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Gluten associated dyspepsia; serology and histological characteristics

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ABSTRACT

Aim: The aim of this study was to assess the prevalence of celiac disease (CD) in dyspeptic patients.

Background: Although severe mucosal abnormality with villous atrophy (lesions Marsh III) is the histology gold standard for the diagnosis of CD, non-specific microenteropathy (Marsh I-II) with positive serology is also common. Patients with dyspepsia, specific CD antibodies and microenteropathy, could have CD.

Patients and methods: From November 2007 to October 2008, 407 randomly chosen patients who underwent diagnostic upper gastrointestinal endoscopy for dyspeptic symptoms (193 male, 214 women; mean age 36.1 years) were studied. Small bowel biopsies were performed in all of them. Histologic characteristics in duodenal biopsy specimens for CD were evaluated according to the modified Marsh Classification. All the patients were also tested for serum total immunoglobulin A and anti-transglutaminase (tTG) antibodies. Those with IgA deficiency were tested for IgG tTG.

Results: Duodenal histology showed Marsh I-IIIc lesions in 6.4% cases. 4 patients (0.98%) were IgA deficient and none of them were positive for IgG tTG. Serology showed positive results for tTGA in 8% of the patients and 2.5% of them had abnormal histology (Marsh I-IIIc) compatible with CD.

Conclusion: The results of this study showed that milder enteropathy (Marsh 0-II) have a low specificity for CD. The prevalence of CD among dyspeptic individuals is significantly (2.5%) higher than in the general population (1%) and CD should be investigated in these patients.

Keywords: Dyspepsia, Celiac disease, Antibody.

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Introduction

Coeliac disease (CD) and dyspepsia are common conditions, and consume considerable resources in both investigation and treatment. In the last years, a considerable change in epidemiology of CD has been observed. A marked increase in CD prevalence and incidence with

milder enteropathy has been reported (1, 2), which can be at least partially explained by both the development of more sensitive serological tests and a high degree of disease suspicion (3, 4). The variability of in particular clinical (5) and histological aspects of CD may face the clinician often with uncertainty as some of the features might not quite fit in the diagnostic models in the current guidelines.

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Malabsorptive symptoms, such as weight loss, diarrhea/steatorrhea and abdominal distension may not be necessarily observed in many celiac patients (6). Atypical forms of CD have increased considerably (7) and the presence of dyspepsia as a unique symptom has been frequently attributed to CD (8). In classical CD with prominent malabsorptive features, dyspepsia may be also one of the symptoms. It has been reported that the frequency of CD in people with dyspeptic complaints is 1.1-3%, which is two to nine times higher than in the general population (6, 8-12). The frequency of CD in the Iranian general population is considered to be around 1% (9).

In the present study we described the prevalence of celiac disease in dyspeptic patients.

Patients and Methods

Between November 2007 and October 2008, 5732 patients aged 15 years or more attended the Gastroenterology section of the Taleghani hospital of Tehran, Iran. Four hundred and seven patients (193 men and 214 women) randomly chosen patients with dyspepsia were prospectively studied. The study was approved by the institutional ethics committees of Gastroenterology and Liver Diseases Research Center, Shahid Beheshti University of Medical Sciences, and all participants signed a written informed consent.

Individuals were considered dyspeptic if they complained of persistent pain or uneasiness in the upper abdomen. Upper GI endoscopies were performed in these patients to diagnose common causes of dyspepsia including esophagitis, peptic ulcers, duodenitis and cancer. In addition, CD was identified by histological alterations characteristic of gluten sensitive enteropathy and by consistent CD serology.

Gastric biopsies were obtained for *H.pylori* detection and biopsies from the second part of the duodenum for histological processing.

Histological diagnosis of CD was based on the presence of intraepithelial lymphocytes, crypts hyperplasia and/or villous atrophy. Biopsy results were classified as absence of CD (Marsh 0) or suggestive of CD (Marsh II to IIIc), according to modified Marsh criteria (13, 14). The histological specimens were examined by two pathologists who did not know the endoscopic results and clinical history of the patients. The sera of these patients were analyzed for IgA class human antitissue transglutaminase (tTG) antibody and total serum IgA values according to standardized methods (15). Serological data were correlated to the endoscopic results and to the histological pattern observed in the small intestine. All patients with confirmed CD diagnosis were treated with a gluten free diet and followed.

Statistical analysis was performed using SPSS software, version 13.5. Descriptive variables such as mean, median and standard deviation were determined. Chi-square (χ^2) test was performed to find out the association between CD and risk factors.

Results

The mean age of the patients was 36.1 years. The gastroenterology symptoms in the subjects were: 78% abdominal pain, 70% bloating, 58% heart burn, 46% early satiety, 32% nausea, 32% flatulence, 31% weight loss and 22% anorexia. Recurrent abdominal pain, heart burn and bloating were present in 60%, 45% and 31% of the patients, respectively (figure 1).

Helicobacter pylori was detected in 90.5% cases. There were 26 cases with enteropathy (12 Marsh I, 4 Marsh II, 2 Marsh IIIa, 6 Marsh IIIb and 2 Marsh IIIc). Four of 407 dyspeptic

patients were IgA deficient and all of them were negative for IgG tTG. Thirty three (8.1%) of the 407 patients tested had tTGA level more than 15 u/ml and considered as tTGA positive. Twenty three of 33 seropositive had normal small bowel mucosa.

The demographic, histologic and serologic characteristics of 33 patients with serology positive and 26 with abnormal histology are shown in table 1.

Table 1. Clinical and laboratory features of seropositive patients

Subjects	Abnormal histology patients	Seropositive patients
No. of cases	26	33
Mean age (yrs)	37.9	42.6
Gender		
Male	11	15
Female	13	20
GI symptoms		
abdominal discomfort	18	25
anorexia	6	8
weight loss	11	9
nausea	5	9
heart burn	14	10
early satiety	8	9
flatulence	7	8
bloating	12	15
<i>H. pylori</i>	21	26
Celiac disease	10	10

Table 2. Cases with histology and serology consistent with celiac disease

Marsh classification	No. of patients	Gender		Mean age (yrs)
		Female	Male	
Marsh I	3	2	1	27.3
Marsh II	2	1	1	39
Marsh III (a-c)	5	4	1	26.8
tTG +ve with normal histology	23	12	11	48.3

In 10 of 33 tTGA positive patients, CD was confirmed by histological analysis of the intestinal biopsy samples, giving a prevalence of CD of 2.45%. Five of these 10 celiac patients were Marsh IIIa-c followed by 3 Marsh I and 2 Marsh II. The highest rate of histological abnormalities and of CD seropositivity was

found in the age categories of 21-30 years and 10-20 years respectively (table 2).

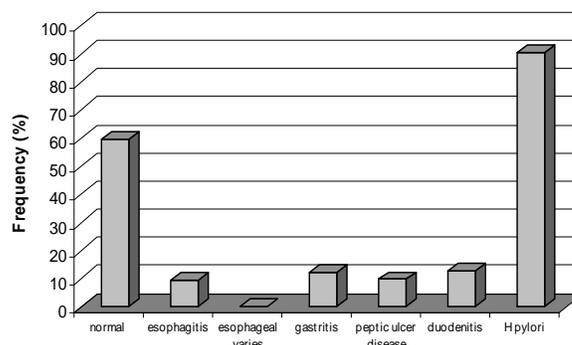


Figure 1. Current endoscopy findings in study population

Discussion

Dyspepsia is a highly prevalent and heterogeneous disorder (16). We know that damages in CD are not confined to the small intestine (17) and not every celiac patient develop severe mucosal small bowel abnormality. Several studies have demonstrated that chronic exposure to gluten may damage the structure and function of the gastric mucosa in CD patients (18, 19). Other surveys indicate that approximately 20% of patients with dyspeptic symptoms have erosive esophagitis, 20% are estimated to have endoscopy-negative reflux disease, 10% have peptic ulcer, 2% have Barrett esophagus and 1% or less have malignancy (20) and the results of the present study suggest that at least 2-3% CD in dyspeptic patients should be added to the list. However, the proportion of celiac autoantibodies in dyspepsia seems to be even higher (serology >8%) and the question is whether these antibodies are representing a different form of gluten related disorders or belong to the spectrum of false positivity.

The most important identifiable causes underlying dyspeptic symptoms in our study group were duodenitis (13%), gastritis (12%), esophagitis (9%) and peptic ulcer disease in 10%. Malignancies of the upper gastrointestinal tract were not found. Approximately, 60% of patients with

dyspepsia showed no abnormality in their mucosa but the majorities were positive for *H. Pylori*.

It is important to note that serology at high level (when 10x >cut-off of normality) is a far more specific marker for atypical CD compared to microenteropathy (Marsh I-II) which seems to have a non-specific nature (23). With other words the specificity of serology at high level for CD seems to be close to 99% in many studies (24). Similarly histology represent the gold standard for CD diagnosis only in cases with severe mucosal abnormality (Marsh IIIa-c). A better definition and differentiation of true value of milder positivity of both histology and serology would be useful in clarifying the expectation of each test (25, 26).

We are aware that there is not a single perfect test available to diagnose CD in its own. Histological abnormalities ranging from mild to severe were found in the small bowel of 6.4% of our patients. Despite high specificity of autoantibodies, this finding would provoke the discussion on seronegative cases and question the sensitivity of serological tests. Although, microenteropathy could be a result of any other intestinal disorder, from previous experience we learned those negative serological tests were less reliable in symptomatic cases presenting with a milder enteropathy (21, 27, 28).

Serology at weak positive level and milder histology (microenteropathy) are both nonspecific for CD. A combination of clinical presentation, histology, serology and HLA typing would contribute in making a more accurate diagnosis. The limitation of this study was lack of second serological test in particular using Endomysial antibodies after tTG and lack of HLA typing for exclusion of non-celiac cases. Coeliac disease with flat mucosa based on which the gold standard was introduced >50 years ago is still a rare condition. It is time to recognize that for a good proportion of CD cases histology is non-specific and hence the pathologist is unable to make the definite

diagnosis in his own. Serology at high level and histology with severe abnormalities are both reliable markers for CD. Milder enteropathy and low positive antibodies require a better identification. Future studies would be needed to assess whether dyspeptic patients presenting with positive antibodies and normal histology would benefit from a GFD.

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