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Original Article

The Epidemiological and Clinical Characteristics of Celiac Disease among Patients with Irritable Bowel Syndrome in Zanjan Province, Iran

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Background: There are some overlaps between celiac disease and irritable bowel syndrome symptoms (IBS). It can lead to misdiagnosis or delayed diagnosis of celiac disease. In some guidelines, it is recommended to screen for celiac in IBS cases. For assessment of the necessity for such diagnostic approaches in patients, this study was done to evaluate the epidemiological and clinical characteristics of celiac disease among IBS cases in Zanjan, Iran.
Methods: In this descriptive cross-sectional study, 121 cases with IBS attending to gastroenterology clinics since 2015 to 2018 were enrolled. The laboratory tests and upper digestive endoscopy were performed for all patients. Endoscopic biopsy specimens were taken from the duodenum, and the samples were examined to confirm diagnosis of celiac disease. Data analysis was done by SPSS software.
Results: Of 121 studied patients, 51.2% were male. The mean age of the patients was 36.65 ± 10.09 years old. The most common IBS subtype was mixed (80.2%). According to the serology results and Marsh grading, 4.1% and 1.6% had celiac disease and potential celiac disease, respectively. There were statistically significant differences among celiac disease in gastroesophageal reflux disease and abdominal discomfort/cramping.
Conclusion: The incidence of celiac disease was evaluated 4.1 cases per each 100 patients with IBS, which was higher than recent similar studies, and screening for celiac disease in these patients is advisable. However, further studies with larger sample size are required to attain more definite results.

Introduction

Irritable bowel syndrome (IBS) is a common problem among subjects attending to gastroenterology clinics (1-3). This idiopathic alimentary dysfunctional disease is characterized with recurrent abdominal pain, flatulence, and change in bowel habits (4-7). In suspected cases, the organic diseases should be ruled out, and it is a centrally-mediated disorder affecting simultaneously the peripheral nerve endings (6, 8). Among organic differential diagnoses, there is celiac disease (CeD) seen in less than one percent of general population as a bowel inflammatory problem and mal-absorption due to gluten hypersensitivity in susceptible cases (7). It is characterized by autoimmune phenomenon affecting the gut or possibly other organs with interaction of environmental and genetic factors (6, 8). The responsible antibody is tissue

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transglutaminase IgA (anti-tTG IgA) accompanied with mucosal gut injury (6). IBS affects nearly 2.9% to 25% of general population, worldwide (5, 9). The prevalence of CeD is up to 3-11 percent among IBS cases (7). The prevalence rate of CeD in Iran ranges from 0.5% to 1.0% and is especially higher in cases with other autoimmune disorders (6). The CeD symptoms range from asymptomatic status to severe cases with chronic diarrhea, weight loss, vitamin deficiency, mal-absorption, and abdominal pain (3). In atypical cases, other symptoms such as anemia, osteoporosis, short stature, neurological symptoms, gastro-esophageal reflux, elevated liver enzymes, and dermatitis are seen beside milder gastrointestinal manifestations (3, 5). CeD is more common among adults versus children (10). There is a genomic susceptibility pattern with presence of some HLA subtypes including DQ8 and DQ2 (6, 7). There are some overlaps between symptoms of CeD and IBS (3). It can lead to misdiagnosis or delayed diagnosis of CeD (6). Nearly thirty percent of CeD cases have symptoms of IBS and also in cases using gluten-free diet may develop IBS symptoms (3). CeD diagnosis is based on positive serology and histological changes. Treatment-resistant IBS cases may propose presence of CeD that may lead to more severe disease in untreated cases (1). Hence in some guidelines, it is recommended to screen for CeD in IBS cases (8). For assessment of the necessity for such diagnostic approaches in patients, this study was done to evaluate the epidemiological and clinical characteristics of celiac disease among known IBS cases.

Materials and Methods

In this descriptive cross-sectional study, all patients aged 18 years or elder with IBS (according to Rome IV criteria) who referred to outpatient gastroenterology clinics in Zanjan, Iran from December 2015 to April 2018 were enrolled. As recommended by Rome IV criteria, IBS has three main subtypes as follows: (i) IBS with predominant diarrhea (IBS-D) (ii) IBS with predominant constipation (IBS-C); (iii) IBS with mixed bowel habits (IBS-M).

Laboratory tests including complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), aminotransferases, alkaline-phosphatase, fasting blood glucose, urea, creatinine, thyroid hormones, stool ova & parasites (O&P) exam, fecal occult blood test (FOBT), anit-tTG IgA antibody, and total serum IgA level were done for each patient. The anti-tTG IgA antibody titer of >10 U/mL was considered positive test result. Anti-gliadin antibodies (AGA) tests were done in patients were seronegative for anti-tTG antibody. One patient was seronegative for anti-tTG and seropositive for AGA with HLA-DQ2 in genotyping.

Patients with evidence of overt GI bleeding, inflammatory bowel disease (IBD), malignancy, family history of IBD or colorectal cancer, elevated ESR or CRP levels, drug addiction, positive FOBT, positive O&P exam, heart failure, chronic kidney, liver, and respiratory diseases were excluded from the study. In addition, we excluded patients with comorbid conditions that could have explained their GI symptoms e.g., celiac disease, scleroderma, small intestinal bacterial overgrowth, uncontrolled thyroid disease, or diabetes and patients with previous GI or intestinal surgery, with the exception of appendectomy or cholecystectomy.

142 patients with IBS were initially enrolled and evaluated. Of these patients, 11 were excluded due to drug addiction (n=2), a previous history of abdominal surgery (n=2), diabetes mellitus (n=3), currently history of GI bleeding (n=2), and family history of colorectal cancer (n=2).

Finally, 121 patients were eligible to participate in the study (Fig. 1).

Upper digestive endoscopy was performed for all patients in order to detect lesions responsible for esophageal and dyspeptic symptoms. In addition, six endoscopic biopsy specimens were taken from the duodenum bulb and distal duodenum by single gastroenterologist to exclude CeD. The samples were examined by one expert pathologist to confirm diagnosis of CeD.

The histological changes were interpreted by modified Marsh classification based on the presence of intraepithelial lymphocytes, villous atrophy, and crypt hyperplasia. CeD was proven based on positive serology and Marsh grade ≥ 2. In patients with suspected CeD and negative serology for anit-tTG IgA antibody, other serology tests such as anti-gliadin antibodies (AGA) and HLA-DQ2/DQ8 genotyping were performed. In addition, potential celiac disease (Potential CeD) was defined as positive serology and Marsh grade ≤ 1. Age, gender, anti-tTG IgA antibody titer, IBS subtype, current clinical manifestations, Marsh grade, and comorbid conditions were recorded in checklist for all understudy participant. Strict adherence to a lifelong gluten-free diet and regular medical follow-up were recommended to patients with CeD and Potential CeD.

Data analysis was done by SPSS version 24.0 (SPSS Inc., Chicago, IL, USA). The utilized tests for comparative purposes were Chi-Square, T-Test, and One-way ANOVA. The p-values less than 0.05 were considered statistically significant. All patients provided informed consent prior to study participation. The study was approved by the Ethical Committee of the Zanjan University of Medical Sciences with an ethic code of IR.ZUMS.REC.1398.109.

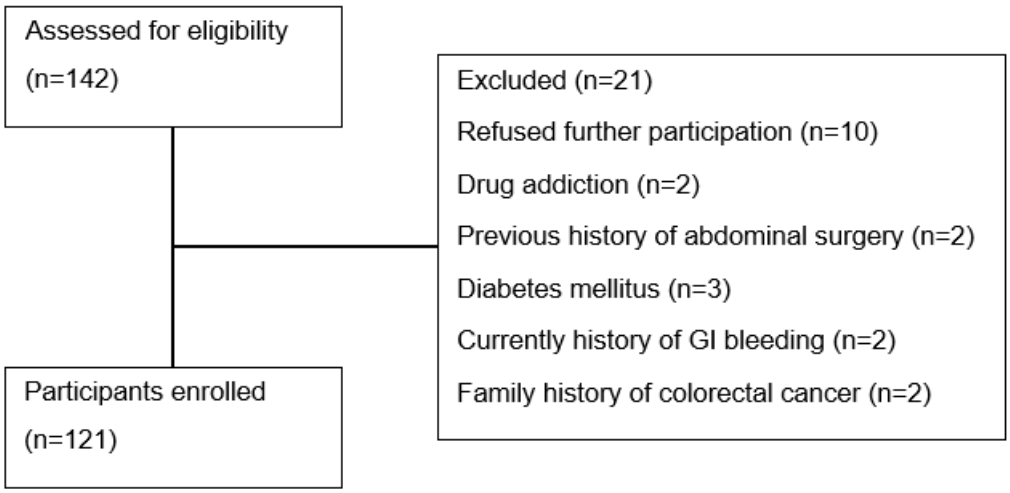

Fig. 1. Flowchart for selecting patients with irritable bowel syndrome.

Results

Of 121 patients affected by IBS, 62 (51.2%) were male and 59 (48.8%) were female. The mean (± standard deviation) age of the patients was 36.65 ± 10.09 years old with a range between 19 and 67 years. The most common IBS subtype was IBS-M (80.2%), followed by IBS-D (11.6%) and IBS-C (8.3%). 46.3% of IBS patients suffered from dyspeptic symptoms. In addition, 46.3% and 24.8% of patients had abdominal discomfort/cramping and bloating, respectively. Gastro-esophageal

reflux disease (GERD), as an endoscopic evidence, was detected in 19% of patients.

According to the serology results and Marsh grading, five cases (4.1%) had CeD, and two cases (1.6%) had Potential CeD with Marsh grade 1. Among five cases with CeD, Marsh grades were 3a in three, and 3b in two cases. Positive anti-tTG results were reported in six out of these seven patients. Among CeD group, one patient was seronegative for anti-tTG antibody, and seropositive for anti-gliadin antibodies (AGA).

IgA deficiency was not reported in laboratory findings. According to the laboratory findings, 15 (12.4%) patients with IBS had iron-deficiency anemia, among them, two patients (28.6%) had CeD and were male. Others were female with a range between 28 and 51 years old that received medical treatment. Two patients (1.7%) complained of weight loss, who had CeD.

The average age of the patients suffered from CeD was 24.40 ± 3.04 years old, who were three males and two females. Among CeD group, abdominal discomfort/cramping and GERD were reported in five and four patients, respectively. There were statistically significant differences among CeD in GERD and abdominal discomfort/cramping. No significant differences were found among CeD in gender, the prevalence of dyspepsia and bloating (P>0.05).

There was no significant difference in the prevalence of CeD among IBS subtypes (Table 1).

Table 1- Association of IBS subtypes and celiac disease.

Variables	IBS-D	IBS-C	IBS-M	P-value
Without CeD	14 (12.3%)	10 (8.8%)	90 (78.9%)	0.399
With CeD	---	---	7 (100.0%)	

CeD, celiac disease; IBS-D, diarrhea-predominant irritable bowel syndrome; IBS-C, constipation-predominant irritable bowel syndrome; IBS-M, mixed irritable bowel syndrome.

Furthermore, no significant differences were reported among IBS subtypes in age, gender, the frequency of bloating, abdominal discomfort/cramping, dyspepsia, and GERD (Table 2).

Laboratory and histological characteristics of patients diagnosed with celiac disease are presented in Table 3.

Table 2- Demographic features, clinical manifestations, and comorbid conditions among IBS subtypes.

Variables n (%)		IBS-D 14(11.6)	IBS-C 10(8.3)	IBS-M 97(80.2)	P-value
Age (years)		31.50 ± 8.75	36.20 ± 5.61	37.44 ± 10.46	.118
Gender	Male	8 (57.14)	5 (50)	49 (50.51)	.895
	Female	6 (42.85)	5 (50)	48 (49.48)	
Bloating		3 (21.42)	3 (30)	24 (24.74)	.891
Abdominal discomfort/cramping		6 (42.85)	5 (50)	45 (46.39)	.941
Dyspepsia		1 (7.14)	5 (50)	50 (51.54)	.008
GERD		0	1 (10)	22 (22.68)	.097

GERD, gastroesophageal reflux disease.

Discussion

In this study, the prevalence of celiac disease among IBS patients was assessed and it was found that 4.1% and 1.6% had CeD and Potential CeD, respectively. There were statistically significant differences among CeD in GERD and abdominal discomfort/cramping. However, the other clinical and demographic factors had no significant association with CeD among IBS cases.

The study by Sharma et al. (10) revealed that among 362 Indian patients with IBS (2011-2012), there were CeD and potential CeD in 0.8% and 5.25%, respectively. Mentioned results were inconstant with our findings. In their study, the anti-tTG IgA antibody was positive in 6.1% of all IBS cases, while this rate was 4.95% in our study. The prevalence of the anti-tTG IgA positive test among IBS cases were similar in both studies, while the incidence of CeD and potential CeD in Sharma's study were inconstant with our findings. For better statistical interpretation, it is necessary to conduct future studies with larger sample sizes in Iran.

Shayesteh et al. (11) assessed 465 patients with IBS during the period of 2007 to 2009 (Ahvaz, Iran), and CeD was approved by pathology in 2.8% of patients. In the mentioned study, the diagnosis of CeD would be considered to be confirmed if modified Marsh types were 1 or higher. In the meta-analysis research by Behzadifar et al. (12), the prevalence of CeD among Iranian participants in studies that had used pathologic features for diagnosis was reported as 2%.

Wang et al. (13) studied on 395 IBS-D patients and 363 healthy subjects during the period of 2010 to 2012 (Wuhan, China). CeD was approved in five cases and among them, four patients (1.01%) were from IBS-D group, and one (0.28%) was from control group.

A case-control study conducted by Sanchez-Vargas et al. (14) on 400 healthy participants and 400 IBS patients (2010-2012). In the study, 55% of patients had IBS-M, 31% IBS-C, and 14% IBS-D. In case and control groups, there were 21 (5.25%) and 6 (1.5%) cases with positive tests for celiac disease. Fourteen patients with IBS (3.5%) and three controls (0.75%) were seropositive for anti-tTG IgA antibody. The IBS-D subtype patients had the highest prevalence of positivity for anti-tTG IgA (12.7%). The IBS-D subtype was most common among the IBS patients with biopsy-proven CeD. CeD was approved in 2.5% and 0.5% of IBS and control groups, respectively. In our study, the most common IBS subtype was IBS-M (80.2%), followed by IBS-D (11.6%) and IBS-C (8.3%). Furthermore, the IBS-M subtype patients had the highest prevalence of CeD and positivity for anti-tTG IgA. Further case-control studies with larger sample size is recommended.

In the meta-analysis study by Mahmoudi et al. (15), the most common IBS subtype in patients was IBS-D (47.87%), followed by IBS-C (17.34%), and IBS-M (27.84%). The serological prevalence of anti tTG-IgA was reported 5.35%. The prevalence of pathology-proven CeD was 6.13% among 2367 Iranian IBS patients. The results are inconsistent with those ones in the present study.

In the study by Danuta Domżał-Magrowska (16), 48 patients with IBS and 20 healthy volunteers were enrolled. The proportion of patients with IBS-D was 56.25%, IBS-C – 29.17%, and IBS-M – 14.58%. Among patients with IBS, three times higher than normal anti-tTG levels were reported in 10.42% of patients, including two patients with IBS-D, and three with IBS-C.

A concomitant positive serologic and genetic test results specific to CeD was found in 12.5% of IBS patients. In mentioned study, CeD was diagnosed on the basis of positive serologic and genetic test results, while in our study, positive serology and Marsh grade ≥ 2 were considered as diagnosis of CeD.

A case-control study conducted by Saito et al. (17) on 533 IBS cases and 531 controls. Individuals with positive both anti tTG-IgA and endomysial antibody (EMA) tests were considered to have CeD. 1.1% cases versus 0.9% controls had positive or weakly positive anti tTG-IgA test. 1.1% cases vs. 0.6% controls confirmed to have CeD. There was no difference in the prevalence of CeD between IBS patients and controls. Their findings do not support routine CeD screening in IBS patients in US populations.

In the cross-sectional study by Hemati et al. (18), 1000 patients with IBS-D were evaluated during 2009-2012 years. 7.6% of IBS-D cases had elevated anti tTG-IgA levels. Biopsy-proven CeD was detected in 75% of patients with elevated levels of anti tTG-IgA. Therefore, the prevalence of CeD was 5.7% among patients with IBS.

In the study by Kibune-Nagasako et al. (19), IBS-D was the most common IBS subtype (46%) among 113 patients, which was followed by IBS-C (32%) and IBS-M (22%). There is variation in the reported IBS subtypes distribution in different studies, and probably depends on the sample size evaluated, geographic region, and the subtype definition (20). In the population-based studies carried out in UK and the United States, IBS-M was reported as the most frequent IBS subtype (21, 22), while IBS-C and IBS-D were the most frequent among Iranian participants and in tertiary hospitals in China, respectively (23, 24). IBS overlap with GERD and functional dyspepsia reported in 65.5% and 48.7% of patients, respectively. In our study, GERD and dyspepsia were detected in 19% and 46.28% of IBS patients, respectively.

Conclusion

Totally, the incidence of CeD was evaluated 4 cases per each 100 patients with IBS, which was higher than recent similar studies, and screening for CD in IBS patients is advisable. However, further studies with larger sample size are required to attain more definite results. The study had several limitations. First, this was a single-urban based study, and as such this data may not be representative of the whole population of Iran. Second, the study was done on small sample size, further case-control studies with larger sample size is recommended.

Conflict on Interests

The authors declared that there was no conflict of interest.

Acknowledgments

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