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BRIEF ARTICLE

Celiac disease in patients with presumed irritable bowel syndrome: A case-finding study

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Abstract

AIM: To estimate the prevalence of celiac disease (CD) in adult patients with presumed irritable bowel syndrome (IBS).

METHODS: Between March 2005 and December 2008, 742 consecutive patients (293 male, median age 43 years, range 18-69 years) fulfilling the Rome Ⅱ criteria for IBS were prospectively enrolled in the study. IBS was diagnosed *via* self-completed Rome Ⅱ modular questionnaires. Anti-tissue transglutaminase (anti-tTG) serology was checked to initially recognize possible CD cases. Patients with a positive test were offered endoscopic duodenal biopsy to confirm the diagnosis of CD.

RESULTS: Thirty two patients (15 male, median age 41 years, range 19-59 years) were found to have organic diseases other than CD. Twenty four patients tested positive for anti-tTG antibodies, and duodenal biopsies confirmed the diagnosis in all of them. Thus, in this patient population with presumed IBS, 3.23% actually had CD.

CONCLUSION: CD is common in patients with presumed IBS. Routine screening for CD in patients with symptoms of IBS is recommended.

Key words: Irritable bowel syndrome; Celiac disease; Anti-tissue transglutaminase; Case-finding; Screening

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INTRODUCTION

Irritable bowel syndrome (IBS) is a highly prevalent disorder. It is found in 10% to 20% of individuals using standard diagnostic tools such as the Rome Ⅱ criteria[1].

Diagnostic approaches to suspected IBS rely on eliciting symptoms that satisfy specific criteria and performing limited tests to exclude organic diseases that produce similar symptoms[2].

IBS can sometimes be difficult to distinguish clinically from adult-onset celiac disease (CD)[3-8]. A broad spectrum of symptoms and signs may be associated with untreated CD. In fact, many patients - especially those presenting in adulthood - have minimal or atypical symptoms[5,7-10].

The recent development of highly sensitive and specific serologic assays for CD has led to the increased realisation that the disease is more common than it was believed[11-15]. This justifies the concern that some IBS-labeled patients may in fact have CD.

Reports of prevalence of CD in IBS patients from the Middle East are scanty.

We aimed to estimate the prevalence of CD in patients masquerading as IBS, and also to describe their clinical features.

MATERIALS AND METHODS

Study population

Ethical approval of the study was obtained from the

Table 1 The modified Marsh classification of celiac disease

Type	Intraepithelial lymphocytes per 100 enterocytes	Crypts	Villi
0	< 40	Normal	Normal
1	> 40	Normal	Normal
2	> 40	Increased	Normal
3a	> 40	Increased	Mild atrophy
3b	> 40	Increased	Marked atrophy
3c	> 40	Increased	Absent

Table 2 The distribution of patients according to gender and IBS type *n* (%)

IBS type	Gender		Total
	Male	Female	
C-IBS	140 (47.8)	217 (48.3)	357 (48.1)
D-IBS	84 (28.7)	122 (27.2)	206 (27.8)
C/D-IBS	69 (23.5)	110 (24.5)	179 (24.1)
Total	293	449	742

IBS: Irritable bowel syndrome; C-IBS: Constipation-predominant IBS; D-IBS: Diarrhea-predominant IBS; C/D-IBS: Alternating constipation-diarrhea IBS.

Institutional Review Board at King Abdullah University Hospital. The potential implication of a positive result for CD was explained to all participants, and their written consent was obtained.

The Rome Ⅱ criteria for IBS were applied to 891 consecutive patients upon their first visit to our outpatient gastroenterology clinic in the period between March 2005 and December 2008. The inclusion criteria were: age greater than 18 years, fulfilling the Rome Ⅱ criteria for IBS; condition not previously investigated; absence of lactose intolerance or giardiasis. The exclusion criteria were: history of gastrointestinal alarm symptoms or signs; unwillingness to be submitted to esophagogastroduodenoscopy and/or colonoscopy. Only 764 individuals were eligible to participate in the study, and 22 (2.9%) of these did not agree to sign a written consent and thus were excluded from the study.

Laboratory testing

Testing for anti-tissue transglutaminase (anti-tTG) serology was performed using the ORG 540A Anti-Tissue-Transglutaminase IgA (ORGENTEC Diagnostika GmbH®).

Quantitative IgA anti-tTG test was determined using the ELISA method. The sensitivity and specificity of this test in our laboratory was previously estimated at 98% and 96%, respectively (unpublished data). Patients with a positive test were submitted to duodenal biopsy to confirm the possibility of CD.

Other investigations included complete blood count, serum chemistry panel, erythrocyte sedimentation rate, thyroid function tests, occult blood stool testing, and stool analysis for ova and parasites. Additionally, patients with diarrhea were put on a 3-wk lactose-free diet to exclude lactose intolerance.

Table 3 The prevalence of celiac disease in different types of IBS patients

	No. of study patients	No. of celiac cases	Prevalence of CD (95% CI)
C-IBS	357	6	1.68 (0.35, 3.01)[a]
D-IBS	206	14	6.80 (3.36, 10.23)[a]
C/D-IBS	179	4	2.23 (0.07, 4.40)
Total	742	24	3.23 (1.96, 4.50)

[a]Significantly different (*P*-value = 0.0026); CI: Confidence interval.

Colonoscopy

All patients older than 45 years or with a family history of colorectal cancer, and those with a positive occult stool blood test were submitted to colonoscopy to rule out structural disease. Furthermore, in patients with diarrhea random colonic biopsies were taken to rule out microscopic colitis.

Intestinal biopsy

Using a standard biopsy forceps, six specimens were taken from the second and third portion of the duodenum. All biopsies were reviewed independently by two histopathologists, and changes of CD were reported using the modified Marsh criteria (Table 1).

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS, version 15). Continuous data were described using mean, median, standard deviation, and range wherever appropriate. Categorical variables were described using proportions. The 95% confidence interval (CI) was used to calculate the interval estimate of the prevalence of CD. Differences in prevalence rates according to different types of IBS were tested using χ^2 test; a *P*-value of less than 0.05 was considered statistically significant.

RESULTS

This study included a total of 742 patients (293 males and 449 females). Their distribution according to gender and IBS type is shown in Table 2. Thirty two patients (15 males and 17 females) with a median age of 41 years (range 19-59 years) were found to have organic diseases other than CD [14 hypothyroidism, three microscopic colitis (two collagenous and one lymphocytic colitis), six lactose intolerance, three ulcerative colitis, and six Crohn's disease]. Twenty four patients [14 diarrhea-predominant IBS (D-IBS), six constipation-predominant IBS (C-IBS), and four alternating constipation-diarrhea IBS (C/D-IBS) tested positive for anti-tTG]. The prevalence of CD in different types of IBS is summarized in Table 3. The prevalence of CD in patients with D-IBS (6.80%, 95% CI: 3.36, 10.23) was significantly higher than that in patients with C-IBS (1.68%, 95% CI: 0.35, 3.01). Duodenal biopsies confirmed the diagnosis in all 24 patients. The modified Marsh criteria (Table 1) were used for the grading of severity of histopathological

Table 4 The demographic and clinical features of celiac disease patients

Variable	*n* (%)
Gender	
Female	13 (54.2)
Male	11 (45.8)
Age (yr)	
18-25	8 (33.3)
26-35	8 (33.3)
36-61	8 (33.3)
mean (SD)	33.5 (11.5)
Body mass index, mean (SD)	26.6 (3.5)
Duration of symptoms (mo), mean (SD)	26.8 (18.1)
IBS type	
C-IBS	6 (25.0)
D-IBS	14 (58.3)
C/D-IBS	4 (16.7)
Malabsorptive features	
Hypoalbuminemia	2 (8.3)
Hypocalcemia	2 (8.3)
Iron deficiency	4 (16.7)
None	16 (66.7)

changes. Among our CD patients, two had Marsh type 1, seven had Marsh type 3a, 10 had Marsh type 3b, and five had Marsh type 3c. Thus, in this patient population with presumed IBS, 3.23% (95% CI: 1.96-4.50) actually had CD. The age of patients with CD (13 females and 11 males) ranged from 18 to 61 years with a mean (SD) of 33.5 (11.5). About 58% of these patients belonged to the D-IBS type, while less than 17% had the C/D-IBS type.

The demographic and clinical features of CD patients are summarized in Table 4. Interestingly, only eight of the CD patients had signs of intestinal malabsorption on further laboratory testing, with iron deficiency being the most common abnormality. The duration of IBS symptoms before the diagnosis of CD ranged between 6 and 72 mo (average 26.8 mo). The body mass index (BMI) of our CD patients was surprisingly higher than the expected, with an average of 26.6. All patients diagnosed with CD were started on a gluten-free diet, with subsequent improvement of their IBS-like symptoms in periods ranging from 2 to 6 wk.

DISCUSSION

A high prevalence of CD in patients with presumed IBS was found in the present study. This implies that even with strict application of the Rome Ⅱ criteria, IBS patients may have undetected CD. The majority of our CD patients had severe histopathological changes in duodenal specimens according to the modified Marsh criteria[16]. The advanced histopathological changes most probably reflect long-standing, untreated disease in our patient population.

The prevalence of CD in several recent population studies from North America ranged from 0.5% to 1%[17-19]. Studies in Europe have shown that up to 1% of the adult population may have CD[11]. In contrast to its high prevalence in Western countries, CD is considered rare in non-Western populations. However, recent studies from the Middle East, Africa and India showed prevalence as high as 7.6% in selected groups of patients[20-22]. To the best of our knowledge, studies on the prevalence of CD in adult Jordanians have never been carried out. A prevalence study of CD in thousands of blood donors in Jordan is being conducted by the authors of the present study. Based on an interim analysis of the data obtained thus far, a prevalence of one in 200 could be projected. Therefore, IBS patients would be 6.5 times more likely to have CD than the general population.

The diagnosing of CD is often delayed, perhaps owing to a failure to recognize the protean manifestations of this disease, especially in the adult population. Patients often have few or no gastrointestinal symptoms and can even be obese[5,8,10]. In fact, in the present study none of the patients had typical symptoms of CD, such as steatorrhea or weight loss, and the majority of them had an average BMI in the overweight range.

Previously regarded as a mainly childhood problem it is now recognized that CD affects mostly adults, with about one quarter of patients being diagnosed at over 60 years of age. In a study by Green *et al*[8], data obtained on 1138 people with biopsy-proven CD showed that the majority of individuals were diagnosed in their 4th to 6th decades. Our study showed that adult CD can manifest at any age. However, it appears that the Jordanian adult patient population tends to present at a relatively younger age, possibly because of differences in gene penetrance as well as a larger wheat consumption by Jordanians (135 kg/head year); data from the Department of Agriculture, Jordan).

Survey data in the United States indicate that the median time to diagnosis in CD patients is 12 mo, and that over 20% of patients have symptoms for 10 years before CD is suspected and diagnostic testing performed[5]. However, the true denominator of undiagnosed CD is not well defined, and evolving data from both Europe and the United States indicate that many adult CD patients probably remain undetected[6,11,23]. In our CD patient population the time to diagnosis ranged between 8 and 72 mo. The delay in diagnosis could be ascribed to the atypical manifestations of the disease, but we believe that limited access to tertiary health care centers in our country could be another contributing factor to the long lag time before diagnosis.

CD can present with a wide spectrum of insidious symptoms. These can mimic symptoms of IBS. Several studies have suggested that the incidence of CD in patients with presumed IBS is higher than that of the normal population. In their case-control study of 300 subjects fulfilling the Rome Ⅱ criteria for IBS, Sanders and colleagues found that the patients were 7 times more likely to have biopsy-proven CD than matched controls[4]. Sixty six patients with IBS tested positive for the antibodies, and 4.6% had active CD as compared with 0.66% of the non-IBS matched controls. The authors concluded that patients who meet the Rome Ⅱ criteria for IBS should be investigated routinely for CD. More recently, the same investigators reported a primary

care-based cross-sectional study in which 1200 patients were recruited and evaluated serologically for CD[24]. The prevalence of CD in this population sample was 1%, while in the 123 participants with IBS the prevalence of CD was 3.3%. Once again, the authors recommended that a low threshold for serological screening of patients with IBS symptoms would be an optimal strategy.

In a recent primary care-based, multicenter study from North America, 976 subjects with symptoms or conditions known to be associated with CD, including IBS, were serologically tested for CD[25]. A diagnosis of CD was established in 22 patients, and thus the prevalence of CD in the serologically screened sample was 2.25%. The most frequent reasons for CD screening in these 22 cases were bloating (12/22), thyroid disease (11/22), IBS (7/22), unexplained chronic diarrhea (6/22), chronic fatigue (5/22), and constipation (4/22). The authors concluded that an active case-finding strategy in the primary care setting is an effective way to improve the diagnostic rate of CD. Of interest, the group of patients with IBS or symptoms of IBS - such as bloating, diarrhea, and constipation - constituted the largest proportion of screening-detected patients in their study.

Conversely, other investigators suggested that the prevalence of CD is not increased in patients with IBS symptoms. Locke Ⅲ and colleagues recently published the results of a case-control study[26]. Using a self-completed questionnaire, the researchers evaluated 150 adult subjects, of whom 72 reported having symptoms of IBS and dyspepsia, and 78 controls who reported no gastrointestinal symptoms. The total number of individuals with CD in each group was surprisingly high: two out of 50 with IBS (4%), two out of 24 with dyspepsia (6%), and two of the 78 controls (2.6%). The researchers concluded that CD alone cannot explain the presence of IBS or dyspepsia in the subjects. The results of their study are interesting, but the sample size is probably not large enough to reach statistical significance.

Other studies suggested that the prevalence of CD in adult patients with IBS is not higher than that in the general population. Hin and colleagues conducted a case-finding study of CD in a primary care setting[27]. None of their 132 patients with IBS symptoms had positive results for CD, suggesting that CD rarely masquerades as IBS. Yet, we believe that this study is limited because of the small sample size.

It is arguable that, similar to IBS patients, other patients with various functional gastrointestinal disorders (i.e. functional dyspepsia) could have a higher prevalence of CD. In a recent study from Italy[28], the authors reported biopsy-proven CD in 2% of their 726 patients with presumed functional dyspepsia, and suggested that routine duodenal biopsy should be considered in all dyspeptic patients undergoing diagnostic esophagogastroduodenoscopy. The results of this Italian study are interesting, but we believe that further prevalence studies of CD in the functional dyspepsia population are needed to corroborate these results.

There are some limitations in the present study. First, IgA test was not checked for all patients, which could underestimate the prevalence of positive serology for CD because of the strict dependence of the anti-tTG test on the level of IgA. Second, because of limited resources, we used the lactose-free diet test to rule out lactose intolerance instead of the more accurate hydrogen breath test. Because of the lower sensitivity and specificity of the lactose-free diet test, some patients with lactose intolerance could be misdiagnosed as IBS or vice versa.

In conclusion, the prevalence of CD in patients with presumed IBS is high. Therefore, serological testing should be considered for all individuals with symptoms of IBS. However, larger, multicenter studies are needed to settle the debate on the utility - or futility - of screening IBS patients for CD.

COMMENTS

Background

Celiac disease (CD) may present with a broad spectrum of subtle or atypical symptoms. Some patients with irritable bowel syndrome (IBS) may have minimally symptomatic CD. The value of screening IBS patients for CD remains a matter of debate.

Research frontiers

There were several early published studies showing minimal, atypical clinical presentations of CD. The widespread availability of highly sensitive and specific serologic tests for CD has allowed for large population-based serologic surveys that have shown this disorder to be very common, especially in at-risk groups such as patients with symptoms of IBS.

Innovations and breakthroughs

The present study underscores the importance of screening IBS patients for CD. The high prevalence of CD found in our large study population is in accordance with the findings of other investigators. However, scattered reports from different regions of the world assert that the prevalence of CD is not increased in patients believed to have IBS. Based on the results of our study, we believe that screening IBS patients for CD should be routinely performed.

Applications

Because the manifestations of CD respond to a gluten-free diet, testing for CD in patients with presumed IBS may prevent prolonged morbidity and unnecessary health care costs. The results of the present study may contribute to raising the awareness of the protean manifestations of CD, as well as settling the ongoing debate on the utility of screening IBS patients for CD. Larger, case-control studies of undetected CD in patients believed to have IBS are required to establish vigorous clinical guidelines for both primary care physicians and gastroenterologists.

Terminology

CD is an immune-mediated enteropathy triggered by the ingestion of gluten-containing grains in genetically susceptible individuals. A case-finding study is a term used to describe a method which involves screening a smaller group of people for specific disorders based on specific baseline clinical characteristics.

Peer review

The peer reviewers of this article believe that it is a valuable contribution to the pertinent literature. The study draws attention to the protean manifestations of CD and the need to be aware of this common disease in particular in conditions such as IBS.

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