ORIGINAL ARTICLE

UNDIAGNOSED CELIAC DISEASE IN PATIENTS PRESENTING WITH IRRITABLE BOWEL SYNDROME SYMPTOMS

Yasir Mohammed Khayyat[1,2]

1. Department of Medicine, Faculty of Medicine, Umm Al Qura University, Makkah-Saudi Arabia
2. Department of Internal Medicine, International Medical Centre, Jeddah-Saudi Arabia

Background: Irritable bowel syndrome (IBS) is a common clinical condition that is often diagnosed based on a set of clinical criteria. Celiac disease (CD) has a similar symptom. The study aims to estimate the prevalence of undiagnosed celiac disease (CD) in patients with criteria-positive IBS and compare with healthy control. **Methods:** A Case control study conducted from August 2013 to July 2016. For the control group with negative ROME 3 criteria for IBS provided serum total immunoglobulin (IgA) level and serum tissue transglutaminase antibody (tTG IgA). The case group with positive criteria interviewed, examined, competed ROME 3 questionnaire and provided blood sample for haematology, biochemistry, and serum tTG IgA and IgG. Positive for CD invited for upper endoscopy and duodenal biopsy for evaluation of pathological involvement using the modified Marsh classification. **Results:** Three controls (1.47%) and 21 cases (6.9%) had positive serology for CD. A statistically significant association found between serum tTG positivity and IBS and IBS-diarrhoea subtypes. No correlation was found between tTG positivity and age and sex of the case group. **Conclusion:** Celiac disease is common in IBS patients especially those with criteria-positive diagnosis. Serology screening for CD is helpful in IBS and IBS-D patients.

Keywords: Diarrhoea; Irritable Bowel Syndrome; Celiac Disease; Disorder; Functional gastrointestinal

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INTRODUCTION

Irritable bowel syndrome (IBS) is commonly encountered in clinical practice. It is a set of clinical symptoms that fit a group of established criteria that are revised periodically by the ROME foundation which supports and establishes a positive diagnosis.[1] IBS affects individuals of all ages and social classes with estimated global prevalence of 11.2%.[2] Imbalance in multiple intestinal factors along with disturbed brain-gut axis plays a major role in the pathogenesis of IBS.[3] In addition, IBS-like symptoms could occur in other luminal intestinal disorders such as bacterial overgrowth and bile acid malabsorption.[4] Gastrointestinal manifestations of CD resemble IBS symptoms. This similarity in symptoms between the two conditions may lead to diagnostic delay up to 7 years.[5] The degree of clinician awareness of such similarity varies. A practice of ruling out other possible diseases as a part of differential diagnosis is done routinely to detect red flag symptoms, as reported in a large study by Whitehead *et al* who revealed a high sensitivity for diagnosing IBS when ruling out red flag signs. However, when positive predictive value was compared prior to and after application of red flag signs to evaluate IBS cases (47.9% and 52.1%, respectively), this practice has a modest benefit.[6] Celiac disease presented as intestinal and extra-intestinal manifestations.[7] Often, the full-blown picture of CD is not common; thus, vigilance is required to recognize it. IBS patients diagnosed according to ROME-positive criteria have an expected high diagnostic probability than CD, with an actual diagnosis in as many as 2.6–5.7% of cases.[8] Several diagnostic tests were developed and used for accurate detection, but these tests have varying accuracies depending on the characteristics of the test.[9,10] In a primary care practice study in the North America for CD detection, CD was diagnosed using serum tissue transglutaminase antibody (tTG) and endomysial antibody (EMA) among common complaints of IBS, bloating, unexplained chronic diarrhoea, and constipation. Other conditions such as thyroid disease and chronic fatigue were estimated to be 2.25%.[11] Such an active effort on a primary care level was achieved by searching for active gastrointestinal and non-gastrointestinal symptoms that suggest CD. On a tertiary care level, in Saudi Arabia, a similar effort is needed to diagnose CD in criteria-positive IBS patients. Prevalence studies of CD based on serology which are done locally are comparable to international figures. However, the prevalence of overlapping CD and IBS in Saudi Arabia is still unknown. This study aimed to identify the prevalence of misdiagnosed CD and labelled as IBS per the standard ROME 3 criteria, compare this

prevalence to that of CD positivity in healthy controls without IBS, and identify the possible association or correlation of IBS subtypes with CD positivity among patients at a tertiary care level at a region where prevalence studies of CD is under-recognized.

MATERIAL AND METHODS

This cross-sectional study evaluated the prevalence of CD among IBS criteria-positive patients versus IBS criteria-negative population expressed as the control group. The study was conducted from August 2013 to July 2016 in a tertiary care private hospital for the case group and a tertiary care government hospital for the control group. Patients age 15 years and over were invited to participate in both arms of the study. Red flag symptoms of anaemia, dysphagia, weight loss, abdominal inflammatory conditions such as diverticulosis, gall bladder disease, pregnant, or lactating mothers were excluded. Sample size was estimated at 300 participants for each group based on literature review and the current prevalence of 1% within the regional and global data.

The control group was comprised of invited group of attendees of a blood donation centre. They were interviewed, and they completed the IBS Questionnaire for ROME 3 criteria of functional bowel disorders for diagnosis of IBS (IBS), IBS-mixed (IBS-M), IBS-diarrhoea (IBS-D), and IBS-constipation (Appendix 1: ROME 3 Criteria), (12) which proved the negative diagnostic criteria of IBS. The questionnaire is administered in Arabic language in which it was validated for reliability and consistency with a Cronbach's score of 0.59 Subsequently, they were included in the control group. Serum tTG was chosen because of its accuracy and characteristics to screen for CD.[9,10,13,14] Individuals with serum tTG IgA >20 µ/mL were considered positive for CD. Serum tTG samples were examined by enzyme-linked immunosorbent assay (QUANTA Lite h-tTG IgA and IgG, Inova Diagnostics, USA), which was described as addition of native human tissue transglutaminase (h-tTG) isolated from fresh red blood cells to microwell plate. Then, prediluted control and patient sera were added to separate wells to bind the immobilized antigen. Unbound sample was washed, and enzyme-labelled anti h-tTG conjugate is added to each well. The sample was incubated for 30 min at room temperature to allow contact with enzyme-labelled anti-h-tTG IgA and IgG to patient antibodies. The sample was washed, and the remaining enzyme activity was measured by spectrophotometry. Patients who were positive for tTG IgA were invited to undergo upper endoscopy and duodenal biopsies (the same applies for the case group). Six samples were obtained from the duodenum using biopsy forceps, transported to the lab on formalin medium, and imbedded in wax. Fine cuts of 4 µm of paraffin blocks and stained with haematoxylin and eosin were examined by an expert pathologist who is blinded to patient data and clinical presentation. Pathological reporting was done using the modified Marsh classification.[15] The case group are IBS patients who completed and verified the questionnaire for IBS and met a positive criteria for IBS subtypes according to ROME 3 criteria provided blood sample for serum complete blood count, electrolyte, blood urea nitrogen, creatinine, thyroid stimulating hormone, erythrocyte sedimentation rate, tTG IgA, and tTG IgG analyses. tTG IgG was included to detect cases in which IgA deficiency was present at low levels of tTG IgA. Patients with positive CD screening were invited as well to undergo upper endoscopy and duodenal biopsies.

Statistical analysis

Data were analysed using Statistical Package for the Social Sciences version 19.0 (Armonk, NY). Descriptive data were presented as median and interquartile range (IQR). Comparison between tTG was done using Fisher's exact test or chi-square test as appropriate. Correlation between IBS and healthy control groups to several parameters such as age, sex, and IBS subtypes was calculated using Spearman's rank correlation with expression of r (rho) as correlation coefficient. The *p*-value of 0.05 (two tailed) was considered statistically significant.

RESULTS

The control group is composed of 204 individuals, in which 122 were male (60%) and 82 were female (40%) healthy individuals. Three patients (1.47%) in the case group had positive serology using serum tTG IgA for asymptomatic CD. Control group recruitment was slow, and only 204 individuals were recruited (Table-1). The difference in the number of male and female patients is related to the recruitment volume at the allotted time of the study. The aforementioned three patients declined the invitation for upper endoscopy and duodenal biopsies. The serum total IgA was measured and only one case of total IgA deficiency was detected (0 mg/dL). The case group was composed of 305 IBS patients, of which 151 were men (49.5%) and 154 (50.5%) were women with predominant IBS-M subtype (96%). Twenty-one patients (6.9%) had positive serology using serum tTG IgA for CD. Table 2 shows the demographic data of both groups, IBS subtypes of the case group, and their laboratory data. A statistically significant difference was found between serum tTG Ig A levels between the two groups.

Table-3 shows details of the positive CD cases and their histological classification. Twelve female patients (57%) have IBS and IBS-mixed subtypes. Ten patients did not undergo upper endoscopy and duodenal biopsy. For the case group, correlation analysis was performed to identify meaningful correlation between the type of IBS and positivity of serum tTG to predict which group might be expected to have CD. IBS subtypes and serum tTG IgA did not correlate with age or sex of the IBS patients (Table 4). With regard to IBS subtypes, IBS and IBS-D correlated significantly with serum tTG IgA (Table-5). Correlation was done between the modified Marsh classification and serum tTG IgA and was not clinically significant (tTG IgA *r*: 0.79, *p*= .1; tTG IgG *r*: 0.63, *p* = .252).

Table-1: Asymptomatic positive CD in the control group

Positive control cases	Age	Gender	serum tTG Ig A (Units)
1	22	Female	24
2	31	Male	32
3	33	Male	40

Table-2: Basic demographic data of the study population:

	Cases (n= 305)	Control (n = 204)	Significance[#]
Gender			
Male	151 (49.5%)	122 (60%)	*p* = .024
Female	154 (50.5%)	82 (40%)	
Age	**Range, Mean±SD**		
	(15–68), 34.89±11.4	(15 – 68), 34.97±12.7	*p* = .94
IBS Subtypes			
IBS-Pain	250 (82%)		
IBS-Mixed	181 (59%)		
IBS-Constipation	40 (13%)		
IBS- Diarrhoea	47 (15.4%)		
TTG IgA status			
Positive (>20 units)	21 (6.9%)	3 (1.47%)	
Negative (<20 units)	284 (93%)	201 (98.5%)	
Laboratory tests	**Median, IQR**	**Median, IQR**	
Haemoglobin (g/dl)	13.6 (12.5, 16.9)		
MCV (fl)	83.4 (77.9, 90)		
Platelets ($\times 10^9$/L)	267 (129, 373)		
Na (mmol/l)	138 (135, 144)		
K (mmol/l)	4.2 (3.4, 5)		
Urea (mg/dl)	20 (6.4, 44)		
Creatinine (mg/dl)	0.7 (0.4, 4.8)		
TSH (uIU/ml)	1.86 (0.3, 5.4)		
ESR (mm/h)	10 (0, 80)		
Glucose (mg/dl)	95 (74, 336)		
TTG IgA (Units)	10.5 (2.3, 19.9)	5.8 (3, 40)	*p* = .001
TTG IgG (Units)	10 (1.5, 23)		
Serum Ig A (g/L)		2.47 (0 , 8)	

using fisher's exact test, *p*-value of .05 denote statistical significance.

Table-3: Positive Celiac Disease findings in the case group.

Case	Age	Gender	tTg IgA	tTg IgG	Modified marsh classification	Clinical subtype
1	47	Male	38	11.6	0	IBS, IBS-M
2	29	Male	72.6	10.8	0	
3	48	Female	38	4.7	Not done	IBS
4	32	Female	21	5.4	Not done	IBS, IBS-M
5	42	Male	179	24	Not done	IBS, IBS-D
6	23	Male	42	8	0	IBS
7	37	Male	22	5.4	Not done	IBS, IBS-M
8	30	Male	145	12.5	3b	IBS, IBS-M
9	28	Male	63	10.4	0	IBS, IBS-M
10	63	Male	21.8	4.7	Not done	IBS, IBS-M
11	41	Female	166	14.2	Not done	IBS, IBS-M
12	43	Female	55.8	44.9	3b	IBS, IBS-M
13	28	Male	100	24	3b	IBS, IBS-M
14	39	Female	141	3.2	3a	
15	52	Female	2.1	22.9	Not done	IBS, IBS-M
16	25	Female	2	25.2	Not done	IBS, IBS-M
17	27	Female	135.6	9	3b	IBS, IBS-M
18	28	Female	179	41.7	Not done	IBS-D
19	28	Female	138.5	80.8	3b	IBS-D
20	30	Female	38.7	3.7	0	IBS,IBS-D
21	58	Female	42	1.7	Not done	IBS-M

Table-4: Correlation between IBS subtypes, TTG values and demographics:

IBS subtype	Age		Gender	
	Correlation coefficient (spearman's *r*)	*p-value*	Correlation coefficient (spearman's *r*)	*p- value*
IBS	-.048	.418	-.015	.792
IBS – Mixed	-.042	.482	-.011	.847
IBS – Diarrhoea	-.101	.088	-.051	.384
IBS – Constipation	0.088	.144	.019	.752
TTG- IgA	-.003	.960	.029	.624
TTG -IgG	.034	.576	.066	.269

Correlation is significant at the *p* .01 level (2-tailed).

Table-5: Correlation between IBS subtypes and TTG IgA:

Correlation of serum tTG level and IBS subtype	Correlation coefficient (spearman's *r*)		*p-value*	
	tTG IgA	tTG IgG	tTG IgA	tTG IgG
IBS	.160**	.142*	.007	.018
IBS – Mixed	-.100	-.086	.096	.154
IBS – Diarrhoea	.211**	.183**	.000	.002
IBS – Constipation	.089	.056	.146	.362

*Correlation is significant at the .05 level (2-tailed). **Correlation is significant at the .01 level (2-tailed).

DISCUSSION

Persistent bowel symptoms that manifest as IBS constitute a chronic troubling issue that alters the quality of life of several groups of active individuals, especially for adults diagnosed with CD and entails use of gluten-free diet as a lifelong commitment.[16] On a national level, this was found to be 9% in young high school students and as much as 40% in school teachers.[16,18] Globally, IBS syndrome is prevalent in the community of up to 11.2% with more female involvement (14% vs. 9%). There is no reported difference in the literature that socioeconomic status differs in the involvement of IBS compared to other patients without IBS.[2] However, given the difficulty in quantifying this status and applying its association to IBS patients, we did not pursue this analysis in our study. Other possible aetiologies with similar symptomatology are bile acid malabsorption, lactose intolerance, bacterial overgrowth, and CD. Interest about the rule of gluten-free diet as healthy diet had gained widespread community acceptance, and more individuals adopt gluten-free diet as a lifestyle eating habit. Restriction of this food item was proved to be a possible remedy to chronic altered bowel habits without investigation for CD.[19] A group of patients with nonceliac wheat allergy gain satisfactory resolution of bowel symptoms despite their negative CD serology.[20] CD is considered not uncommon globally. Its seroprevalence is 1.4% and 0.7% based on biopsy.[21] Undoubtedly, this leaves us with the need to reconsider the diagnosis of IBS in most patients encountered daily. Application of diagnostic clinical criteria helps to establish IBS diagnosis, and this group of patients was particularly found to be four times more likely to have CD positivity, especially in the high prevalence group.[22] However, extensive diagnostic workup could be diverse and costly.[23] Despite the financial burden posed in relation to screening for CD in IBS patients, it improves health-related quality of life in general and from bowel habits in particular.[24,25] This increased cost would translate into a better clinical benefit when CD prevalence is 1%, which is similar to the currently reported global prevalence. Our study demonstrated a high prevalence of CD serology among positive criteria IBS patients compared to a group of healthy control (7% vs 1.47%). Correlation analysis found that IBS and IBS-D subtypes constitute a statistically significant association with a positive serum tTG test. This is in line with the reported immunopathogenesis of IBS-D individuals who carry CD genes of *HLA-DQ2* and *HLA-DQ8* and express small bowel fast transit features as proved by motility studies.[26] For further evidence on the association between IBS-D and CD positivity, Shahbazkhani *et al* found positive serology of CD (EMA and AGA) of 19% in patients with chronic non-bloody diarrhoea.[27] Moreover, Cash et al. investigated CD between non-constipated IBS types and healthy control with serology and biopsy and reported that more than 7% of patients with non-constipated-IBS had CD-associated antibodies.[28] A recent systemic review and meta-analysis by Irvine et al. shed light on the issue of screening of CD in IBS patients and showed a high prevalence of positive serology of CD (2.6-5.7%) and high prevalence of biopsy-proven CD (3.3%). The odds ratio of positive serology is high in IBS-D than in IBS-C (6.09 vs 4.84).[8] Therefore, from a practical point of view and according to these findings, when CD prevalence is more than 1%, screening for CD in IBS patients in general is appropriate and cost effective. Beside the findings of clinical correlation reported above for IBS subtypes

and serum tTG, our study did not associate serum tTG positivity with age nor sex of IBS patients. However, literature has reported that female sex is predominantly involved in IBS prevalence mainly of constipation subtype.[29] Our study as well as another regional study by Al-Ajlan demonstrated increased prevalence of CD diagnosis in patients with criteria-positive IBS patients at 6.9% and 9.6%, respectively.[30] This support that our region needs attention and more consideration in introducing CD as a part of workup in patients with altered bowel habits.

The limitations of this study included its lack of histological confirmation in the positive groups, which made us unable to accurately obtain serological and pathological correlation. Larger study size would be helpful. However, sample size estimation with other reported studies in several countries showed great similarity. At the time of publication of the manuscript, the ROME 4 criteria were already launched and used clinically but not used in this study because of recruitment had been already started. It was found that the difference between ROME 3 and ROME 4 criteria based on a study by Aziz *et al* reported that most ROME 3 criteria-positive patients (85% of their study population) still fulfil the ROME 4 criteria, and such update will not pose major implications in diagnostic coding.[31]

CONCLUSION

With increased prevalence and burden of IBS in the Saudi community and globally, screening for CD in the diagnostic armamentarium for chronic altered bowel symptoms along with histopathological confirmation of positive cases is recommended. Increased awareness of physicians and patients of this association is essential.

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Address for Correspondence:

Yasir M Khayyat, Department of medicine, Faculty of Medicine, Umm AlQura University, Makkah-Saudi Arabia.
Ph: +966 553591669
Email: YMKHAYYAT@UQU.EDU.SA