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Original Article

Prevalence of Celiac Disease in Patients with Irritable Bowel Syndrome

Emami MH[1], **Kouhestani S**[2], **Gholamrezaei A**[2], **Hashemi M**[2], **Mahzouni P**[3], **Raeisi M**[2], **Daghaghzadeh H**[4], **Daneshgar H**[5]

[1] Associate Professor, Poursina Hakim Research Institute and Iranian Celiac Society, Department of Gastroenterology, Isfahan University of Medical Sciences, Isfahan, Iran

[2] Researcher, Poursina Hakim Research Institute and Iranian Celiac Society, Isfahan, Iran

[3] Assistant Professor, Department of Pathology, Isfahan University of Medical Sciences, Isfahan, Iran

[4] Assistant Professor, Poursina Hakim Research Institute and Iranian Celiac Society, Department of Gastroenterology, Isfahan University of Medical Sciences, Isfahan, Iran

[5] Professor, Poursina Hakim Research Institute, Department of Gastroenterology, Isfahan University of Medical Sciences, Isfahan, Iran

ABSTRACT

Background: Celiac disease (CD) may be misdiagnosed as Irritable Bowel Syndrome (IBS) resulting in long delays in diagnosing CD. There are contradictory reports on the association of CD with IBS. Appropriateness of screening all patients with IBS for CD and how to screen them are still under question.

Materials and Methods: In a cross-sectional study, 328 IBS patients (Rome II) referred to the Poursina Hakim Gastroenterology Clinic were investigated for CD. Total serum anti-tissue transglutaminase IgA (anti-tTG IgA) concentration was measured in all patients. In IgA deficient cases, antigliadin antibody (AGA) IgG concentration was also measured. Moreover, in patients who underwent upper endoscopy (as their necessary workup) duodenal biopsies were taken.

Results: Fifty-eight patients were excluded. The remaining patients were 166 (61.5%) women and 104 (38.5%) men with the mean age of 35.3 years (SD = 11.8). No one had positive serological test of IgA anti-tTG antibody. Five patients were IgA deficient; none of them had positive IgG AGA. Duodenal biopsies were taken in 60 patients and pathologic evaluation showed 53 Marsh 0, three Marsh I, three Marsh II, and one Marsh IIIa. Only the patient with Marsh IIIa adhered to gluten-free diet (GFD) which led to decrease in severity of symptoms. In patients who did not adhere to GFD, no one had positive serological test after 12 months of follow-up.

Conclusion: Prevalence of CD in patients with IBS referred to outpatient gastroenterology clinic might be significant but serum anti-tTG IgA antibody is not helpful in detecting CD in these patients. Further studies are needed to clarify this issue.

Keywords: Celiac disease, Irritable bowel syndrome, Screening

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Corresponding author:
Poursina Hakim Research Institute and Iranian Celiac Society, Department of Gasteroenterology, Isfahan University of Medical Sciences, Isfahan, Iran.
Telefax: +98 311 2667544 E-mail: mh_emami@med.mui.ac.ir

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INTRODUCTION

Celiac disease (CD) is an immune-mediated enteropathy, triggered by ingestion of gluten-containing grains in genetically susceptible persons.(1), CD may manifest with variety of symptoms and severities, which may begin anytime during the life. Gastrointestinal symptoms may include diarrhea, abdominal pain, vomiting, bloating, anorexia, and even constipation.(2), The classic presentation of severe malabsorption syndrome with chronic diarrhea, steatorrhea, and weight loss, however, is less common which is known as the "iceberg" condition.(3), The variety of clinical presentations often results in delay in diagnosis, which may end up to serious complications.(4), Irritable bowel syndrome (IBS) is characterized by abdominal pain or discomfort plus disturbed defecation with the prevalence of about 10-15% in general population. As there is no structural or biochemical marker for diagnosing IBS, diagnosis is based on symptomatic criteria.(5), IBS-like symptoms could be the presentation of CD and a major challenge for its early detection, especially in areas in which the prevalence of CD is still thought to be low.(6), Some studies demonstrated considerable prevalence of CD in suspected IBS patients both in primary (7) and secondary care units.(8,9), Based on these studies, it is recommended that screening for CD by serological tests should be part of the routine investigation for all suspected IBS patients.(10,11) However, some studies do not show such a considerable association of CD with IBS.(12-15), Considering IBS as one of the most common disorders encountered by gastroenterologists, deciding to screen all patients increases the cost of care, which is a major challenge in managing IBS.(16), The aim of the present study was to assess the association of CD with IBS in patients referred to an outpatient clinic of gastroenterology.

MATERIALS AND METHODS

This cross-sectional study was conducted from October 2004 to November 2005 at Poursina Hakim Gastroenterology Clinic, which is a referral gastroenterology clinic in Isfahan, central Iran. Patients who diagnosed to have IBS were enrolled in the study, consecutively. Considering the estimated prevalence of CD in IBS patients as 5% and the estimated prevalence of CD in general population as 0.5%, a sample size of 300 IBS patients was calculated. The diagnosis of IBS was determined by a gastroenterologist according to the Rome II criteria (17), complete clinical and physical examination, and routine laboratory tests to rule out organic diseases. Patients were excluded if diagnosed previously having CD, have been evaluated or referred for diagnosis of CD, or had alarm features including anemia, family history of colon cancer or inflammatory bowel disease, fever, leukocyte or blood in stool, new or recent onset of symptoms in patient older than 50 years, nocturnal diarrhea, palpable abdominal or rectal mass, persistent diarrhea or severe constipation, and weight loss. Baseline investigations included full blood count, erythrocyte sedimentation rate, blood urea nitrogen, thyroid function tests, and three times stool exam. Considering the significant overlaps between IBS and other gastrointestinal disorders (e.g., gastroesophageal reflux disease), other paraclinical workups were ordered if clinically indicated, including upper endoscopy, colonoscopy, small bowel barium study, and abdominal ultrasonography. In upper endoscopy, at least three biopsies from the second portion of the duodenum (D2) were taken routinely. Each patient was interviewed by a general practitioner and a clinical questionnaire was completed. The questionnaire contained demographic data, signs and symptoms related to CD, and history of associated diseases related to CD such as insulin dependent diabetes mellitus, autoimmune hepatitis and sclerosing cholangitis.(1), The objectives of the study and potential significance of a positive test were explained to all patients and informed consent was obtained. Ethical approval was obtained from the Ethics Committee of Isfahan University of Medical Sciences.

Serology

Recombinant human anti-tissue transglutaminase IgA antibody (anti-tTG IgA), reported as a highly sensitive and specific test, was used for initial screening. (18), We measured anti-tTG IgA antibody with a commercially available kit (Orgentec Diagnostika GmbH) with a good reported sensitivity (94%) and specificity (100%) by the enzyme-linked immunosorbent assay (ELISA) method. (19), Total serum IgA concentration was measured in all patients to find IgA deficient patients (IgA concentration <10 mg/dl). In these patients, antigliadin antibody (AGA) IgG concentration was also measured. All of the serological tests were done in a clinical laboratory.

Histological evaluations

Patients who were positive for anti-tTG IgA antibody or AGA IgG were recommended to undergo upper gastrointestinal endoscopy and D2 biopsies. At least three pieces of biopsies were taken with biopsy forceps through a conventional forward viewing endoscope (EG 2940, Pentax EPM-3300). All biopsy specimens were reviewed by gastrointestinal oriented pathologists and were classified according to the modified Marsh classification.(20), Pathologists were blinded on the clinical symptoms and serological tests of the patients. Crohn's disease, lymphoma, severe malnutrition, and chemotherapy were considered in differential diagnosis. Giardia Lamblia infection was ruled out by stool examination and D2 biopsy study.

Criteria for diagnosis of celiac disease

Diagnosis of CD was established according to the revised ESPGAN criteria. The criteria included a duodenal biopsy showing Marsh II or more and improved symptoms after starting a gluten-free diet (GFD).(21)

Statistical analysis

Data are expressed as percentages or absolute number for categorical variables and means and standard deviation (SD) for continuous variables. Comparisons were made using the Student T-Test for quantitative and Chi-Square test for categorical variables. A p-value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS-13.0 for Windows software (SPSS Inc, Chicago, IL).

RESULTS

During the study period, 328 of patients who were referred to our gastroenterology clinic fulfilled the Rome II criteria for IBS. Out of these patients, 58 were excluded; 34 had alarm features (16 with anemia, 17 with weight loss and one with anemia and weight loss), 10 patients did serological test for CD in other clinical laboratories with different diagnostic kits of CD, and 14 patients did not cooperate. So, data of 270 patients considered for analysis: 166 (61.5%) women and 104 (38.5%) men with the mean age of 35.3 years (SD = 11.8, ranged 12-74 years). Symptom duration ranged from three months to 20 years (median = 24 months, SD = 12-60 months). Symptoms included constipation (75.7%), abdominal pain (67.3%), diarrhea (60.3%), flatulence (53.9%), bloating (46.4%), abdominal discomfort (32.7%), fatigue (24%), bone pain (14.7%), malodor stool or gas (10.5%), and steatorrhea (6%). Bowel habits were constipation (32.2%), diarrhea (17.6%), alternated constipation and diarrhea (43.8%) and unclassified (6.4%). Only one patient had associated disease, type II diabetes mellitus (patient 1 in table 1).

Serology and histology

Of 270 patients, no one had positive serological test of IgA anti-tTG antibody. Five patients (1.8%) were selective IgA deficient; none of them had positive IgG AGA. Upper GI endoscopy was done in 60 patients (as their necessary workup) and D2 biopsies were obtained routinely. Histological findings included 53 Marsh 0, three Marsh I, three Marsh II, and one Marsh IIIa (table 1). Patients with histological findings suggestive of CD were not significantly different from other patients in demographic characteristics or symptoms (p>0.05).

Table 1: Characteristics of patients with histological findings of celiac disease

PN	Gender	Age	Bowel habit	Histology	First Serology Anti-tTG IgA	Second Serology Anti-tTG IgA
1	F	36	ADC	Marsh IIIa	N	N
2	F	30	ADC	Marsh II	N	N
3	M	62	Diarrhea	Marsh II	N	-
4	F	24	ADC	Marsh II	N	-
5	F	47	ADC	Marsh I	N	N
6	F	43	ADC	Marsh I	N	-
7	F	41	Constipation	Marsh I	N	N

F: Female, M: Male, ADC: Alternative Diarrhea and Constipation, N: Negative, P: Positive.

Follow-up

Only four of seven patients with histological findings of CD came to follow-up visits. Only the patient with Marsh IIIa adhered to GFD with excellent symptomatic response to GFD after three weeks. Although patients with Marsh II or less did not adhere to GFD, they had moderate to complete reduction in symptoms after about 12 months and no one had positive test in second serology.

DISCUSSION

The results of this study showed that screening IBS patients (referred to outpatient gastroenterology clinic) with serum anti- tTG IgA antibody is not helpful for detecting CD. Why our patients with Marsh I and II had no positive serology, could be described by direct association of the degree of villous atrophy and the sensitivity of serological tests particularly anti-tTG IgA antibody.(22,23), In fact, wheat is a major component of the Iranian diet for many centuries. It may be argued that continuous and high level exposure to wheat proteins has induced some degrees of immune tolerance, leading to milder histopathological changes.(6), In our recent study, the overall sensitivity and specificity of anti-tTG IgA antibody in Iranian population were 38% and 98%, respectively.(24), Moreover serological tests, even with a sensitive and specific kit, have been shown to have lower sensitivity and specificity in clinical settings as compared to research laboratories.(25), During the past decade, a large body of literatures pertaining to a possible association of CD and IBS has shown contradictory results. In a study by Sanders et al (9) at a university hospital clinic in UK, 14 of 237 (6%) suspected IBS patients had CD based on serology [AGA IgA/IgG, and endomysial antibody (EMA)] and duodenal histology compared to two (0.6%) controls. In their further cross-sectional study at primary care unit, four (3.2%) new cases of CD were diagnosed in 123 patients with IBS.(7), The higher association of CD with IBS in secondary care compared to primary care may be that patients with IBS symptoms who have underlying CD are more symptomatic (7) and thus are more likely to be referred to gastroenterologists, but our results do not support it. The median age of patients was 56 years in the study of Sanders et al (9) and 35 years in our study. Although CD can occur at any age, but in adults the peak incidence is in the fifth decade.(26) This is while the first presentation of IBS patients to a physician is between the ages of 30 and 50 years.(27), However, in other studies in Iran, CD was diagnosed in 11.4% (12/105) and 6.6% (10/150) of IBS patients referred to a university hospital clinics. The mean age were 37.9 (SD = 11.7) and 35.4 (SD = 12.2) years in these studies, respectively. (8,28)

Besides studies showing the association of CD

and IBS, results of others are contradictory. In a UK primary care based study, by analysis of EMA, Holt and colleagues (14) found no new cases of CD among 138 consecutive IBS patients (Rome I criteria). Hin et al (13) screened 1000 patients for CD in primary care setting by using EMA. The overall prevalence of CD was 3% (30/1000). None of 132 patients with IBS had positive EMA results. In another study (12), by testing for anti-tTG IgA antibody in primary care patients, only three of 367 adults with IBS (0.8%) found to have CD, which was similar to the general population. Moreover in these three cases, two had anemia and one had dermatitis.(12), Finally, in a recent report from outpatient clinic, van der Wouden et al, investigated 152 patients with IBS using EMA and total IgA level, but in none of them EMA was positive.(29), Given these contradictory results in different settings with different characteristics of patients and different serological tests, should we look for CD in suspected IBS patients? The AGA guidelines (27,30) and also recent publication of the Rome Working Team (5) do not recommend routine serologic tests for CD in the work up of all IBS patients. Rome III suggests testing for CD only if indicated by clinical features and local prevalence.(5), Human anti-tTG IgA antibody currently appears to be the initial test of choice for individuals suspected of having CD.(30,31), Our results showed that at least routine testing for serum anti-tTG IgA antibody in IBS patients (without any red flags) referred to outpatient clinics of gastroenterology is not justified. Clinical judgment of gastroenterologists may be more effective than routine serological tests for CD in IBS patients.(30),However, we should remember that serology has a limited value in diagnosing early phases of CD and therefore, a negative serology result does not rule out CD.(32,33), Using only one serological marker is insufficient for establishing the true prevalence of CD. Indeed, a combination of the tests including endomysial and Anti-tTG IgA antibodies will increase the sensitivity as well as the cost of serology for detection of CD.(34)

There are limitations to our study. Unfortunately, we did not test for anti-tTG IgG antibody in patients with IgA deficiency and in these patients D2 biopsies were not obtained that may affect the results. There was no control group in our study, though recent researches demonstrated that the prevalence of CD in general population in Iran using anti-tTG IgA antibody followed by duodenal biopsy is about 1%.(35,36), However, most patients in these studies have had alarm features like severe weight loss or anemia. Also, in our study, serological tests were done in a clinical laboratory, which may have lower expertise than that of the research laboratories.

COUNCLUSION

Prevalence of CD in patients with IBS referred to outpatient gastroenterology clinic might be significant but serum anti-tTG IgA antibody is not helpful in detecting CD in these patients. Further works are needed to clarify this issue.

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