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Original Article

Prevalence of Celiac Disease in Patients with Recurrent Aphthous Stomatitis

Abbas Yazdanbod[1], Rasoul Nemati[1], Manouchehr Iranparvar Alamdari[1], Ahad Azami[1], Nasrollah Maleki[1]

[1] Department of Internal Medicine, Imam Khomeini Hospital, Ardabil University of Medical Sciences, Ardabil, Iran

ABSTRACT

Background:
Celiac disease (CD) is an immune-mediated inflammation of the small intestine caused by sensitivity to dietary gluten and related proteins in genetically sensitive individuals. Recurrent aphthous stomatitis (RAS) is an inflammatory condition characterized by painful recurrent, single or multiple ulcerations of the oral mucosa. The association between CD and RAS has been evaluated in several studies. The purpose of this study was to determine the prevalence of CD in patients with RAS.

Materials and Methods:
This was a prospective cross-sectional study that enrolled 181 patients with recurrent oral ulcers (at least three attacks per year). Patients' peripheral blood samples were studied in terms of anti-tissue transglutaminase (anti-tTG) antibodies (IgA), anti-endomysial antibody (IgA) and serum IgA levels. Each patient that had a positive celiac serology underwent a duodenal biopsy. Information from all patients was entered into checklists. After completion of the checklists, the obtained data were analyzed by SPSS v19 statistical software.

Results:
Of the 181 enrolled patients with recurrent aphthous, 43 (23.75%) were male and 138 (76.25%) were female. Average age of these patients was 28.45 ± 12.27 years. The average age of disease onset was 23.39 ± 9.46 years. Serologic survey results showed that only 2 patients were positive for these antibodies - both were women whose average age was 29 years. The average age of their disease onset was 22.5 years and biopsy results confirmed the presence of lymphocytic enteritis with crypt hyperplasia (Marsh II).

Conclusion:
According to the results of this study, although there is a low prevalence of CD in patients with RAS, screening RAS patients for key serological markers of CD has clinical value.

Keywords: Aphthous stomatitis; Celiac disease; Gluten-free diet

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Corresponding author:
Nasrollah Maleki MD,
Department of Internal Medicine, Imam Khomeini Hospital, Ardabil University of Medical Sciences, 6368134497, Ardabil, Iran
Tel: + 98 451 5521903
Fax:+ 98 916 3057715
E-mail: malekinasrollah@yahoo.com
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INTRODUCTION

Celiac disease (CD), formerly named gluten sensitive enteropathy (GSE) is an immune-mediated intolerance to gluten from wheat, barley, or rye in genetically susceptible individuals(1,2). CD occurs in adults and children at rates approaching 1% of the population(3-7). The minimum prevalence of gluten sensitivity among the general population of Northern and Southern Iran is 1:104(8). Prevalence rates of 1:120 to 1:300 have been reported in Western Europe(9-11). As a general rule, testing should begin with serologic evaluation. The most sensitive and

specific tests are IgA anti-tissue transglutaminase (anti-tTG) and IgA endomysial antibody, which have equivalent diagnostic accuracy. Patients with a positive IgA endomysial or transglutaminase antibody test should undergo an upper endoscopy with small bowel biopsy. Multiple biopsies should be obtained from the duodenal bulb and the second and third portion of the duodenum(12). The histologic features range from a mild alteration characterized only by increased intraepithelial lymphocytes to a flat mucosa with total mucosal atrophy, complete loss of villi, enhanced epithelial apoptosis, and crypt hyperplasia. The histologic findings in CD can be described using the Marsh-Oberhuber classification(13).A gluten-free diet is recommended in patients with CD (classic disease, atypical CD, and asymptomatic or silent CD). Patients with latent CD (positive IgA endomysial antibody, but normal small bowel biopsy) are currently not advised to be on a gluten-free diet but should continue to be monitored and rebiopsied if symptoms develop. However, it is important that histologically evident CD is adequately evaluated in these patients by performing multiple intestinal biopsies since the histologic abnormalities can be patchy(14). The rapidity of the response to a gluten-free diet is variable. Approximately 70% of patients have noticeable clinical improvement within two weeks(15).

Recurrent aphthous stomatitis (RAS) is the most common idiopathic intraoral ulcerative disease in the USA. It is characterized by multiple recurrent small, round or ovoid ulcers with circumscribed margins, erythematous haloes, and yellow or grey floors, appearing first in childhood or adolescence. The disease occurs in men and women of all ages, races and in all geographic regions. Its prevalence in the general population is estimated to vary from 5% to 66%, with a mean of 20%(16,17).

An association between RAS and CD has been proposed for the last 30 years as some RAS patients show evidence of small bowel changes suggestive of CD; nevertheless, there is still considerable dispute concerning the actual prevalence of CD in RAS patients. CD has been documented in 4% to 25% of examined RAS patients(18). In 1976, Ferguson et al(19) bserved that 8 (24%) of 33 patients with RAS showed histological evidence of CD as determined by jejunal biopsy. In another study conducted by Ferguson et al.(20) 2 (4%) of 50 RAS patients were diagnosed with CD. Subsequently, Jokinen et al(21) showed an association between RAS and CD (11%). A study by De Freitas et al(22) has shown that a significantly increased percentage of patients with CD suffer from aphthous stomatitis. A detailed analysis performed by these authors revealed that up to 31% of patients with CD showed clinical manifestations of aphthous stomatitis.

The aim of this study was to determine the prevalence of CD in patients with RAS, using relevant serologic as well as histologic tests and to assess whether patients with confirmed CD improved with a gluten-free diet.

MATERIALS AND METHODS

This was a prospective cross-sectional study. Patients who presented with RAS to the Dermatology Outpatient Clinic of Imam Khomeini Hospital in Ardabil between May 2011 and June 2012 were recruited. Given the prevalence of CD as 1% in Iran and a 95% confidence interval, we estimated the sample size for this study at 181 patients. Patients included in the study had at least three episodes of oral aphthae during the year. Patients with any of the following criteria were excluded: Behcet's disease, inflammatory bowel disease, systemic lupus erythematosis, tumors of the oral cavity, Reiter syndrome and oral lesions due to drugs and radiation. The diagnosis of RAS was performed by one dermatologist according to history and physical examination based on accepted criteria.

All patient data were entered into checklists. Demographic information including gender, age, complete history of oral aphthous, gastrointestinal symptoms (epigastric pain, heartburn, diarrhea, steatorrhea, weight loss, abdominal distension/ bloating, and regurgitation), medication history, and laboratory test results were recorded.

Fasting venous plasma samples were drawn for antibodies. Indirect immunofluorescent technique was used to determine antibodies to endomysium (EMA). IgA antibodies to tissue transglutaminase were assessed by ELISA using recombinant human tTG as the antigen (Genesis Diagnostics, Cambridgeshire, UK). The cutoff value for a positive outcome was considered to be 7 AU, according to the instructions in the kit. Serum IgA level was measured to rule out IgA deficiency.

Patients with positive serologic test (EMA or tTG) underwent upper endoscopy and six biopsies were taken from the second and third portion of the duodenum. The material was fixed in buffered formalin (for future histologic study) and stained with hematoxylin-eosin. The histological assessment included examination for significant alteration in main mucosal measurements and lymphocytic infiltration

according to the Marsh criteria. The presence of positive tTG or EMA plus abnormal duodenal histology was defined as CD.

Data are presented as mean ± SD or percentages. Statistical analyses were performed using SPSS software version 19.

RESULTS

Of the 181 patients with RAS, 43 (23.75 %) were male and 138 (76.25 %) were female. Average age of these patients was 28.45 ± 12.27 years (range: 18–64 years). The average age of this disease onset was 23.39 ± 9.46 years. Gastrointestinal symptoms such as epigastric pain were noted in 16 (8.8%) patients with RAS, 19 (10.5%) patients had heartburn, 21 (11.6%) patients had regurgitation, 14 (7.73%) patients had abdominal distension/bloating, and none had any history of diarrhea, steatorrhea, or weight loss.

After serologic studies for CD, only 2 (1.1 %) female patients had positive EMA and tTG tests. Both underwent upper GI endoscopies with duodenal biopsies. In one patient endoscopic finding was compatible with CD (mild villous atrophy) and the other patient was normal. Pathological finding was compatible with Marsh II (lymphocytic enteritis and crypt hyperplasia) in both patients. Mean age of patients with CD was 29 years. These patients had symptoms of RAS for an average duration of 7.5 years.

One patient was a 35-year-old female who referred to our outpatient clinic with a 6-year history of pronounced aphthous stomatitis. Laboratory investigations showed mild anemia. In this patient, the pathological finding was compatible with Marsh II classification. The patient was introduced to a gluten-free diet which produced significant improvement within three months and total clearance of all lesions of the oral mucosa within six months. The patient has since remained on a gluten-free diet and free from any lesions for several months.

The other patient was a 23-year-old female. She had a 9-year history of severe, continuous RAS with no gastrointestinal complaints. All basic laboratory tests, including blood count and iron plasma levels, were within the normal range. In this patient, histopathology of her duodenal biopsy was compatible with Marsh II. The patient was instructed to follow a gluten-free diet. Within the next six months the oral lesions were almost completely healed.

DISCUSSION

CD (also called gluten-sensitive enteropathy and nontropical sprue) was first described by Samuel Gee in 1888 in a report entitled "On the Coeliac Affection", although a similar description of a chronic, malabsorptive disorder by Aretaeus from Cappadocia (now Turkey) was published as far back as the second century AD(23).

In this study of a large group of patients with RAS, a 1.1% prevalence of CD was observed compared with an estimated prevalence of 0.9% in the general population of Iran(24). Although a first report of aphthous oral ulcers in patients with CD was published by Ferguson et al.(20) several years ago, just recently the question has been raised by several authors as to whether RAS might be pathogenetically related to CD and whether treatment of CD may induce improvement in RAS. It has been reported that RAS is at least among the fifth most common presentations of CD(25,26). In addition, oral mucosal lesions or dental enamel defects may be the sole presenting features of CD(27).

Some authors have reported that patients with RAS have an increased prevalence of CD and have suggested that RAS may be their presenting complaint. Natah et al.(17) estimates the prevalence of RAS in patients with CD at 10%–18%.

Aydemir et al.(28) described two cases with coexisting RAS and CD in a group of 41 RAS patients. Veloso et al.(29) reported villous atrophy in 4 (16%) of 25 patients with RAS. Additionally, Olszewska et al.(30) concluded that each patient with RAS should be asked specifically about gastrointestinal symptoms and screened for IgA EMA (positive in 4.7% of subjects). Tyldesley(31) reported that CD was associated with recurrent aphthae. Campisi et al.(32) reported an epidemiological association between CD and aphthous-like ulcers. These researchers suggested that recurrent aphthous-like ulcers should be considered a risk indicator for CD and that a gluten-free diet would lead to ulcer amelioration. Shakeri et al.(33) reported that a significant minority (2.83%) of RAS patients have GSE. This study suggested that evaluation for CD was appropriate in patients with RAS. Additionally, the unresponsiveness to conventional anti-aphthae treatment could be an additional risk indicator.

Yasar et al.(34) have reported no apparent etiological link between RAS and CD. These researchers believe that screening RAS patients for CD is of little clinical value. Additionally, regurgitation of gastric acid to the oral cavity may precipitate the formation of aphthous stomatitis (Table 1). Currently, some authors consider RAS to be a clinical manifestation of CD(17,35).

On the other hand, several authors doubt the

Table 1: **Prevalence of celiac disease (CD) in patients with recurrent aphthous stomatitis (RAS).**

References	No. of RAS patients	No. of RAS patients with CD	Improvement in RAS on a gluten-free diet
Aydemir et al.[28]	41	2 (4.8%)	Not reported
Campisi et al.[32]	269	61 (22.7%)	Yes
Ferguson et al.[19]	33	8 (24%)	Yes
Ferguson et al.[20]	50	2 (4%)	Yes
Jokinen et al.[21]	82	4 (4.9%)	Not reported
De Freitas et al.[22]	48	6 (31%)	Not reported
Veloso et al.[29]	24	4 (16%)	Not reported
Olszewska et al.[30]	42	2 (4.7%)	Yes
Tyldesley et al.[31]	97	6 (6.2%)	Yes
Shakeri et al.[33]	247	7 (2.83%)	Yes
Robinson et al.[37]	87	0	Not reported
Yasar et al.[34]	82	1 (1.2%)	Not reported

existence of a relationship between CD and RAS. Sedghizadeh et al.(11) could not confirm increased prevalence of aphthous stomatitis in patients with CD. Nowak et al.(36) focused on patients with RAS and evaluated their sera for presence of IgA EMA. In an investigation, which included 20 RAS patients only one patient was IgA EMA positive. The patient however, was not evaluated for CD. Similar results were obtained in a Singapore study(37).

Our study has some limitations. We did not take duodenal biopsies from patients who had negative serological tests. Decreased sensitivities of the serological tests have been reported in GSE patients with minor mucosal damage(38,39). We could not exclude the possibility of missing some GSE patients who had negative serological tests and Marsh I/II mucosal lesions (e.g. seronegative GSE). However, a patient with a negative serological test and duodenal mucosal lesion may suffer from other disorders such as autoimmune enteropathy, giardiasis, common variable immunodeficiency, tropical sprue, peptic duodenitis, and Crohn's disease. Including such patients (e.g., those with negative serological tests with duodenal mucosal damage) in the spectrum of GSE could increase the rate of false positive results unless symptomatic and histological improvements have been confirmed by a gluten-free diet. Therefore, in epidemiological studies, a positive result from a highly specific serological test (EMA or tTG) in conjunction with any degree of duodenal mucosal lesion might provide reasonable criteria for identifying patients with GSE.

As the endoscopic procedures are invasive and costly, evaluation of RAS patients for CD must include serologic markers. We conclude from the results of this study that the prevalence of CD in patients with RAS has a low frequency. However screening RAS patients for key serological markers of CD has clinical value.

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