THE IMPORTANCE OF DUODENAL BIOPSY IN THE ADULTS WITH IRON DEFICIENCY ANEMIA

Original Article

ERİŞKİNDE DEMİR EKSİKLİĞİ ANEMİSİNDE DUODENAL BİYOPSİNİN ÖNEMİ

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ABSTRACT

AIM

To evaluate the outcomes of the duodenal biopsy done for the assessment of mucosal disease in patients investigated for iron deficiency anemia (IDA), underwent upper and lower gastrointestinal system endoscopies that revealed no remarkable macroscopic pathologic findings.

METHOD

One hundred and ninety adult patients with IDA who had inspection and biopsy of the stomach and second part of the duodenum during endoscopy. The control group consisted of 237 subjects, who had undergone upper and lower gastrointestinal system screening for any reason, and in whom duodenal biopsy was done despite the assessment of no remarkable pathological finding. Endoscopic and histopathologic findings were compared between groups.

RESULT:

Patient's mean age was 43.39± 14.00 years (17 and 87 years) and with the mean age of for the study and control groups mean age was 43.20±14.35 years. Of the subjects in the study group, 75.3% and 59.9% of subjects in the control group were female. Celiac disease was determined in 2.6% (n=5) subjects in the

study group. Three women patient with celiac had IDA with no diarrhea or dyspepsia- like complaints. Two men patient with celiac disease had IDA and diarrhea. Routine duodenal biopsy was statistically significant in patients investigated for IDA (P=0.017). Other gastric mucosal changes didn't differ in patients with IDA than normal subjects. Atrophic gastritis and H. pylori gastritis didn't influence iron status in these patients.

CONCLUSION

Duodenal biopsy should perform in all patients referred to gastroscopic examination for iron deficiency anemia.

Keywords: *Iron deficiency anemia;duodenal biopsy.*

ÖZET

AMAÇ

Demir eksikliği anemisi için gastroskopiye yönlendirilen ve endoskopik bir lezyon saptanmayan hastalarda duodenal biyopsilerin değerlendirilmesi.

METOD

Demir eksikliği nedeni ile gastroskopiye yönlendirilen 190 erişkin hasta çalışmaya katılmıştır. Kontrol grubu olarak herhangi bir neden için gastroskopiye gönderilen ve duodenal biyopsisi alınmış 237 hasta alınmıştır. Her iki grubun endoskopik ve histolojik bulguları karşılaştırılmıştır.

BULGULAR

Hastaların yaş ortalaması 43.39± 14.00 yıl (17-87 yıl) ve control grubunun yaş ortalaması 43.20±14.35 yıl idi. Hasta grubunda %75.3 ve kontrol grubunda %59.9 hasta kadın idi. Hasta grubunda %2.6 (n=5) oranında çölyak hastalığı saptanmıştır. Hastaların 3'ü kadındı ve ishal veya dispeptik semptomları yoktu. İki erkek hastada ise ishal vardı. Demir eksikliği anemisinde rutin duodenal biyopsi

almak istatisitksel anlamlı olarak çölyak hastalığı tanısı koydurmaktadır (P=0.017). Diğer mukozal patolojiler açısından her iki grup benzerdi. Bu grupta atrofik gastrit ve H.pylori gastritis demir eksikliğini etkilememekte idi.

SONUÇ

Demir eksikliği anemisi için gastroskopiye yönlendirilen hastalarda duodenal biyopsi alınmalıdır.

Anahtar kelimeler: *Demir eksikliği anemisi; duodenal biyopsi.*

INTRODUCTION

Iron deficiency anemia (IDA) is the most common cause of microcytic, hypochromic anemia worldwide. The different lesions responsible for chronic blood loss include both upper and lower gastrointestinal tract and the absorption disorders are the commonest causes of IDA (1).Esophagogastroduodenoscopy (EGD) is the method to investigate the upper gastrointestinal (GI) system for etiology of IDA when evaluation of colon is normal. The assessment of the mucosal disease is important, when any remarkable organic cause such as ulcer or erosion could not be determined. Celiac disease may present with nonspecific GI symptoms of dyspepsia, abdominal pain, and nausea, and also with iron-deficiency anemia in the absence of GI symptoms The most common extraintestinal manifestation of celiac disease is iron deficiency anemia, being found in as many as 50% of celiac patients at the time of diagnosis (2).In various studies, the prevalence of celiac disease has been determined between 1.23 - 11% in patients investigated for IDA (3-7). Endoscopic duodenal biopsy is a diagnostic tool in the management of patients with chronic diarrhea and ferropenic anemia (8).

In the present study, we aimed to investigate whether routine duodenal biopsy is necessary for the assessment of

mucosal disease in patients without pathological findings in upper and lower gastrointestinal system endoscopies.

MATERIAL AND METHOD

The present study consisted of 427 patients who undergo EGD for IDA or other reasons between July 2009 - January 2011. Patients were selected among those applied to outpatient clinics of internal medicine and gastroenterology, whose abdominal ultrasonography and other system examinations revealed no pathological finding, and for whom gastrointestinal system screening was planned. The eligibility criteria were a hemoglobin concentration below 13 g/dl in males and below 12 g/dl in females, and an iron level below 58 µg/dl (normal: 58-158) in males and below 37 µg/dl (normal: 37-145) in females. The control group was selected among patients who did not have iron deficiency anemia and underwent duodenal biopsy for any reason. Exclusion criteria were the presence of ulcer, vascular abnormalities of GI system or macroscopic malignancy determined in the gastrointestinal system, diverticulum or polyp greater than 1 cm, the presence of active colitis, gastrointestinal bleeding history within the last three months or positive fecal occult blood test (FOBT), previous gastric and/or duodenal surgery, bleeding/clotting disorder, anticoagulant use, and the presence of gynecological or genitourinary pathologies that may lead to iron deficiency. On the other hand, anemic patients who had anemia other than IDA such as thalassemia, anemia of chronic disease, macrocytic or megaloblastic anemia (folate or vitamin B 12 deficiency) were excluded. EGD and colonoscopy procedures were performed via Pentax and Fujinon video endoscopy systems. Routinely 3 biopsies were taken from the second part of the duodenum and 2 biopsies were taken from the antrum. The biopsy specimens were fixed with 10% formalin and embedded in paraffin blocks. The sections were stained with periodic acid-schiff, alcian blue, hematoxylin eosin and Giemsa, and were histologically examined. The duodenal damage was classified according to the modified Marsh system (9). The histological features of gastric mucosa were categorized using the Sydney classification (10).

STATISTICAL ANALYSES

Calculations were performed using NCSS (Number Cruncher Statistical System) 2007 and PASS 2008 Statistical Software (Utah, USA). In addition to descriptive statistical methods; Student t test was used for comparison of the quantitative data. Chi-square and Fisher's exact Chi square tests were used for the comparison of the qualitative data. The results were evaluated within the 95% confidence interval and at a significance level of $p < 0.05$.

RESULTS

Of total 427 patients, 190 patients were in IDA group and 237 patients in control group. The mean age of patients was 43.29±14.18 years (range, 17-87). There was no difference between the mean age of IDA group and of control group (43.39±14.00 years vs 43.20±14.35 years, $p > 0.05$). Female ratio was higher in IDA group than in the control group (75.3% vs. 59.9%; $p < 0.01$). It was determined that hemoglobin, hematocrit, the mean corpuscular volume (MCV) and the mean platellet volume (MPV) were significantly lower in patients than the controls ($p < 0.01$). The red cell distribution width (RDW) measurements was significantly high in the study group as compared to the control group ($p < 0.01$). Whereas iron and ferritin levels were significantly low in the study group ($p < 0.01$), TIBC levels were significantly high ($p < 0.01$) **(Table 1).**

There was not any difference between groups in terms of endoscopic appearance of duodenitis, gastritis and presence of erosion ($p > 0.05$). Histopathologic examination of gastric biopsies showed that there were no difference between

groups for the presence of lymphoid aggregate, atrophy, intestinal metapasia and intestinal metaplasia subtypes (p>0.05) Helicobacter pylori (H. pylori) presence and severity didn't differ between two groups (p>0.05) Although celiac disease was detected at 5 patients (2.6%) with IDA, none of patients with normal hemoglobin values had celiac disease (p=0.017). Endoscopic and histopathologic features of study population are summarized in **Table 2.**

Table 1: *The distribution of demographic characteristics according to the groups.*

	Anemia group	Control group	p
Number of patients	190	237	
†Age; mean±SD	43.39± 14.00	43.20±14.35	0.89
† Gender; F/M (%)	143/47 (75.3/24.7)	142/95 (59.9/40.1)	0.001**
†Hb; mean±SD	9.92±1.85	13.65±1.13	0.001**
†Hct; mean±SD	31.53±5.01	41.25±3.24	0.001**
†MCV; mean±SD	75.59±9.92	88.70±4.47	0.001**
†RDW; mean±SD	18.32±3.52	14.27±1.20	0.001**
†MPW; mean±SD	8.70±1.58	8.35±1.18	0.009**
†Iron; mean±SD	25.84±18.75	84.43±30.86	0.001**
†TIBC; mean±SD	403.00±76.39	335.00±60.60	0.001**
†Ferritin mean±SD	15.95±48.31	71.00±93.35	0.047*

+ Student t test   † Chi-square test

   *p<0.05   **p<0.01

Table 2: *Histopathologic characteristics according to the groups .*

	Anemia group n (%)	Control group n(%)	p
† H. pylori			
Negatif	66 (27.8)	44 (23.2)	
+	88 (37.1)	69 (36.3)	
++	52 (21.9)	48 (25.3)	
+++	31 (13.1)	29 (15.3)	0.62
†Lymphoid aggregate	97 (51.1)	133 (56.1)	0.29
† Intestinal metaplasia			
Negative	164 (86.3)	197 (83.0)	
Complete	20 (10.5)	33 (13.9)	0.57
Incomplete	6 (3.2)	7 (3.1)	
† Erosion	31 (16.3)	50 (21.1)	0.21
◆ Celiac	0 (0)	5 (2.6)	*0.017

† Chi-square test   ◆ Fisher's exact test

*p<0.05

DISCUSSION

In various studies, prevalence of celiac disease has been determined between 1.2 - 11% in patients investigated for IDA (3-7). The prevalence of celiac disease has been determined to be 20% in patients, who do not respond to the iron replacement therapy (11). To perform routine investigational duodenal biopsy for the presence of mucosal disease in patients with iron deficiency anemia causes an additional task. However, the celiac disease is also seen in adults even without signs of diarrhea and malabsorption (3,12,14).

In a study, the prevalence of celiac disease was determined by 2.6% when the patients with IDA were screened via EGD, flexible sigmoidoscopy and barium enema, and the EGD of 3 patients

diagnosed with celiac disease revealed normal mucosal appearance(4).In another study conducted on 504 patients were included, and they were grouped by age according to being under or over 65 years. The celiac disease was determined 1.2% in patients, who were under the age of 65 years, without diarrhea and weight loss, but with anemia. In this group, prevalence of the celiac disease was determined to be 10.5% in those with chronic diarrhea. While prevalence of the celiac disease was 0.7% in the group over 65 years of age, with anemia but without diarrhea, it was determined to be 21.4% in those with chronic diarrhea (15).

The majority of the adult patients with celiac disease have subclinical progression or nonspecific gastrointestinal symptoms (16). The duodenal biopsy has become important, if asymptomatic progression of the celiac disease in patients, investigated for iron deficiency, was taken into consideration, and also, if it was taken into consideration that the celiac disease could be determined via biopsy in those with normal mucosal appearance. In the present study, the mucosal disease has been investigated by means of duodenal biopsies taken from all of the patients, as well as from the control group. The pathological examination revealed celiac disease in 2.6% (2 male / 3 female) of patients. Furthermore, anti-endomsyium IgA and IgG analyses were done in these patients. The antibody tests were found positive in 4 out of 5 patients. This rate is similar with that of the previous studies (17,18). In a patient, anti-endomisium IgA was determined between the normal ranges, although the pathological examinations of the specimens taken from the duodenum mucosa were indicative of the celiac disease. Patient's hemoglobin increased by 1.5 g/dl after 3-month gluten-free diet. Celiac disease or any mucosal disease was not determined in any of the patients in the control group. Based on these findings, the rate of celiac disease in the patients who are investigated for iron deficiency, and has no diarrhea, is similar with results of the

population screenings. The rate of celiac disease has been found high in the patients who had diarrhea and concomitant iron deficiency anemia. Diarrhea was determined in two male cases. Women who had celiac disease presented solely with IDA, because these women patients are at the reproductive age, and menstrual blood loss is likely the dominant factor determining IDA. Dyspepsia-like complaints were less likely to draw attention in women with celiac disease. However, it is expected that IDA is the first presentation of celiac disease in women. Despite the fact that there was no clinical diarrhea and the mucosal appearance was normal on EGD examination, the prevalence of the celiac disease via biopsy was higher than the results of the population screenings (4,15,19). Although it was thought that routine duodenal biopsy will contribute to the determination of the mucosal disease, additional studies are thought to be appropriate for the cost-effectivity.

Gastric mucosal changes without evidence of abnormal blood loss or gastrointestinal symptomatology is increasingly understood in the etiology of IDA. Beside celiac disease, other significant causes of IDA in the upper GI system included: atrophic gastritis and gastritis related to Helicobacter pylori infection (20). Iron absorption is severely impaired in atrophic gastritis, and impaired iron absorption in pernicious anemia is corrected by normal gastric juice, indicating that lack of gastric acidity is the key factor in abnormal iron absorption. Although atrophic gastritis may impair both vitamin B 12 and iron absorption simultaneously, in young women in whom menstruation represents an added strain on iron requirements, iron deficiency will develop many years before the depletion of vitamin B 12 stores (21).However, we couldn't find difference between anemic and normal patients for atrophic gastritis.

The role of H. pylori in the causation of IDA is of considerable current interest.

Although the mechanisms remain unclear, clinical and epidemiologic studies suggest that infection with H. pylori is associated with iron deficiency and IDA (22,23). Moreover, in two recent meta-analysis showed that eradication of H. pylori improve iron and hemoglobin (24,25) . Our result isn't consistent with these findings. The prevalence of H. pylori is about 75% in both IDA and control groups. High prevalence of H. pylori seems to shade the effect of infection on iron deficiency. On the other hand, severity of H. pylori infection didn't differ between groups.

Consequently, IDA is the main presentation of celiac disease, and especially refractory patients to iron replacement must be evaluated for celiac disease. Gastric mucosal changes seem less important contrubitor of IDA. Further studies are needed to understand the effects of H. pylori gastritis and atrophic gastritis on IDA.

REFERENCES

1)Rockey DC, Cello JP. Evaluation of the gastrointestinal tract in patients with iron-deficiency anemia. N Engl J Med 1993; 329: 1691-5.

2)Ransford RA, Hayes M, Palmer M, Hall MJ. A controlled, prospective screening study of celiac disease presenting as iron deficiency anemia. J Clin Gastroenterol 2002; 35: 228-33.

3)Corazza GR, Andreani ML, Venturo N, Bernardi M, Tosti A, Gasbarrini G. Subclinical coeliac disease is a frequent cause of iron-deficiency anaemia. Scand J Gastroenterol 1995;30: 153-6.

4)McIntyre AS, Long RG. Prospective survey of investigations in outpatients referred with iron deficiency anaemia. Gut 1993; 34:1102-7.

5)Kepczyk T, Kadakia S. Prospective evaluation of gastrointestinal tract in patients with iron-deficiency anemia. Dig Dis Sci 1995; 40: 1283-9.

6)Bampton PA, Holloway RH. A prospective study of the gastroenterological causes of iron deficiency anaemia in a general hospital. Aust N Z J Med 1996; 26: 793-9.

7)Zuckerman GR, Prakash C, Askin MP, Lewis BS. AGA technical review on the evaluation and management of occult and obscure gastrointestinal bleeding. Gastroenterology 2000; 118: 201-21.

8)Riestra S, Domínguez F, Fernández-Ruiz E, García-Riesco E, Nieto R, Fernández E, Rodrigo L. Usefulness of duodenal biopsy during routine upper gastrointestinal endoscopy for diagnosis of celiac disease. World J Gastroenterol 2006;12: 5028-32.

9)Marsh MN, Crowe PT. Morphology of the mucosal lesion in gluten sensitivity. Baillieres Clin Gastroenterol 1995; 9: 273-93.

10)Dixon MF, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. Am J Surg Pathol 1996; 20: 1161-81.

11)CarroccioA, Iannitto E, Cavataio F, Montalto G, Tumminello M, Campagna P, Lipari MG, Notarbartolo A, Iacono G. Sideropenic anemia and celiac disease: one study, two points of view. Dig Dis Sci 1998; 43: 673-8.

12)Maki M, Collin P. Coeliac disease. Lancet 1997; 349: 1755-9.

13)Johnston SD, Watson RG, McMillan SA, Sloan J, Love AH. Coeliac disease detected by screening is not silent--simply unrecognized. QJM 1998; 91: 853-60.

14)HankeyGL, Holmes GK. Coeliac disease in the elderly. Gut 1994;35: 65-7.

15)Mandal AK, Mehdi I, Munshi SK, Lo TC. Value of routine duodenal biopsy in diagnosing coeliac disease in patients with iron deficiency anaemia. Postgrad Med J 2004; 80: 475-7.

16)Baccini F, Spiriti MA, Vannella L, Monarca B, Delle Fave G, Annibale B. Unawareness of gastrointestinal symptomatology in adult coeliac patients with unexplained iron-deficiency anaemia presentation. Aliment Pharmacol Ther 2006; 23: 915-21.

17)Goddard AF, McIntyre AS, Scott BB. Guidelines for the management of iron deficiency anaemia. British Society of Gastroenterology. Gut 2000; 46 Suppl 3-4: IV1-IV5.

18)Gonen C, Yilmaz N, Yalcin M, Simsek I, Gonen O. Diagnostic yield of routine duodenal biopsies in iron deficiency anaemia: a study from Western Anatolia. Eur J Gastroenterol Hepatol 2007; 19: 37-41.

19)Tatar G, Elsurer R, Simsek H, Balaban YH, Hascelik G, Ozcebe OI, Buyukasik Y, Sokmensuer C. Screening of tissue transglutaminase antibody in healthy blood donors for celiac disease screening in the Turkish population. Dig Dis Sci 2004; 49: 1479-84.

20)Hershko C, Ianculovich M, Souroujon M.A hematologist's view of unexplained iron deficiency anemia in males: impact of Helicobacter pylori eradication. Blood Cells Mol Dis 2007; 38: 45-53.

21)Hershko C, Ronson A. Iron deficiency, Helicobacter infection and gastritis. Acta Haematol 2009; 122: 97-102.

22)Barabino A. Helicobacter pylori-related iron deficiency anemia: a review. Helicobacter 2002; 7: 71-5.

23)DuBois S, Kearney DJ. Iron-deficiency anemia and Helicobacter pylori infection: a review of the evidence. Am J Gastroenterol 2005; 100:453-9.

24)Qu XH, Huang XL, Xiong P, Zhu CY, Huang YL, Lu LG, Sun X, et al. Does Helicobacter pylori infection play a role in iron deficiency anemia? A meta-analysis. World J Gastroenterol 2010; 16: 886-96.

25)Huang X, Qu X, Yan W, Huang Y, Cai M, Hu B, Wu L, et al. Iron deficiency anaemia can be improved after eradication of Helicobacter pylori. Postgrad Med J 2010; 86: 272-8.