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# Celiac disease prevalence in patients with iron deficiency anemia of obscure origin

## Nedeni belirsiz demir eksikliği anemili hastalarda çölyak hastalığı prevalansı

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***Background/aims:*** *Anemia, especially due to iron deficiency, is a frequent feature in celiac disease. In this study, we aimed to define the prevalence of celiac disease in Turkish patients with iron deficiency anemia of obscure origin.* ***Methods:*** *One thousand four hundred and eighty-six consecutive patients with iron deficiency anemia were evaluated for etiology. Of those, 77 patients were found to have iron deficiency anemia of obscure origin. Sera from 77 patients with iron deficiency anemia of obscure origin and 119 healthy controls were tested for IgA and IgG tissue transglutaminase (tTG) antibodies by ELISA. Endoscopic mucosal biopsies were taken from the second part of the duodenum in these patients. Histopathologic examination results of patients were stratified according to Marsh classification.* ***Results:*** *IgA and IgG class anti-tTG antibodies were found positive in 6 (7.8%) and 3 (3.9%) patients with iron deficiency anemia of obscure origin, respectively. Three patients had only IgA anti-tTG and 3 had both IgA and IgG anti-tTG antibodies. In the control group, 1 subject was positive for both IgA and IgG anti-tTG antibodies (0.7%). Six patients (7.8%) and 1 control subject (0.8%) had histopathologic findings of celiac disease (p=0.02).* ***Conclusions:*** *Patients with iron deficiency anemia of obscure origin had increased prevalance of celiac disease. Our study results suggest that serological screening may be recommended for early detection of celiac disease in patients with iron deficiency anemia of obscure origin.*

**Key words:** Celiac disease, iron deficiency anemia, tissue transglutaminase

***Amaç:*** *Anemi, özellikle demir eksikliği anemisi, çölyak hastalığında sık görülür. Bu çalışmada, nedeni belirsiz demir eksikliği anemili Türk hastalarda çölyak hastalığı prevalansını belirlemeyi amaçladık.* ***Yöntem:*** *Ardışık 1486 demir eksikliği anemili hasta etyoloji için değerlendirildi. Bunların 77'sinde nedeni belirsiz demir eksikliği vardı. Nedeni belirsiz demir eksikliği olan 77 hasta ve 119 sağlıklı kontrolün serumlarında ELISA yöntemiyle IgA ve IgG doku transglutaminaz antikorları araştırıldı. Bu hastalarda duodenum ikinci kısmından endoskopik mukozal biyopsiler alındı. Histopatolojik değerlendirme sonuçları Marsh sınıflandırmasına göre derecelendirildi.* ***Bulgular:*** *Nedeni belirsiz demir eksikliği anemisi olan 6 hastada (7.8%) IgA, 3 hastada (3.9%) IgG sınıfından doku transglutaminaz antikoru pozitif bulundu. Üç hastada sadece IgA doku transglutaminaz antikoru, 3 hastada hem IgA hem de IgG doku transglutaminaz antikoru vardı. Kontrol grubunda 1 bireyde (0.7%) IgA ve IgG doku transglutaminazı saptandı. Altı hastada (7.8%) ve 1 kontrolde (0.8%) çölyak hastalığı histopatolojik bulguları saptandı (p=0.02).* ***Sonuç:*** *Nedeni belirsiz demir eksikliği anemili hastalarda çölyak hastalığı prevalansı yüksektir. Çalışmamızın sonuçlarına göre, nedeni belirsiz demir eksikliği hastalarında çölyak hastalığının erken tanısı için serolojik tarama yapılması önerilebilir.*

**Anahtar kelimeler:** Çölyak hastalığı, demir eksikliği anemisi, doku transglutaminaz

## INTRODUCTION

Celiac disease (CD) is characterized by malabsorption of nutrients, chronic inflammation and damage of the small intestinal mucosa caused by the ingestion of gliadin fraction of wheat gluten and similar alcohol-soluble proteins of barley and rye in genetically susceptible subjects (1). The clinical presentation of CD is extremely heterogeneous. Typical symptoms include chronic diarrhea, abdominal distension, and failure to thrive (2, 3). However, only a few patients with CD show clinical malabsorption, while most patients have subtle symptoms (1). Therefore, the disease is clearly underdiagnosed (3).

The prevalence of CD has changed over the last

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30-40 years with the help of highly sensitive serologic tests, such as anti-endomysial antibodies (EMA) and anti-tissue transglutaminase (tTG) antibodies, which have made CD diagnosis easier in subclinical cases and several risk groups (1, 3-5). Screening studies show a high prevalence of CD (between 1/130-1/300) among both healthy children and adult populations in European countries (6, 7). In a recent study, the prevalence of CD in 2000 healthy blood donors was found to be 1.3% (1/77) in Turkey (8).

Iron deficiency anemia (IDA) is the most common form of anemia, occurring in 2–5% of adult men and post-menopausal women in the developed world (9, 10). While menstrual blood loss is the most common cause of IDA in pre-menopausal women, blood loss from the gastrointestinal (GI) tract is the most common cause in adult men and post-menopausal women (11-14). In practice, young female patients with IDA have been treated with iron supplementation. However, men and post-menopausal women have been investigated further.

Iron deficiency anemia is a commonly observed sign in CD (2). Only a minority of CD patients present with classical malabsorption symptoms, whereas most patients have subclinical or silent forms in which IDA can be the sole presentation (15). The prevalence of CD was found between 4.7-5% in patients with IDA (16, 17).

To our knowledge, there is no published study from Turkey about prevalence of CD in patients with IDA of obscure origin. The aim of this study was to define the prevalence of CD in Turkish patients with IDA of obscure origin.

## MATERIALS AND METHODS

### Patients Studied

Between November 2007 and June 2008, we evaluated 1486 consecutive patients with IDA referred to the Hematology and Gastroenterology Departments of Kirikkale University School of Medicine, Research and Training Hospital. Initially, IDA diagnosis was restored to all 1486 patients. IDA was defined as: hemoglobin level less than lower limits (13.5 g/dl for male adult, 12.0 g/dl for female adult), ferritin level <15 ng/ml (normal 20-300 ng/ml), transferrin saturation less than 15%, and mean corpuscular volume less than 80 fL. Patients with the following conditions were excluded from the study: age <16 years or >80 years, known or previous investigation for CD, acute or chronic obvious blood loss (e.g. melena, hematochezia, hemoptysis, recurrent epistaxis, hematuria, trauma), previous treatment for IDA, known malignancies or chronic diseases (e.g. chronic renal or liver disease, severe respiratory or cardiac disease, connective tissue disorders), pregnancy, hypermenorrhea (cycles ≥7 days), menometrorrhagia, alcoholism, and gastric surgery. We then performed an extensive evaluation of IDA etiology, including detailed bleeding questionnaire, physical examination, urine analysis for hematuria, occult blood loss analysis in feces, upper GI endoscopy, and colonoscopy. After this evaluation, the remaining 77 patients (47 female, 30 male) aged between 17 and 79 years (mean age: 41.0±9.3 years) with IDA of obscure origin and 119 healthy blood donors (69 female, 50 male) aged between 18-58 years (mean age: 38.8±8.5 years) as a control group were included into the study. Informed consent was obtained from patients and control subjects. The study protocol was approved by the ethics committee of Kirikkale University Hospital.

### Endoscopic and Histological Examination

All patients with IDA of obscure origin and a female blood donor in the control group who had both positive IgA and IgG anti-tTG antibodies underwent upper GI endoscopy and colonoscopy. Both endoscopic examinations were performed consecutively in the same session by two of the authors (SG, FY) using a Fujinon EG 450 HR video endoscope (Fuji Photo Optical Co., Ltd., Saitama, Japan). Before endoscopic examination, intravenous midazolam was given to all patients for sedation. Two biopsy specimens were taken from the second part of the duodenum, and a venous blood sample was also taken for anti-tTG IgA and IgG measurements from patients with normal endoscopic and colonoscopic examination. These specimens were immediately fixed in 10% buffered neutral formalin and embedded in paraffin. The tissue sections were stained with hematoxylin-eosin. Samples of duodenal mucosa were graded according to the modification of Marsh classification (18, 19) by a single pathologist.

### Antibody Test

Sera from study patients and controls were stored at -70 °C. IgA and IgG anti-tTG antibody assays were carried out by enzyme-linked immunosorbent assay (ELISA) (Aida Gmbh, Germany). Cut-off values were 15 IU/ml defined by the manufacturer.

### Statistical Analyses

Fisher's exact test was used to compare CD prevalences and gender differences between the two groups. The comparisons of mean ages and body mass indices (BMIs) between the two groups were done by Student t test. The statistical analysis was performed using a statistical program for PC (SPSS 11.0 for Windows, SPSS Inc., IL, USA). p values of less than 0.05 were considered statistically significant.

## RESULTS

The age, gender, and BMIs were similar in both groups (p=0.08, p=0.67, and p=0.16, respectively) (Table 1). Totally, 6 patients (4 F, 2 M) with IDA of obscure origin were found to be positive for at least one of the anti-tTG antibodies. IgA anti-tTG antibody was found to be positive in 6 (7.8%) patients with IDA of obscure origin. IgG anti-tTG antibody was found to be positive in 3 (3.9%) patients with IDA of obscure origin. Three patients were positive for both IgA and IgG anti-tTG antibodies (Table 2). In the control group, a female blood donor was positive for both IgA and IgG anti-tTG antibodies (0.8%). The frequency of anti-tTG IgA in the IDA group was significantly higher than in the control group (p=0.02) (Table 1). There was no difference in the frequencies of anti-tTG IgG between the IDA and control groups (p=0.3) (Table 1).

All subjects who were positive for anti-tTG IgA had histopathological findings of CD on duodenal biopsy, which were classified as Marsh IIIc in 2, Marsh IIIa in 2, Marsh II in 1, and Marsh I in 1 patient with IDA, and as Marsh I in 1 blood donor (Table 2).

The prevalence of CD was significantly higher in IDA of obscure origin patients than the control subjects (p=0.02). In the patients group, 3 women with CD were in premenopausal and 1 in postmenopausal period, and 2 had dyspeptic complaints.

**Table 1.** Demographic and serologic features of patient and control groups

| | Patients (n=77) | Controls (n=119) | p |
|---|---|---|---|
| **Age (year, mean±SD)** | 41.0±9.3 | 38.8±8.5 | 0.08 |
| **Gender (female/male)** | 47/30 | 69/50 | 0.67 |
| **Body mass index (kg/m²)** | 27.5±4.5 | 26.7±4.0 | 0.16 |
| **tTG IgA (n, %)** | 6 (7.8) | 1 (0.8) | *0.02* |
| **tTG IgG (n, %)** | 3 (3.9) | 1 (0.8) | *0.3* |
| **CD histology (n, %)** | 6 (7.8) | 1 (0.8) | *0.02* |

One control subject with CD was premenopausal. All subjects with histologically proven CD were prescribed gluten-free diet.

## DISCUSSION

Celiac disease has a wide clinical spectrum including GI and extra-GI findings, which can be diagnosed at any age from childhood to the elderly (2). Classical or typical form of CD is associated with features of malabsorption; however, a substantial number of CD patients have atypical manifestations, including hematologic, endocrinologic, renal, neurologic, psychiatric, dermatologic, and cardiovascular symptoms. Anemia, especially IDA, is a frequent feature in CD and may be the only presenting symptom (2). Increased prevalence of CD has been found in patients with IDA (16, 17). An early identification of CD in patients with IDA has great importance, since a strict adherence to a gluten-free diet not only provides management of anemia but also prevents the severe complications such as ulcerative jejunoileitis, intestinal lymphoma and neoplasm (20). Using a highly sensitive screening test (tTG antibody test) and duodenal histological examination, we confirmed that IDA may be the only presenting symptom of CD. To our knowledge, this is the first study investigating the prevalence of CD in patients with IDA of obscure origin in a Turkish population.

Serologic tests developed in the last decade provi-

**Table 2.** Characteristics of 6 patients with IDA and CD

| Patient no. | Sex (M/F) | Age (years) | BMI (kg/m²) | Anti-tTG IgA | Anti-tTG IgG | Duodenal biopsy (modified Marsh) | Clinical details |
|---|---|---|---|---|---|---|---|
| 1 | F | 36 | 26.89 | Positive | Negative | I | |
| 2 | M | 41 | 24.14 | Positive | Negative | II | Dyspepsia |
| 3 | F | 44 | 25.33 | Positive | Positive | IIIa | Dyspepsia |
| 4 | F | 39 | 27.00 | Positive | Positive | IIIa | |
| 5 | M | 43 | 21.64 | Positive | Negative | IIIc | |
| 6 | F | 59 | 26.03 | Positive | Positive | IIIc | Menopause |

IDA: Iron deficiency anemia. CD: Crohn disease. BMI: Body mass index. Modified Marsh classification: I= intraepithelial lymphocytosis (>40/100 epithelial cells), II: intraepithelial lymphocytosis + crypt hyperplasia, IIIa=mild villous atrophy, IIIc= total villous atrophy.

de a non-invasive tool to screen both individuals at risk for the disease and the general population. IgA anti-tTG assays by ELISA seem to be highly sensitive (90-98%) and specific (94-97%) for diagnosis of CD. Moreover, it is now widely available, less costly, and easier to perform than the immunofluorescence assays used to detect IgA EMA (2).

Screening studies show a high prevalence (between 1/130-1/300) of CD among both healthy children and adults in European countries (6,7). The prevalence of CD in 2000 healthy blood donors has recently been found to be 1.3% (1/77) in Turkey (8). This study shows that the prevalence of CD in the Turkish population is relatively high in comparison to the Western world.

In the literature, there are some studies in which the prevalence of CD was investigated in newly diagnosed IDA, with different results. Corazza et al. (17) reported the prevalence of CD as 5% in 200 patients with IDA. The prevalence had risen to 8.5% when patients with macrocytic anemia or microcytic anemia due to previous bleedings or those responsive to oral iron therapy were excluded. Three patients had diarrhea and seven patients had only anemia in their study group. Howard et al. (16) reported the prevalence of CD as 4.7% in 333 anemic patients with iron and/or folate deficiency. Annibale et al. (21) had investigated 71 patients with IDA for GI causes using colonoscopy and gastroscopy with gastric and duodenal biopsies. Four patients (5.6%) had CD. Unsworth et al. (22) found the CD prevalence as 6% in female blood donor volunteers with IDA. Recently, Zamani et al. (23) found the CD prevalence as 14.6% in patients with IDA of obscure origin.

In our study, the prevalence of CD in patients with IDA of obscure origin was found as 7.8%. This rate was significantly higher than in the control (0.7%) group (p=0.02). Our prevalence rate was similar with the literature discussed above. IgG anti-tTG was found positive in three of six patients with CD in the IDA of obscure origin group, revealing 50% sensitivity. The small number of patients with CD in our study group may account for this much lower sensitivity of the IgG anti-tTG test.

In conclusion, we found that the prevalence of CD was higher in patients with IDA of obscure origin than control subjects. Therefore, serological screening is recommended for early detection of CD in these patients. There are some important benefits of CD screening in patients with IDA. It may prevent the need for other often useless tests, treatment failure, and intestinal lymphoma, since CD may easily be treated with a gluten-free diet. The relatively small sample size may be considered a limitation of our study. Studies with larger populations would provide more accurate results.

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