any patient with unexplained IDA (2). There are at least two important clinical reasons why an active search for silent CD should be carried out in patients with IDA. The first one is that IDA may lead to retardation of mental and psychomotor functions, growth retardation, and impaired physical performance in children (7). The second reason is that CD may be complicated by intestinal lymphoma, even in the subclinical form, and thereby, strict compliance with gluten-free diet protects against this complication with early diagnosis (7,10,12,20). Additionally, early recognition and treatment may help optimize growth (10).

As the prevalence of CD is high in the community, it should therefore be considered as a potential cause in any patient presenting with IDA. Recent guidelines from the British Society of Gastroenterology recommend that duodenal biopsies should be taken during endoscopy if no obvious cause of iron deficiency could be found (21).

Pediatricians must be aware that only a portion of CD cases are clinically overt, atypical forms are more common in children than previously considered, and CD may become apparent at any age, even years after gluten diet initiation (22).

The findings in the present study have two important implications. First, screening of CD by anti-tTGA should be done as a routine investigation in children with IDA. Second, biopsy should be recommended in patients with IDA who have positive CD serology.

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