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Celiac disease in patients having recurrent aphthous stomatitis

Rekürren aftoz stomatitli hastalarda celiac hastalığı

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Background/aims: *Celiac disease is a condition related to the small intestine's intolerance to gluten. In epidemiologic studies the prevalence is highly variable. The diagnosis can be difficult due to the wide spectrum of signs and symptoms. As the risk for intestinal lymphoma is higher in these patients, early diagnosis has its privileges. The higher prevalence of recurrent aphthous stomatitis in celiac disease led us to investigate the celiac disease prevalence in patients with recurrent aphthous stomatitis, which might assist in diagnosis of asymptomatic celiac disease patients. The aim of this study was to determine the prevalence of celiac disease in patients presenting with recurrent aphthous stomatitis.* ***Methods:*** *The study group consisted of patients having a history of recurrent aphthous stomatitis. The control group included patients not having aphthous stomatitis. Antibodies to gliadin IgG and IgA and antibodies to endomysium were determined from the serum samples of all patients. Biopsies were obtained from the distal part of the duodenum.* ***Results:*** *Biopsies of two patients (4.8%) out of 41 belonging to the study group were diagnosed as celiac disease. In serum samples of both, antibodies to gliadin IgA and antibodies to endomysium were found to be positive. Antibodies to gliadin IgG antibody were positive in only one of these two patients. None of the 49 patients in the control group was diagnosed as celiac disease.* ***Conclusion:*** *Further evaluation of recurrent aphthous stomatitis patients for celiac disease must be performed. As the endoscopic procedures are invasive and costly, evaluation of recurrent aphthous stomatitis patients for celiac disease must include serologic markers at the beginning. If any positivity is determined in markers, then endoscopic procedures including biopsies of the duodenum must be considered as the second-step interventi-*

Key words: Celiac disease, prevalence, antibodies, recurrent aphthous stomatitis

Amaç: *Celiac hastalığı ince barsakların glütene intoleransı sonucu oluşan bir hastalıktır. Epidemiolojik çalışmalarda prevalansı hakkında çok farklı veriler vardı. Hastalarda genellikle çok geniş spektrumda semptom ve bulgulara neden olabildiğinden celiac hastalığı tanısının konulması zor olabilmektedir. Hastalığın erken evrede yakalanması önemlidir. Çünkü bu hastalarda barsak lenfoması gelişme riski artmıştır. Celiac hastalığı olan hastalarda rekürren aftoz stomatit prevalansındaki yükseklik nedeniyle rekürren aftoz stomatitli hastaların celiac hastalığı yönünden araştırılması asemptomatik celiac hastalığı olan hastaların tanı almasını sağlayabilir. Bu çalışma rekürren aftoz stomatit nedeniyle başvuran olgularda celiac hastalığı prevalansını saptamak için planlanmıştır.* ***Yöntem:*** *Çalışma gurubu olarak rekürren aftoz stomatit öyküsü olan, kontrol grubu olarak ise rekürren aftoz stomatit öyküsü olmayan olgular alındı. Tüm olgularda anti gliadin IgG, antigliadin IgA ve anti endomisium antikorları bakıldı. Ayrıca endoskopi yapılarak duodenum distal kesiminden biyopsiler alındı.* ***Bulgular:*** *Rekürren aftoz stomatit öyküsü olan 41 olgunun ikisinde patolojik inceleme ile doğrulanan celiac hastalığı bulundu (%4.8). Celiac hastalığı saptanan bu iki olgunun her ikisinde de anti gliadin IgA ve endomisium antikorları pozitif bulundu. Anti gliadin IgG antikoru ise olguların birinde pozitifti. Kontrol grubundaki 49 olgunun hiçbirinde celiac hastalığı saptanmadı.* ***Sonuç:*** *Rekürren aftoz stomatit olgularında celiac hastalığı açısında ileri incelenmeler yapılmalıdır. Endoskopinin invaziv ve daha pahalı olması nedeniyle rekürren aftoz stomatitli olgularda celiac hastalığı ı araştırmak için öncelikli olarak serolojik tetkikler yapılmalı, seroljik markır pozitif olan olgularda endoskopik olarak duodenum ikinci kesiminden biyopsiler alınmalıdır.*

Anahtar kelimeler: Celiac disease, prevalans, antikorlar, recurrent aphthous stomatitis

INTRODUCTION

Celiac disease (CD) is caused by gluten sensitivity of the small intestines. Gluten is a component of cereals like barley, wheat, oat and rye. Environmental and genetic factors contribute in presenta-

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tion of the disease (1; 2). In epidemiologic studies, the prevalence of CD is highly variable. Prevalence rates of 1:120 to 1:300 have been reported in Western Europe (3-5). Diagnosis of CD may be somewhat hard to achieve in some of the patients due to the wide spectrum of signs and symptoms. Other systems may be affected by the disease such as dermatitis herpetiformis in the skin (6). Skin lesions in the latter improve when patients start a gluten-free diet (7).

Recurrent aphthous stomatitis (RAS) is one of the most common mucosal diseases known to humans. The lesions of RAS are characterized by recurrent ulcerations of the oral mucous membranes. An aphthous lesion is a painful, round ulcer with a necrotic center and swollen rim surrounded by an erythematous halo. It may be solitary or multiple in number. The diagnosis of RAS is achieved by history and physical examination. There have been numerous proposed etiologic mechanisms for RAS, including local, microbial, systemic, nutritional, immunologic, and genetic factors. Nevertheless, despite much research, the cause remains idiopathic or a result of a variety of predisposing factors (8-10).

Some authors state that CD prevalence in patients with RAS is higher than in the normal population. Therefore RAS may be the presenting sign of the disease (11-13). In this study we searched for CD in patients with RAS by serum markers and endoscopic biopsies of the duodenum.

MATERIALS AND METHODS

Patients presenting with RAS to the dermatology and family practice out-patient clinics in Zonguldak Karaelmas University Hospital between June 2002 and September 2003 were recruited for the study group. The control group consisted of patients referred to the gastroenterology out-patient clinic for reasons other than RAS.

The diagnosis of RAS was concluded by history and physical examination. Prior to the diagnostic procedures, informed consent was obtained from all the patients in the study and control groups. Fasting venous plasm samples were drawn for antibodies. ELISA technique was used to determine antibodies to gliadin (AGA) IgG and IgA. Indirect immunofluorescent technique was used to determine antibodies to endomysium (EMA).

Endoscopic samplings were performed with Pentax EG2930K endoscopic equipment after an overnight fasting. Two biopsy specimens for each patient were obtained from the distal duodenum. The material was fixed in buffered formalin (for future histologic study) and stained with hematoxylin-eosin, and the following aspects were evaluated: villi-crypt relationship, crypt's regenerative activity, characteristics of inflammatory infiltrate of the lamina propria, and type of atrophy. Patients identified as having CD in biopsy specimens were started on a gluten-free diet. Six months later duodenal biopsies were repeated and searched for histopathologic clues indicating healing.

Results are presented as mean ± standard deviation. Comparison between groups was performed with Student's t test and the p value for statistical significance was less than 0.05.

RESULTS

The study group consisted of 41 subjects whose mean age was 40±10.8 [23 (56%) female, 18 (44%) male]. The control group consisted 49 subjects whose mean age was 38±12.9 [28 (57%) female, 21 (43%) male]. There were no statistically significant differences between groups regarding age and gender ($p>0.05$) (Table 1).

Table 1. Demographic data and results of participating patients

	Recurrent aphthous stomatitis	**Control**
Number of patients (n)	41	49
Mean age ± SD (years)	40±10.8	38±12.9
Female/male ratio	23/18	28/21
Antibodies to gliadin IgG	5 (12%)	2 (4%)
Antibodies to gliadin IgA	3 (7.3%)	2 (4%)
Antibodies to endomysium	2 (4.8%)	0 (0%)
Celiac disease	2 (4.8%)	0 (0%)

In the study group, five (12%) were AGA IgG positive, three (7.3%) were AGA IgA positive and two (4.8%) were EMA positive. Duodenum was natural in appearance in all patients in the study group. In two (4.8%) of them, biopsy specimens obtained from the distal part of the duodenum revealed CD. Microscopic findings improved significantly in these two patients after six months on gluten-free diet.

In the control group, two (4%) were AGA IgG positive, two (4%) were AGA IgA positive and none were EMA positive. The distal part of the duodenum was natural in appearance in all patients in the control group. None of the biopsies obtained revealed CD.

DISCUSSION

Recurrent aphthous stomatitis was found in 10-40% of untreated CD patients (14-16). The prevalence of RAS in the general population is approximately 20% (5; 16). As RAS is frequently seen in CD patients, evaluation of individuals with this symptom may reveal the patients with undiagnosed CD.

Although the exact cause for aphthous stomatitis is still unknown, nutritional factors play a well defined role, and contribute to the relationship between CD and RAS (10;16;17).

In our study, two (4.8%) of the 41 subjects having RAS were diagnosed as CD. None of the 49 patients in the control group was diagnosed as CD. Their use in screening various population groups has significantly altered our perception of the clinical manifestations and prevalence of CD. According to previous reports, the prevalence of CD is highly variable, with clinical disease ranging from 1:500 to 1:10,000 individuals in different countries (4). Prevalence rates of 1:120 to 1:300 have been reported in Western Europe, although epidemiologic data are insufficient to provide an accurate estimation of the incidence of CD in the global population (3-5). The frequency of celiac sprue in our study was found to be 5 to 15 times higher than that of the general population.

There are a number of studies in the literature investigating the relationship between RAS and CD. Veloso et al. (13) reported villous atrophy in jejunal biopsies in four (16%) of 25 patients having RAS, which improved with gluten-free diet. In the same study, when compared to the healthy subjects, jejunal biopsies of RAS patients demonstrated significantly more intra-epithelial lymphocytes. According to these findings, Veloso et al. suggested that a significant number of patients with RAS may have a mild form of gluten enteropathy. In another study, Ferguson R et al. (18) found eight (24%) of the jejunal biopsies of 33 RAS patients compatible with CD. In the study of Ferguson MM (11), two (4%) of 50 RAS patients were diagnosed as CD. Jokinen et al. (16) searched for serum markers in 27 RAS patients and performed endoscopic biopsies in marker positive ones. Three (11%) of these patients were diagnosed as CD.

The important question when investigating RAS patients for CD is to establish the investigation technique, whether serologic or endoscopic. In our study group consisting of 41 RAS patients, five (12%) were AGA IgG positive and three (7.3%) were AGA IgA positive, whereas in the 49 subjects in the control group, two (4%) were AGA IgG positive and two (4%) were AGA IgA positive. EMA were only positive in two of the patients in the study group. In duodenal biopsies of the study group, two were diagnosed as CD, whereas no case of CD was determined in the control group. In one of the patients diagnosed as CD, all three serum markers were positive. The second patient was positive for AGA IgA and EMA, but negative for AGA IgG. As a result, the specificity and sensitivity of EMA were 100%, specificity and sensitivity of AGA IgA were 96% and 100%, respectively, and specificity and sensitivity of AGA IgG were 93% and 50%, respectively.

In previous studies, AGA antibodies were found to be moderately sensitive and specific in diagnosing CD, among them IgA being slightly more specific (19;20). The sensitivity and specificity of EMA were defined as almost 100%, but may be negative in isolated IgA deficiency (4). Although these previous findings are concordant with our results, the relatively few number of subjects in our study decreases the value for sensitivity and specificity. In conclusion, further evaluation of RAS patients for CD must be performed.

As the endoscopic procedures are invasive and costly, evaluation of RAS patients for CD must include serologic markers, of which AGA was found to be relatively less sensitive whereas EMA was highly sensitive and specific. According to the serum markers, endoscopic procedure including biopsy of the second part of the duodenum must be considered as the second-step intervention.

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