ORIGINAL ARTICLE

TJG
The Turkish Journal of Gastroenterology

Celiac disease prevalence in patients with iron deficiency anemia

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Background/aims: *Iron deficiency anemia may be the first presenting finding of celiac disease, which is a common autoimmune disorder triggered by the intake of certain proteins. The aim of this study was to determine the prevalence of celiac disease in patients with iron deficiency anemia of obscure origin.* ***Materials and Methods:*** *Eighty-four patients with the diagnosis of iron deficiency anemia of obscure origin were included in the study. Histologic findings for celiac disease were investigated in biopsy specimens taken from the second part of the duodenum of all subjects. Patients were also screened using anti-endomysial and anti-gliadin antibodies. The diagnosis of celiac disease was confirmed by both serological positivity and histopathological findings.* ***Results:*** *In 6 of 84 patients (7.14%), both serologic and histopathologic findings were correlated with celiac disease. After six months under a gluten-free diet, their mean hemoglobin levels increased from 10.3±0.64 to 12.97±1.48 g/dl (p=0.002). One patient with positive serology for celiac disease but normal duodenal mucosal biopsies also improved clinically after a gluten-free diet at the end of the follow-up and was considered as celiac disease. Six of these 7 celiac disease patients (85.7%) were premenopausal women, with a mean age of 37.5±8.45 years.* ***Conclusions:*** *Clinicians should consider celiac disease as a possible cause of anemia in all patients with iron deficiency anemia of obscure origin, even in menstruating women. Serologic screening tests should be performed in premenopausal women with iron deficiency anemia, especially when anemia is refractory to oral iron treatment.*

Key words: Celiac disease, iron deficiency anemia, premenopausal women

Demir eksikliği anemisi olan hastalarda çölyak hastalığı prevelansı

Amaç: *Demir eksikliği anemisi bazı proteinlerin alımı ile tetiklenen otoimmun bir hastalık olan çölyak hastalığının ilk belirtisi olabilir. Bu çalışmada sebebi belli olmayan demir eksikliği olan hastalarda çölyak hastalığı prevalansını araştırmayı amaçladık.* ***Gereç ve Yöntem:*** *Sebebi bilinmeyen demir eksikliği anemisi olan 84 olgu çalısmaya dahil edildi. Olgularda duodenum ikinci kesiminden alınan biyopsi örneklerinde histopatolojik olarak çölyak hastalığı varlığı arastırıldı. Tüm hastaların serum antigliadin ve endomisyal antikor varlığı araştırıldı. Çölyak hastalığı tanısı pozitif serolojik testler ve histolojik bulgular ile konuldu.* ***Bulgular:*** *Seksendört hastanın 6'sında (%7,14) hem serolojik hem de histolojik olarak çölyak hastalığı ile uyumlu bulgular saptandı. Hastaların 10,3±0,64 gr/dl olan ortalama hemoglobin değerleri altı aylık glutensiz diyet sonrası 12,97±8,45 gr/dl'ye yükselmiştir (P=0,002). Endomisyum IgA ve IgG antikorları pozitif bulunan bir hastada histopatolojik bulgu saptanmamıştır. Bu hastada, hemoglobin değerlerinin glutensiz diyet sonrası yükselmesi nedeniyle çölyak hastalığı düşünülmüştür. Tanı konulan 7 hastanın 6'sı (%85,7) ortalama yaşı 37,5±8,45 olan premenapozal kadınlardır.* ***Sonuç:*** *Klinisyenler, premenapozal kadınlarda bile, sebebi belli olmayan demir eksikliği anemisi ile karşılaştıklarında muhtemel sebep olarak çölyak hastalığını düşünmelidirler. Özellikle oral demir replasman tedavisine cevap vermeyen premenapozal kadınlar serolojik testlerle taranmalıdır.*

Anahtar kelimeler: Çölyak hastalığı, demir eksikliği anemisi, premenapozal kadın

INTRODUCTION

Celiac disease (CD) is an immune-mediated small intestinal enteropathy. The disease is characterized by malabsorption of nutrients, chronic inflammation and damage of the small intestinal mucosa caused by the ingestion of a gluten-containing diet, such as products containing wheat, barley

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Manuscript received: 02.01.2012 **Accepted:** 17.01.2012

Turk J Gastroenterol 2012; 23 (5): 490-495
doi: 10.4318/tjg.2012.0467

and rye, in genetically susceptible subjects (1,2). The pathological features are a typical flat mucosa, abnormal surface epithelium, and villus atrophy and hyperplastic crypts in the small intestine.

Celiac disease (CD) is often assumed to have its onset in childhood, but it has recently been suggested that adults can also develop CD (3). Clinical manifestations vary according to age group: infants and young children present with diarrhea, abdominal distention and failure to thrive, whereas adults who develop CD not only present diarrhea, but can also have silent manifestations such as anemia, osteoporosis or neurological symptoms (4).

The prevalence of CD has increased dramatically in the last 30-40 years with the help of highly sensitive serologic tests, which have made CD diagnosis easier in subclinical cases and several risk groups (1,5-7). Screening studies show that CD affects more than 1% of populations in European countries (8,9). In a recent study in Turkey, the prevalence of CD in 2000 healthy blood donors was found to be 1.3% (1/77), but it remains largely unrecognized (11). Considering the broad spectrum of clinical manifestations of CD, including anemia, osteoporosis, dermatitis herpetiformis, and neurologic disorders and life-threatening complications such as non-Hodgkin's lymphoma, small intestinal adenocarcinoma, esophageal cancer, and melanoma, early diagnosis of CD is essential, as it is otherwise associated with increased mortality (10,12-15).

Iron deficiency anemia (IDA) is a commonly observed sign in CD, and is the only abnormality in 40% of patients (16). In fact, only a minority of CD patients present with the classical malabsorption symptoms of diarrhea and weight loss; most patients have subclinical or silent forms in which IDA can be the sole presentation (17). If anemia is a common presenting feature of CD, what is the likelihood of encountering CD in patients presenting with IDA?

The present study was conducted to define the prevalence of CD among patients with IDA of obscure origin.

MATERIALS AND METHODS

In this study, we evaluated patients with a diagnosis of IDA who were referred to the Gastroenterology Department of Antalya Training and Research Hospital. IDA was defined as: hemoglobin concentration <13.5 g/dl in males and <11.5 g/dl in females, mean corpuscular volume (MCV) <80 fl, and ferritin level <30 ng/ml. From May 2009 - January 2011, patients aged between 16 and 80 years old were evaluated.

Patients with obvious blood loss, such as those with a history of melena, hematochezia, hemoptysis, recurrent epistaxis, hematuria, trauma, pregnancy, hypermenorrhea (cycles ≥7 days), or menometrorrhagia, and those with alcoholism, gastric surgery, known chronic diseases (e.g. chronic liver disease, chronic renal failure, heart failure, collagen vascular disease, etc.), and hematologic diseases were excluded from the study. Physical examination, urine analysis for hematuria, occult blood loss analysis in feces (3 times), upper gastrointestinal (GI) endoscopy, and colonoscopy were performed in all of the patients. Patients who had GI etiology of IDA (such as duodenal ulcer, polyps, cancer, arteriovenous malformations, etc.) were also excluded from the study.

As the study group, 84 patients were found to have IDA of obscure origin. Venous blood samples for endomysial (EMA) and gliadin (AGA) antibodies were obtained from 84 IDA patients of obscure origin. EMA and AGA were investigated using indirect immunofluorescence technique.

All patients with IDA of obscure origin underwent upper GI endoscopy and colonoscopy. Gastroduodenal endoscopic examination, after an overnight fast, was performed using the Pentax EG2985 gastroscope. For histopathological examination, three biopsies were obtained from the second section of the duodenum by endoscopic biopsy forceps. The duodenal biopsy specimens were fixed immediately in formalin solutions for 4-6 hours (h) at room temperature and were routinely processed for conventional histological evaluation. For diagnosis of CD, intraepithelial lymphocytosis, villous flattening or complete loss of villi, and presence of crypt hyperplasia were investigated on the histological examination of the biopsy specimens. Diagnosis of CD was made according to the European Society of Pediatric Gastroenterology and Nutrition (ESPGAN) criteria, histopathologic examination of duodenal biopsies taken from the second section of the duodenum, and demonstration of clinical and histological improvement after maintaining a gluten-free diet (GFD).

Informed consent was obtained from the patients.

The study protocol was approved by the ethics committee of Antalya Training and Research Hospital.

Statistical Analyses

The statistical analysis was performed using a statistical program for PCs (Statistical Package for the Social Sciences 12.0 for Windows, SPSS Inc., Chicago, IL, USA).

RESULTS

From the 84 patients with IDA of obscure origin, 25 were males, with a mean age of 50.8±14.5 years, and 59 were females, with a mean age of 39.7±15.5 years.

Serological screening tests showed positivity of at least one of the EMA or AGA tests in 8 patients (Table 1). Seven patients had positive EMA IgA and 2 had positive EMA IgG. Five patients had positive AGA IgA (Table 1). Six patients had histopathological findings of CD on duodenal biopsy.

Among the 6 patients with abnormal duodenal histology, all had EMA IgA-positive serologic tests. All of the patients with positive serological tests were followed with a GFD for at least six months. All of the 7 patients with EMA IgA-positive serological test had clinical improvement in IDA and had normal hemoglobin levels after GFD. Mean hemoglobin increased from 10.31±0.64 to 12.97±1.48 g/dl (p=0.002), and mean serum ferritin level increased from 8±3 to 23±6 ng/dl. Of those 7 patients, only 1 patient had normal duodenal histology, and she was considered as CD since her hemoglobin level increased from 10.4 to 11.8 g/dl after GFD in addition to the positive serology. Another patient with positive AGA IgA and IgG and normal duodenal biopsy did not show any improvement in hemoglobin level after GFD and was not considered as CD.

Table 1. Demographic features and findings

Iron deficiency anemia (n=84)	Female	Male
Number	59	25
Mean age	39.7±14.5	50.8±15.4
AGA IgA	4	1
AGA IgG	3	1
EMA IgA	6	1
EMA IgG	5	-
Celiac disease	6	1

AGA: Anti-gliadin antibody. EMA: Endomysial antibody.

DISCUSSION

Because of the improvement in diagnostic methods for identifying CD, asymptomatic cases are now the commonest form of the disease, and are seven times more common than clinically diagnosed patients (18). In a recent case-control study, only anemia (odds ratio [OR]: 26.3; 95% confidence interval [CI]: 6-120) and diarrhea (OR: 4.5; 95% CI: 2-10) were identified as independent predictors of an eventual diagnosis of CD among the different clinical presentations in general practice during the five years prior to the diagnosis of CD (19). There has been a marked increase in the proportion of subjects identified as celiac patients who do not have the classical manifestations of the disease, but have IDA (20-25). Guidelines from the British Society of Gastroenterology recommend that duodenal biopsies should be taken during endoscopy if no obvious case of IDA can be found (26). Studies using serologic tests and small-bowel biopsies in patients referred for evaluation of IDA have reported CD in 1.8%-14.6% of patients (27,28). This prevalence may be especially high in those unresponsive to oral iron therapy (29). In a sub-group study of patients who did not respond to iron replacement, the prevalence of CD was found as 20% (30,31).

In our study, the rate of CD seroprevalence was 8.33% (7/84) in patients with IDA of obscure origin, which is similar to the literature (27). EMA IgA was positive in 7 patients. Six of the patients with positive serology had duodenal biopsy findings supporting CD, typically showing villous atrophy, crypt hyperplasia and inflammation (32,33). EMA IgA and EMA IgG tests were positive in 1 patient with normal duodenal biopsy (Table 2). Duodenal biopsy is still considered by most authors as the "gold standard" in the diagnostic process, albeit its usefulness in adults remains slightly controversial. If results of the histological study are negative but serologic tests are positive, CD is strongly suspected (34). A proportion of individuals with normal mucosa and positive CD serology may in fact have microscopic enteritis (35,36). CD seropositivity predicts forthcoming CD even if the duodenal histological findings are normal (37-40). In our study, the patient with normal duodenal biopsy was accepted as CD since her hemoglobin level showed a significant objective improvement after six months of GFD, as observed in the other 6 CD patients (Table 2) (28).

Endomysial antibodies (EMA) are measured in serum by indirect fluorescence using monkey esop-

Table 2. Demographic and clinical data of CD patients

Patient No.	Gender	Age	Antigliadin IgA	Antigliadin IgG	Endomysium IgA	Endomysium IgG	Pathology	Hb level before GFD (g/dL)	Hb level 6 mo after GFD (g/dL)
1	F	26	Pos	Pos	Pos	Neg	Pos	10.3	12.3
2	F	29	Neg	Neg	Pos	Pos	Pos	10.6	14.8
3	M	47	Pos	Pos	Pos	Neg	Pos	11.1	12.5
4	F	41	Neg	Neg	Pos	Neg	Pos	10.5	15.4
5	F	48	Neg	Neg	Pos	Pos	Neg	10.4	11.8
6	F	43	Pos	Neg	Pos	Neg	Pos	10.2	12.1
7	F	38	Pos	Pos	Pos	Pos	Pos	9.0	11.9

F: Female, M: Male, GFD: Gluten free diet, Hb: Hemoglobin, Pos: Positive, Neg: Negative.

hagus or human umbilical cord as a substrate. The specificity and sensitivity of EMA are estimated at 99% and over 90%, respectively, in both adults and children (24). In studies conducted to determine CD, AGA had a moderate sensitivity and specificity, but EMA IgA-type antibodies were reported to be more specific (41). In our study, 5 of 7 patients with CD had AGA IgA (71.4%) positivity. AGA IgG was positive in 3 patients (42.8%) and EMA IgA was positive in all 7 cases (100%) (Table 2). The antibody positivity rates were found compatible with those given in the literature in patients diagnosed as CD (41). As EMA are highly specific and sensitive in the diagnosis of CD, many authors have suggested the use of these antibodies especially in the screening of CD (41).

Iron deficiency is common in the general population. If it occurs in young women, it is often attributed to excess menstrual loss, and an empiric therapy with oral iron supplementation is given. However, older patients or those with anemia that is refractory to treatment are often investigated further. Similarly, the persistence of anemia after menopause may be an important clue that leads to the detection of CD (23). Nevertheless, IDA is a very common illness in primary care and often does not spur investigation in younger patients. In this situation, further investigation and the diagnosis of CD were delayed in patients without significant GI symptoms. Uçardağ et al. (22) investigated 77 Turkish patients with IDA of obscure origin using serologic tests and gastroscopy with duodenal biopsies. Six patients (7.8%) had CD and 3 of them were premenopausal women. Aydemir et al. (21) reported the prevalence of CD as 10.2% in 39 Turkish patients with IDA of obscure origin, and all of the patients were premenopausal women. Carter et al. (42) investigated 116 premenopausal women with IDA. They reported that *Helicobacter pylori* gastritis and CD (6%) were the most common pathologic findings, and they recommended celiac serology test for the initial evaluation of premenopausal patients with IDA. The frequency of CD in women with IDA is higher than in other risk groups of CD, with a female:male ratio of 2:1 (27). Several studies have reported that 73%-100% of IDA patients diagnosed with CD were premenopausal women (17,20,22-24,27). In our study, 6 of 7 CD patients (85.7%) were premenopausal women, and the mean age was 37.5±8.45 years. Since premenopausal women have higher iron demand as a result of menstrual loss, they demonstrate a higher prevalence of CD in the IDA patient group (27). A characteristic feature of IDA associated with CD is its refractoriness to oral iron treatment (18). The diagnostic work-up in premenopausal women is not clearly established. The British Society of Gastroenterology recommends gastroscopy only in IDA women younger than 45 years presenting with GI symptoms (26). Gastroscopy is an invasive procedure associated with a high number of refusals (43). Thus, noninvasive tests with high specificity and sensitivity may be helpful in the detection of IDA women with a high probability of CD (44).

Early identification of CD in patients with IDA is of great importance, since a strict adherence to a GFD not only provides management of anemia but also prevents severe complications, such as ulcerative jejunoileitis, intestinal lymphoma and neoplasm (45).

Clinicians should consider CD as a possible cause of anemia in all patients with IDA of obscure origin, even in menstruating women, and should biopsy the duodenum when an endoscopy is performed in patients with IDA, even if biopsies are not specifically required. Serologic screening tests should be performed in premenopausal women with IDA, especially when the anemia is refractory to oral iron treatment.

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