Screening for Celiac Disease in Patients with Irritable Bowel Syndrome Fulfiling Rome III Criteria

Khaldoon Thanoon Al-Abachi

1 Department of Medicine, University of Ninevah, Ninevah College of Medicine, Mosul, Iraq

Address for correspondence Khaldoon Thanoon Al-Abachi, CABM, ESEGH, Department of Medicine, University of Ninevah, Ninevah College of Medicine, Mosul, Iraq (e-mail: al_abachi_kt@yahoo.com).

Abstract

Background Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder. Celiac disease (CD), a treatable autoimmune enteropathy, may simulate clinically symptoms of IBS. The aim of the present study is to screen for CD in patients with IBS diagnosed based on the Rome III criteria.

Patients and Methods A cross-sectional study was conducted at a secondary care gastrointestinal unit in Al-Salam General Hospital in Mosul city, Iraq, from November 2015 to October 2016. All patients fulfilling the Rome III criteria for IBS were screened for CD using antitissue transglutaminase IgA antibodies (anti-tTG). Patients who tested positive were subjected to endoscopic duodenal biopsy to confirm the diagnosis of CD.

Results A total of 100 patients were included in the present study (58 female and 42 male), the mean age of the participants was 40.8 years old (standard deviation [SD] ± 11.57). Ten patients (10/100, 10%) tested positive for anti-tTG antibodies. Five of the seropositive patients (5/10, 50%) showed positive biopsy results according to the Marsh classification, 3 of whom having diarrhea, and 2 with constipation.

Conclusion Positive serology and biopsy results suggestive of CD are common among patients with IBS. Screening patients with IBS for CD is justified.

Introduction

Irritable bowel syndrome (IBS) is a common functional bowel disorder of unestablished etiology, characterized by recurrent symptoms of abdominal pain, bloating, and altered bowel habit without detectable structural, inflammatory, or biochemical abnormalities. The worldwide prevalence rate is of between 10 and 15%. The diagnosis of IBS is based on clinical symptoms, and investigations are done to exclude organic diseases simulating IBS rather than to diagnose this disorder.

Reliable diagnostic symptom-based criteria have been established, starting with the criteria of Manning (1978), followed by Kruis et al. (1984), and later on with the emergence of the international working group that developed the Rome I (1992), Rome II (1999), Rome III (2006), and Rome IV (2016) criteria. Organic diseases causing alarm

Keywords

► irritable bowel syndrome
► celiac disease
► anti-tTG antibodies
► duodenal biopsy

Organic diseases simulating IBS are common among

Interruption

Organic diseases simulating IBS are common among

Organic diseases simulating IBS are common among
Box 1  Rome III Criteria for Irritable Bowel Syndrome (IBS) With Subtypes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. IBS with constipation</td>
<td>Hard or lumpy stools (IBS-C).</td>
</tr>
<tr>
<td>2. IBS with diarrhea</td>
<td>Loose or watery stools (IBS-D).</td>
</tr>
<tr>
<td>3. Mixed IBS</td>
<td>Diarrhea, constipation, and symptoms of IBS fulfilling the Rome III criteria</td>
</tr>
</tbody>
</table>

Symptoms of IBS may mimic the gastrointestinal symptoms of CD; these similarities between symptoms impart difficulty in clinical differentiation. It has been shown that testing patients with IBS to detect undiagnosed CD using serology is cost-effective. Alexander et al. did a meta-analysis of 14 studies and reported a prevalence of more than 4-fold of CD in IBS cases compared with control without IBS. However, fewer studies did not show a higher prevalence of CD among IBS patients compared with the general population. The aim of the present study is to evaluate the frequency of positive serology and biopsy consistent with CD among patients presenting with symptoms of IBS fulfilling the Rome III criteria.

Patients and Methods

All patients with symptoms of IBS presenting to the secondary care gastroenterology clinic of the Al-Salam General Hospital in Mosul between November 2015 and October 2016 were attended to and offered standard medical care including clinical interview and physical examination. The patients were requested to complete a questionnaire on symptoms of IBS based on the Rome III criteria (Box 1).

The exclusion criteria were: weight loss, anemia, jaundice, bleeding from the rectum, high erythrocyte sedimentation rate (ESR), systemic diseases, endoscopic gastrointestinal lesions, and patients reluctant to perform the serologic test.

The total number of evaluated patients was 210, and only 100 patients were eligible to be included in the study. The age range was between 13 and 65 years old, with a mean age of 40.8 years old (SD ± 11.57). Antitissue transglutaminase IgA (Anti-tTG IgA) antibody test was used to screen the selected patients for CD by measuring IgA antibodies to human recombinant tTG through the commercial kit Aeskulisa tTG-A 3503, a new generation of a solid phase enzyme immunoassay using human recombinant tTG crosslinked with gliadin-specific peptides. A positive test should exceed a cutoff value of 15 U/ml. Other investigations included complete blood count, ESR, blood sugar, blood urea, microscopic stool examination, and, for selected patients, thyroid function test, abdominal sonography, and bone profile. All patients > 50 years old were offered colonoscopic examination to exclude underlying organic disease. Patients with positive tTG-IgA test were subjected to upper gastrointestinal endoscopy; two biopsies were taken from the duodenal bulb and four from more distal areas. All biopsy specimens were subjected to a histopathological examination performed by expert pathologists and the results were reported based on the modified Marsh criteria.

Data were analyzed using IBM SPSS Statistics for Windows, Version 18.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were applied to calculate the mean, median, range, percentage, p-value, and SD wherever appropriate.

The study protocol was approved by the Medical Ethics Committee of the Ninevah University and Mosul health directorate; all participants agreed to sign the written informed consent form.

Results

Out of the 100 patients diagnosed with IBS based on the Rome III criteria, 58 were female (mean age: 40.4 years old; SD ± 12.34), and 42 were male (mean age: 41.5 years old; SD ± 12.40).
SD ± 10.54). Their bowel habit characteristics are shown in (Table 1).

The duration of symptoms ranged from 1 to 32 years (mean: 10.3 years). Ten patients (7 female and 3 male) out of the total 100 (10%) tested positive for tTG-IgA antibody ($p < 0.00001$ compared with a CD seroprevalence rate of 2% in some normal populations). Six patients (3 female, 2 male) of the 10 seropositive (5/100, 5%) showed abnormal histopathological changes according to the modified Marsh criteria (2 Marsh I, 1 Marsh II, and 2 Marsh IIIc), and 3 patients displayed Marsh 0 (negative biopsy result). Two seropositive patients refused to undergo duodenal biopsy. Five of the 10 seropositive patients (5/10; 50%) had predominantly diarrhea, 3 (3/10; 30%) had predominantly constipation, and 2 (2/10; 20%) had a mixed pattern. The characteristics of the seropositive patients are shown in (Table 2).

**Discussion**

Despite being a common gastrointestinal disorder and the development of symptom-based parameters to diagnose IBS, there is no clinical criterion or result of investigation that is pathognomonic of IBS. Further confusing the issue, symptoms of IBS frequently overlap and may coexist with symptoms of other gastrointestinal and nongastrointestinal disorders.

In the present study, patients were selected according to the Rome III criteria, which are more suitable for the definition of the symptoms of our patients compared with other criteria, considering the duration of symptoms and subtyping of bowel habits.

Patients were screened serologically by IgA-tTG antibody test alone to detect CD. It is an enzyme-linked immunoassay (ELISA) test, operator independent, and is recommended as a screening test for CD, with a sensitivity of 94% and a specificity of 97%.

Reports from different regions in the world showed mostly an increased prevalence of CD in patients with IBS compared with the general population, and fewer reports showing no such increase (Table 3). A large meta-analysis by Irvine et al. involving 36 studies found a higher prevalence of positive serology and biopsy for CD in patients with IBS compared with healthy controls. Another study, by Almazar et al., conducted in a USA tertiary care center and recruiting 533 patients and 531 controls, found no difference in the prevalence of CD between patients with IBS and controls. Recently, Mohammad et al. from Iraq detected 5 seropositive patients for CD (7.1%) in a sample of 70 patients with IBS fulfilling the Rome III criteria. This variation in results might be ascribed to different geographical locations, racial differences, study characteristics, sample size, and selection bias.

In the present study, three seropositive patients had negative biopsy results (Marsh 0) and two showed Marsh grade I, which is nonspecific for CD. Both grades are regarded as potential CD, which means that these patients are at increased risk of developing overt CD in the future. Also, Marsh grade II lacks diagnostic support for CD, while villous atrophy, which was identified in two of the seropositive

**Table 1** Distribution of patients according to gender and bowel habit type

<table>
<thead>
<tr>
<th>Gender</th>
<th>IBS-D n; %</th>
<th>IBS-C n; %</th>
<th>IBS-M n; %</th>
<th>No. of patients Total 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>36/58; 62.1%</td>
<td>12/58; 20.7%</td>
<td>10/58; 17.2%</td>
<td>58/100</td>
</tr>
<tr>
<td>Male</td>
<td>20/42; 47.6%</td>
<td>16/42; 38.1%</td>
<td>6/42; 14.3%</td>
<td>42/100</td>
</tr>
</tbody>
</table>

Abbreviation: IBS, irritable bowel syndrome.

**Table 2** Characteristics of seropositive patients

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years old)</th>
<th>Gender</th>
<th>IBS subtype</th>
<th>tTG-IgA U/ml cutoff: 15</th>
<th>Marsh type</th>
<th>Duration of symptoms (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23</td>
<td>F</td>
<td>IBS-D</td>
<td>18.6</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>F</td>
<td>IBS-M</td>
<td>35</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>F</td>
<td>IBS-C</td>
<td>16</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>34</td>
<td>F</td>
<td>IBS-D</td>
<td>17.9</td>
<td>I</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>F</td>
<td>IBS-D</td>
<td>17.1</td>
<td>I</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>51</td>
<td>M</td>
<td>IBS-C</td>
<td>41.16</td>
<td>II</td>
<td>13</td>
</tr>
<tr>
<td>7</td>
<td>28</td>
<td>M</td>
<td>IBS-C</td>
<td>98.88</td>
<td>IIIc</td>
<td>15</td>
</tr>
<tr>
<td>8</td>
<td>46</td>
<td>F</td>
<td>IBS-D</td>
<td>166.8</td>
<td>IIIc</td>
<td>20</td>
</tr>
<tr>
<td>9</td>
<td>30</td>
<td>M</td>
<td>IBS-M</td>
<td>18.2</td>
<td>Refused biopsy</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>34</td>
<td>F</td>
<td>IBS-D</td>
<td>100</td>
<td>Refused biopsy</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: F, female; IBS, irritable bowel syndrome; M, male.
patients, is more typical of CD. These two patients with total villous atrophy displayed a very high titer of tTG-IgA antibody level. Studies in children and adults with CD have concluded that serum tTG antibody level correlates positively with the severity of small intestinal histopathology. One female patient, 34 years old, with high tTG- antibody titer (100 U/ml) did not undergo endoscopy and biopsy, and it is highly expected that this patient has CD.

The classic presentation of adult CD is diarrhea, which was identified in 5 of the seropositive patients (50%). Constipation is not an uncommon symptom in adult CD and it was present in 3 seropositive patients (30%).

Four of the seropositive patients (4/10; 40%) (1 with Marsh grade II, 2 with Marsh grade IIIc, and 1 female patient with an antibody titer of 100 U/ml who refused biopsy) responded to GFD within a period of 4 weeks, with improvement in the general well-being and intestinal symptoms. Improvement of clinical symptoms on GFD is not enough to confirm the diagnosis of CD, since a subset of patients with IBS may also improve on GFD. To be more stringent in the diagnosis of CD, an improvement on diet should be supported by serial measurements of serum antibody level and possibly repeated duodenal biopsy after a reasonable follow-up period (between 3 and 6 months). It was not possible to confirm the actual prevalence of CD in all seropositive patients in our sample, as many of them are noncompliant with extended future follow-up and doing necessary tests. Anyway, we can roughly estimate the prevalence of CD in the IBS patients included in the present study to be not less than 3% (p = 0.02 compared with a 1% prevalence rate in normal populations), which is comparable with the results of many other studies.

The patients included in the present study were referred from primary care health centers and represent more severe and chronic conditions of IBS, which may have an impact on the ultimate prevalence of CD in patients who manifested symptoms of IBS.

**Conclusion**

In the present study, the frequency of positive anti-tTG antibody test in patients with IBS based on the Rome III criteria was of 10%, and the likelihood of CD in these patients was high (at least 3%).

Antibody testing for CD in patients who fulfill the IBS diagnostic criteria is recommended in Mosul, Iraq.

Further well-controlled studies including larger samples of patients are needed and follow-up of seropositive and biopsy-positive patients to ascertain the diagnosis of CD is required, which includes GFD, repeated serology tests, and duodenal biopsy.

**Ethical Approval**

Ethical approval was granted by the Medical Ethics Committee of the Ninevah University.

**Informed Consent**

All participant agreed to sign an informed written consent form.

**Note**

Hospital-based study supported by Iraqi ministry of health. The patients were not charged, and no charge was received by the author.

**Conflict of Interests**

The author has no conflict of interests to declare.

**Acknowledgement**

The author would like to express his thanks and gratitude to the staff of the Laboratory Department, Pathology Department, and Endoscopy Unit of the Al-Salam General Hospital in Mosul for their support and cooperation during the execution of the present study.

**References**


**Table 3** Studies of celiac disease in patients with irritable bowel syndrome

<table>
<thead>
<tr>
<th>Authors (Ref.)</th>
<th>Country</th>
<th>Number of patients</th>
<th>Prevalence of CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanders et al.</td>
<td>UK</td>
<td>300</td>
<td>4.7%</td>
</tr>
<tr>
<td>Sanders et al.</td>
<td>UK</td>
<td>123</td>
<td>3.3%</td>
</tr>
<tr>
<td>Fasano et al.</td>
<td>USA</td>
<td>5073</td>
<td>3.85% with diarrhea, 2.6% with constipation</td>
</tr>
<tr>
<td>Shahbazkhan et al.</td>
<td>Iran</td>
<td>105</td>
<td>11.4%</td>
</tr>
<tr>
<td>Jadallah et al.</td>
<td>Jordan</td>
<td>742</td>
<td>3.2%</td>
</tr>
<tr>
<td>Korkut et al.</td>
<td>Turkey</td>
<td>100</td>
<td>2%</td>
</tr>
<tr>
<td>El-Sahly et al.</td>
<td>Norway</td>
<td>968</td>
<td>0.4%</td>
</tr>
<tr>
<td>Hin et al.</td>
<td>UK</td>
<td>132</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Abbreviation:** CD, celiac disease.
Screening for Celiac Disease in Patients with Irritable Bowel Syndrome

Al-Abachi


