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Diagnostic Prevalence of Celiac Disease by Routine Duodenum Biopsy in Adult Patients with Iron Deficiency

Demir Eksikliği Olan Erişkin Hastalarda Rutin Duodenum Biyopsi ile Çölyak Hastalığının Tanısal Prevalansı

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Abstract

Objective: Iron deficiency anemia (IDA) frequently emerges as a consequence of Celiac disease (CeD), and in some cases, it can be the sole clinical manifestation of the condition, especially among patients with subclinical or atypical forms. Histological analysis plays a pivotal role in the diagnostic process. Our study aimed to assess the significance of duodenal biopsies in diagnosing CeD among patients with IDA of unknown origin and to determine the prevalence of CeD within the group of patients with unexplained IDA.

Method: Between June 2019 and December 2022, we enrolled 248 consecutive patients aged 18 and above who underwent duodenal biopsies during esophagogastroduodenoscopy procedures for evaluating unexplained IDA in our endoscopy unit. A retrospective analysis of CeD prevalence was performed. Patients with abnormal duodenal histology were tested for anti-endomysium antibody and tissue transglutaminase antibody levels. A positive serological test along with abnormal duodenal histology confirmed the diagnosis of CeD. Histopathological changes were categorized according to the Marsh classification.

Results: A total of 248 patients, including 171 women, meeting the study criteria were included. CeD was identified in 8 (3.2%) patients who underwent duodenum biopsies. The average age of celiac patients was 36±14 years, and the female-to-male ratio was 1.3:1. Histopathology revealed Marsh III in 5 (62.5%) patients, Marsh II in 2 (25%), and Marsh I with lesions in 1 (12.5%) patient. All patients with pathological changes in duodenal biopsies (Marsh I, II & III) tested positive serologically. No significant differences were observed in mean hemoglobin, mean corpuscular volume, and ferritin levels between patients with and without CeD accompanied by IDA.

Öz

Amaç: Çölyak hastalığı (ÇH), demir eksikliği anemisinin (DEA) iyi bilinen bir nedenidir. DEA, özellikle subklinik veya atipik ÇH olan hastalarda, ÇH'nin tek klinik belirtisi olabilir. Histolojik inceleme en önemli tanı aracıdır. Çalışmamızda nedeni bilinmeyen DEA ile başvuran hastalardan alınan duodenal biyopsilerin ÇH tanısındaki rolünü ve nedeni bilinmeyen DEA'lı hastalarda ÇH prevalansını incelemeyi amaçladık.

Yöntem: Haziran 2019-Aralık 2022 tarihleri arasında endoskopi ünitemizde nedeni bilinmeyen DEA'nın değerlendirilmesi kapsamında özofagogastroduodenoskopi işlemi sırasında duodenal biyopsi yapılan 18 yaş üstü ardışık 248 hasta çalışmaya dahil edildi. ÇH prevalansı retrospektif olarak değerlendirildi. Anormal duodenal histolojiye sahip hastaların anti-endomysiyal antikor ve doku transglutaminaz antikor seviyeleri değerlendirildi. ÇH tanısı pozitif serolojik test ve anormal duodenal histoloji ile konuldu. Histopatolojik değişiklikler Marsh sınıflamasına göre değerlendirildi.

Bulgular: Çalışma kriterlerini karşılayan toplam 248 hasta (171 kadın) çalışmaya alındı. Duodenum biyopsisi alınan 8 (%3,2) hastada ÇH saptandı. ÇH'nin yaş ortalaması 36±14 idi. Kadın erkek oranı 1,3:1 olarak bulundu. Histopatoloji 5 hastada (%62,5) Marsh evre III, 2 hastada (%25) Marsh evre II ve 1 hastada (%12,5) Marsh evre I lezyonları gösterdi. Duodenal biyopside (Marsh I, II & III) patolojik değişiklik gösteren tüm hastaların serolojisi pozitifti. ÇH olan ve olmayan DEA olan hastalar arasında ortalama hemoglobin, ortalama alyuvar hacmi ve ferritin düzeylerinde anlamlı fark yoktu.

Sonuç: DEA hastalarının üst endoskopik muayenesi sırasında alınan rutin duodenal biyopsiler ÇH'de tanısal fayda sağlamaktadır. Bu nedenle,

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Abstract

Conclusion: Routine duodenum biopsies performed during upper endoscopic examinations of IDA patients contribute to a diagnostic yield of 3.2% for CeD. Thus, even in cases where the endoscopic appearance of the mucosa seems normal, this procedure should be routinely integrated into the diagnostic evaluation of patients with IDA.

Keywords: Celiac disease, duodenal biopsy, iron deficiency anemia

Öz

bu uygulama, mukozanın endoskopik görünümü normal olsa bile, DEA'lı hastaların tanısal çalışmalarında sistematik olarak yer almalıdır.

Anahtar kelimeler: Çölyak hastalığı, demir eksikliği anemisi, duodenal biyopsi

Introduction

Celiac disease (CeD) is an enteropathy triggered by gluten sensitivity, characterized by small intestine villous atrophy, primarily affecting genetically predisposed individuals. Its global prevalence is estimated to range between 0.5% and 1% (1). While classic malabsorption symptoms such as diarrhea and weight loss are only present in a small fraction of celiac patients, the majority exhibit subclinical or silent forms (2). Early consideration of CeD disease is crucial for accurate diagnosis. Despite the estimated prevalence of CeD in our country being around 0.5-1%, it is believed that asymptomatic or atypical cases are more common. Thus, CeD should be considered in the differential diagnosis, particularly for patients presenting with atypical symptoms.

Anemia frequently accompanies CeD and sometimes can be its sole manifestation. The cause of anemia might stem from deficiencies in vitamin B12 and folic acid absorption. Iron deficiency is the primary cause of anemia in CeD. Iron deficiency anemia (IDA) is a common extraintestinal manifestation of subclinical and silent CeD presentations (3).

The prevalence of IDA in subclinical CeD has been reported to be up to 46% in adults compared to children (4). The IDA observed in CeD arises from impaired iron absorption due to duodenal mucosal villous atrophy and the multifaceted etiology that triggers the mechanism leading to anemia of chronic disease (5).

Guidelines for managing IDA from the American Academy of Family Physicians and the British Society of Gastroenterology recommend considering CeD in the differential diagnosis of patients undergoing anemia investigation (6,7). The prevalence of CeD among adult patients with IDA is estimated to be around 2-3%. Specific serum antibody testing should be conducted for suspected CeD cases. Upper GI endoscopy and small bowel biopsy play a crucial role in diagnosing suspected CeD and are recommended for confirming the diagnosis (6-8). Common serological tests for CeD involve measuring serum endomysium antibodies (EMAs) and antibodies against tissue transglutaminase (tTG). According to studies, anti-tTG immunoglobulin A (IgA) exhibits a sensitivity and specificity of 92.5% and 97.9%, respectively. While the anti-tTG IgA test is less sensitive, the EMA IgA test boasts greater specificity, with sensitivity and specificity of 79.0% and 99.0%, respectively (9). The primary CeD screening test is anti-tTG IgA, while EMA IgA is often utilized for confirmation. The presence of villous atrophy, crypt hyperplasia, and intraepithelial lymphocytosis in duodenal mucosal biopsy remains the gold standard for diagnosing CeD. Positive serology specific to CeD among patients with villous atrophy confirms the diagnosis. Although limited population-based screening is performed on specific adult groups in our country, no comprehensive study has been conducted.

Turkey has seen limited studies exploring the prevalence of adult CeD among patients with unexplained IDA. Our study seeks to determine the prevalence of CeD detected through routine duodenum biopsies during endoscopy in patients with unexplained IDA.

Materials and Methods

Patients and Methodology

Conducted between 2019 and 2022 at the Gastroenterology Endoscopy Unit of University of Health Sciences Turkey, İstanbul Haseki Training and Research Hospital, our study focused on patients over 18 referred to the institute's endoscopy department for IDA evaluation. Ethical approval for this retrospective study was obtained from the University of Health Sciences Turkey, İstanbul Haseki Training and Research Hospital Clinical Research Ethics Committee (07/04/2023, no: 166). Informed consent was collected from patients, and anemia was defined as a hemoglobin (Hb) level <13 g/dL for men and <12 g/dL for women (10).

Patients with evident blood loss, such as those with a history of melena, hematochezia, hemoptysis, recurrent epistaxis,

hematuria, trauma, hypermenorrhea (lasting 7 days or more), menometrorrhagia, pregnancy, gastric surgery, severe respiratory or cardiac conditions, known chronic diseases, and hematological diseases were excluded.

Endoscopies were performed by two gastroenterologists (ND, BY) following standard procedures using a fiber optic Olympus gastro-duodenoscope. Patients without sedation received a topical anesthetic of 5% xylocaine for the oropharynx. Sedation (propofol 1 mg/kg, ketamine 0.5 mg/kg, fentanyl 1 µg/kg) was administered at the anesthesiologist's discretion.

Duodenal biopsy was taken from all patients in the study. According to the Marsh categorization method, the patients' histological examination results were categorized (11): Normal mucosa was defined as Marsh 0; Increased intraepithelial lymphocyte count as Marsh I; crypt hyperplasia as Marsh II; Partial or complete villous atrophy as Marsh III; Incomplete development (hypoplasia) of the small intestine as Marsh IV.

CeD has been defined as the presence of elevated levels of Anti-tTG and/or EMA in addition to abnormal duodenal histology (such as Marsh 1, 2, or 3). Anti-tTG Ig A and anti-tTG IgG antibodies were analyzed via Enzyme Linked Immunoabsorbent Assay (ELISA) method using a diagnostic kit (IMMCO42 diagnostics, ImmuLisaTM, Buffalo, NY, USA). Patients with anti-tTG Ig A, anti-tTG IgG, and anti-EMA antibody levels of <10 EU/mL were considered seronegative, of 10-15 EU/mL borderline, and of >15 EU/mL seropositive.

Statistical Analysis

The data obtained from the research were analyzed using the statistical package program SPSS (Statistical Package for Social Sciences) 15.0. The data were expressed as mean and standard deviation. The normal distribution of the measurement parameters was examined by the "Kolmogorov-Smirnov test", and in the comparison of groups, independent groups t-test was used for parametric data. P-value was determined as <0.05 and confidence interval was accepted and evaluated as 95%.

Results

A total of 248 patients, including 171 women and 77 men, who underwent duodenal biopsy due to iron deficiency anemia, were included in the screening. The mean age of the patients was 3±15 years. CeD was detected in 8 of these patients, resulting in an incidence of 3.2%. The mean age of patients with CeD was 36±14 years. The incidence of CeD was higher in women (6F/2M), with a female-to-male ratio of 1.3:1. The demographic characteristics of the study patients are summarized in Table 1.

The mean Hb value, mean corpuscular volume (MCV), and median ferritin level in patients with CeD were 9.89±1.56 g/dL, 72.57±6.22, and 8.13 ng/mL±8.71, respectively. Table 2 compares the mean Hb, MCV, and serum ferritin levels of patients with IDA and CeD with those of patients with IDA but without CeD. For (Hb: 9.89±1.56 versus 10.23±1.63 g/dL), MCV (72.57±6.22 versus 73.76±6.64 fL), and ferritin levels (8.13±8.71 versus 8.93±9.96 ng/mL) between the two groups, there were no statistically significant differences (p>0.05). Histopathology indicated Marsh III lesions in 5 (62.5%) patients, Marsh II lesions in 2 (25%) patients, and Marsh I lesions in 1 (12.5%) patient (Figure 1).

Discussion

In our study, CeD was observed three times more frequently in women than men. Among the 248 patients who underwent duodenal biopsies for unexplained IDA, CeD

Table 1. Patient characteristics

Characteristics	Patients with iron deficiency anemia n (%)	Patients with disease CeD n (%)
Patient no	248	8
Sex (female /male)	171 (69%)/77 (31%)	6 (75%)/2 (25%)
Age (mean ± SD, yr)	39±15	36±14

SD: Standard deviation, CeD: Celiac disease

Table 2. Hematological parameters in IDA patients with and without CeD

Index	IDA patients with coeliac disease	Patients without coeliac disease	p*
Hb (g/dL)	9.89±1.56	10.23±1.63	0.456[t]
MCV (fL)	72.57±6.22	73.76±6.64	0.089[t]
Ferritin (ng/mL)	8.13±8.71	8.93±9.96	0.170[t]

IDA: Iron deficiency anemia, [t]: Student's t-test, *p<0.05 was considered significant, CeD: Celiac disease, MCV: Mean corpuscular volume, Hb: Hemoglobin

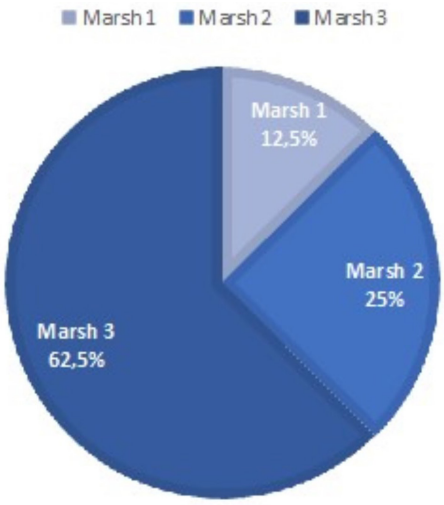

Figure 1. Histopathological examination in patients with disease (Marsh classification)

was identified in 8 (3.2%) cases. However, no significant differences in mean hemoglobin, MCV, and ferritin levels were found between patients with and without CeD accompanied by iron deficiency anemia.

CeD may manifest with various gastrointestinal tract symptoms, extraintestinal findings, or accompanying autoimmune diseases. The etiology of the disease is thought to involve immunological and genetic factors, as well as demographic characteristics such as age, gender, nutritional habits, and the extent of mucosal inflammation (12).

A majority of patients with atypical complaints in our study did not present with gastrointestinal symptoms. While only a small proportion of adult CeD patients exhibit classic symptoms of diarrhea and/or malabsorption, most patients have subclinical or silent forms. IDA is the most common extraintestinal finding in CeD (2). Anemia, especially idiopathic IDA, raises strong suspicion of CeD without any other apparent cause. For many patients, IDA may be the sole reason for presentation (13), with reports indicating that patients with unexplained iron deficiency are more likely to have CeD than adults in the general population (14).

The recommendations of the British Society of Gastroenterology suggest taking duodenal endoscopic biopsies when no obvious cause for iron deficiency is identified (8). In our study cohort, the prevalence of CeD among patients who underwent duodenal biopsies for unexplained IDA was 3.2%, consistent with previous reports of 2-3% in adult IDA patients (8).

A systematic review and meta-analysis by Mahadev et al. (15) in 2018, including 2998 individuals, reported that biopsy-proven CeD is relatively common in patients with IDA, with a prevalence ranging from 2.6% to 3.9% (15).

Studies conducted with children in Turkey (16-20) found an average prevalence of 4.1%. Similarly, Gonen et al. (20) performed duodenal biopsies in adult patients with IDA, revealing a prevalence of 3% for celiac disease.

Similar results in terms of hematological parameters are present in other studies. Our research found no differences in MCV, hemoglobin, or ferritin levels between patients with CeD and those with anemia of unknown origin (Table 2). Zamani et al. (21) did not identify a statistically significant relationship between hemoglobin and ferritin levels in patients with CeD and their histopathological changes. Ganji et al. (22) reported that there was no definitive link between the severity of anemia and intestinal mucosal damage according to the Marsh classification. However, some studies support the hypothesis of a potential relationship between the severity of anemia and the degree of intestinal atrophy in celiac patients (23).

CeD is more prevalent in women (24). In our study, CeD was observed three times more frequently in women than men, consistent with the higher prevalence of CeD in women in our country (25,26). While gender differences are significant in many diseases, autoimmune diseases provide a striking example, with women having a 2-3 times higher risk of developing autoimmune diseases than men. Similar trends are observed in celiac disease.

The retrospective nature of this study, which might introduce inherent referral bias due to the selection of patients referred for endoscopy, is one of its limitations. Additionally, like other observational studies, it is challenging to distinguish between causality and correlation. Selection bias may also be present, as women are more prone to disruptions in iron absorption, either due to iron loss or related conditions.

Conclusion

Given that CeD, the prevalence of which is on the rise, can be managed through a gluten-free diet, early detection is crucial to prevent potential complications and improve patient quality of life. Although IDA is often the initial complaint in cases of non-classical/extraintestinal celiac disease, many physicians rarely screen for CeD as part of their initial assessment. Our findings underscore the importance of identifying anemic patients who may have underlying celiac disease. Recognizing and diagnosing celiac disease, even in cases where IDA is the sole

manifestation, can prevent complications and enhance patient outcomes by enabling timely intervention and dietary management.

Ethics

Ethics Committee Approval: Ethical approval for this retrospective study was obtained from the University of Health Sciences Turkey, İstanbul Haseki Training and Research Hospital Clinical Research Ethics Committee (07/04/2023, no: 166).

Informed Consent: We had oral consent of patients.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.D., S.G.B., Concept: N.D., B.Y., Design: N.D., B.Y., E.K., Data Collection or Processing: N.D., B.Y., E.K., S.G.B., Analysis or Interpretation: N.D., E.K., S.G.B., Literature Search: N.D., E.K., Writing: N.D.

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