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Research Article

PREVALENCE OF CELIAC DISEASE IN PATIENTS OF IRRITABLE BOWEL SYNDROME: PROSPECTIVE STUDY AT A TERTIARY CARE CENTER

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A B S T R A C T

Aim: To study prevalence of Celiac disease in patients of Irritable Bowel Syndrome at a tertiary care center. **Material & Method**: The study included the patients of Irritable bowel syndrome .The patients included were both males and females in urban and rural population. Patients between age 15 years to 70 years were interviewed and diagnosed irritable bowel syndrome on the basis of Rome III criteria. These patients were tested for CBC, Thyroid function test, IgA anti tTG, stool routine microscopy, stool for occult blood, USG abdomen. UGI endoscopy, D2 biopsy and colonoscopy were done if deemed necessary by the physician. **Results**: 253 patients of irritable bowel syndrome were included in the study. The mean age was 41.8 ± 13.1 years. Out 253 patients ,122 patients (48.2%) were IBS-C, 105 patients (41.5%) were IBS-D and 26 patients (10.3%) were IBS-M. In both Male and Female, IBS-C was more common (47.9% and 48.7% respectively). IgA anti tTG was positive in 2 out of 253 patients. One patient was male and other female. Both the patients had diarrhea predominant IBS. Of the two IgA anti tTG positive patients, one patient had D2 biopsy showing complete villous atrophy, cypt hyperplasia and intraepithelial lymphocytosis (Marsh grade 3c) suggestive of celiac disease. Other patient had D2 biopsy negative for celiac disease thus potential/latent celiac disease. **Conclusions:** The prevalence of potential/latent celiac disease in IBS patients at our center is 0.4%. The prevalence of celiac disease in IBS patients at our center is 0.4%.

INTRODUCTION

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder characterized by abdominal pain and altered bowel habits in the absence of a specific and unique organic pathology.In modern GI practice approximately one third of patients have functional bowel disorder and most of them have IBS [1]. IBS is an important disease entity as it has high prevalence, substantial morbidity and treatment costs enormously to the patient [2]. All over the world nearly 11.2 %people are affected by this condition [3]. In United States of America, approximately 12% of patients seen by physicians have IBS [4]. The condition is commoner in South America than in Southeast Asia [5]. It is twice as common in women as in men. In India, the prevalence of IBS is 4%and males represent 70-80% of patients with irritable bowel syndrome [6].

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There are subsets of functional bowel disease patients harbouring organic disease, so their diagnosis relies on thorough history, clinical examination and absence of red flag signs which includes weight loss, rectal bleed and anaemia. To overcome this, Manning criteria was devised for diagnosis of IBS in 1978. With refinement in due course, Rome criteria was introduced to exclude organic disease. These diagnostic criteria were supported by various studies and long terms follow up of patients with these symptoms. Among the patients meeting the diagnostic criteria for IBS the pre-test probability for inflammatory bowel disease, colorectal malignancy and infectious diarrhoea is less than 1% [7]. However, the pre-test probability of celiac disease (CeD) in patients meeting symptom-based criteria for IBS was ten times higher than the prevalence of celiac disease in the general population [7].

The association between celiac disease and IBS is bidirectional, that is patient with CeD may have IBS symptoms and patients with IBS symptoms may have celiac disease.

Aim

To estimate the prevalence of Celiac disease in patients of Irritable bowel Syndrome at a tertiary care centre

MATERIALS AND METHODS

Study setting and design

It was a cross sectional prospective study carried out at Indraprastha Apollo hospital, New Delhi over 2 years from April 2014 to March 2016. Ethical clearance was obtained according to the declaration of Helsinki from the Institute's ethical committee. Prior informed consent was obtained from the patients before including them in the study. Patients between the age of 15 years to 70 years meeting Rome III criteria for irritable bowel disease were included in the study [8]. Patients with IBS having alarming signs (anaemia, weight loss, fever and abdominal mass), inflammatory bowel disease, diarrhoea due to organic causes other than celiac disease, lactose intolerance and patients unwilling for upper gastrointestinal endoscopy or colonoscopy (if deemed necessary by the physician) were excluded from the study. Based on the Bristol stool charting and history, patients with IBS were further classified as follows: (i) constipation-predominant IBS (IBS-C) if they had hard or lumpy stools with no loose, watery mushy or watery stools in the previous three months; (ii) diarrhoea-predominant IBS (IBS-D) if they had loose, mushy or water stools in the previous three months with no hard or lumpy stools; and (iii) mixed IBS (IBS-M) if they had both loose and hard stools in the previous three months.

Sample size was calculated using the formula $(Z^2 \times p \times q)/d^2$), when the estimated prevalence of celiac disease in IBS patients (p) was 4% (varies from 0.4% -11.4% in previous studies), precision error of estimation (d) = 0.01, and alpha = 0.05, a sample size of at least 1120 cases were needed to estimate the prevalence[9-13].Since the study was time bound, all consecutive patients meeting the eligibility criteria during the study period were enrolled. Total of 253 Irritable Bowel Syndrome patients were recruited in the study.

All the patients were screened by complete blood counts, thyroid function test and ultrasound abdomen. IgA anti-tTG antibody was identified using ELISA. The sensitivity and specificity of IgA anti tTG is 95%-100% and 96%-100% respectively [14].

Serological essay and laboratory method

5ml of blood was collected in first visit and sera was stored at -70oC. IgA anti tTG was performed using ELISA kit (EUROIMMUNE, Germany) as per the instructions by manufacturer. The sample value greater than or equal to 20 RU/ml was considered to be positive.

Microwells were precoated with recombinant human tTG antigen. The calibrators, controls and diluted blood samples were added to wells and auto antibodies recognizing tTG antigen bind during the first incubation. After first washing, purified peroxidase labelled rabbit anti-human conjugate was added. The conjugate bound to the captured human antibody and excess unbound conjugate was removed by further wash. Bound conjugate was visualized with 3, 3', 5, 5' tetramethylbenzidine substrate which gave a blue reaction product, the intensity of which was proportional to the concentration of autoantibody in the sample. Phosphoric acid was added to each well to stop the reaction. Optical density of each microwell was measured at 450 nm on a microplate reader within 30 min of stopping of reaction. Each sample was run twice and average OD of each sample was calculated. An OD value of >20 units was taken as positive result.

Esophagogastroduodenoscopy (EGD), small intestinal mucosal biopsy, colonoscopy

All patients with the diagnosis of IBS underwent EGD.Biopsy from second part of duodenum (D2) was done on case to case basis depending upon the findings of endoscopy to rule out structural abnormality. However, in patients who had IgA anti tTG positive underwent D2 biopsy without exclusion. Colonoscopy was done in patients whenever physician found it appropriate to rule out other structural diseases.

Histological examination

The D2 biopsy specimens were reviewed by one expert pathologist. Biopsy specimens were evaluated for crypt depth, villous height, architectural changes, lamina propria inflammation and intraepithelial lymphocytes.Marsh criteria was used for diagnosing CeD (Table 1). Diagnosis of CeD was based on the status of IgA anti tTG and D2 biopsy findings (Table 2).

Table 1 Marsh Criteria

Grade	IEL / 100 enterocytes - duodenum	Crypt hyperplasia	Villi
0	<30	Normal	Normal
1	>30	Normal	Normal
2	>30	Increased	Normal
3a	>30	Increased	Mild atrophy
3b	>30	Increased	Marked atrophy
3c	>30	Increased	Complete atrophy

Table 2 Diagnosis of Celiac disease

IgA anti tTG Negative	Non Celiac
IgA anti tTG Positive with D2 biopsy negative	Potent/latent Celiac
IgA anti tTG Positive + D2 biopsy changes	Celiac disease
IgA anti tTG Negative +D2 biopsy changes	Consider other diagnosis

Statistical analysis

Descriptive statistics was analysed with SPSS 17.2 (IBM, Armonk, NY, USA). Continuous variables were presented as mean ± SD. Categorical variables were expressed as frequencies and percentages. The Pearson's chi-square test or Fisher's exact test was used to determine the relationship between two categorical variables. $P<0.05$ was considered significant.

RESULTS

Total of 253 patients of IBS were included during the study period. All the patients were diagnosed cases of IBS on ROME III criteria. The mean age of the cohort was 41.8 ± 13.1 years. Out of 253 patients, 140 were male and 113 were female (M: F – 1.2: 1).

IBS Subtypes

Out 253 patients, 122 patients (48.2%) were IBS-C, 105 patients (41.5%) were IBS-D and 26 patients (10.3%) were IBS-M. In both the sexes IBS-C was more common (Table 3). Male to Female ratio in IBS-C, IBS-D and IBS-M was 1.21 :1, 1.23:1 and 1.36:1 respectively.

Table 3 Sex distribution in subtypes of IBS

Sex	Diagnosis		
	IBS-C	IBS-D	IBS-M
	Frequency/Percentage	Frequency/Percentage	Frequency/Percentage
Female	55 (48.7%)	47 (41.6%)	11 (9.7%)
Male	67 (47.9%)	58 (41.4%)	15 (10.7%)
Total	122 (48.2%)	105 (41.5%)	26 (10.3%)

Seropositivity in IBS patients

IgA anti tTG was done in all 253 patients and was positive in two patients. One patient was male and another female. Both the patients had diarrhoea predominant IBS. Of the two IgA anti tTG positive patients, one patient had D2 biopsy showing complete villous atrophy, crypt hyperplasia and intraepithelial lymphocytosis (Marsh grade 3c) suggestive of CeD. Other patient had positive IgA anti tTG antibody and biopsy negative thus classifies as potential celiac disease. IgA anti tTG positivity rate was 0.8%. Prevalence of CeD in IBS patients was 0.4%. The prevalence of celiac disease in IBS patients in our study was not statistically significant (P-0.242) (Table 4).

Table 4 Seropositivity in IBS patients

Anti tTG	Total	Diagnosis			P value
		IBS-C	IBS-D	IBS-M	
		Frequency/ Percentage	Frequency/ Percentage	Frequency/ Percentage	
Negative	251	122 (48.6%)	103 (41.0%)	26 (10.4%)	
Positive	2	0 (0.0%)	2 (100%)	0 (0.0%)	0.242
Total	253	122 (48.2%)	105 (41.5%)	26 (10.3%)	

Characteristic of seropositive patients

Out of the two seropositive patients, one was 26 years old male with diarrhoea predominant IBS. The D2 biopsy of this patient was negative for celiac disease and EGD revealed gastritis. Another patient was 55 years old female with diarrhoea predominant IBS.The D2 biopsy of this patientrevealed intra epithelial lymphocytosis, crypt hyperplasia and complete villous atrophy (Marsh 3c) and her EGD was normal.

Esophagogastroduodenoscopy (EGD), small intestinal mucosal biopsy, colonoscopy

All 253 patients underwent EGD. Of these patients 125 (49.4%) had gastritis, 79 patients (31.22%) had Gastroesophageal reflux disease (GERD) and remaining 49 patients (19.36%) had normal EGD findings.

Colonoscopy was done in 145 patients. Out of these 145 patients, 39 (26.89%) patients had haemorrhoids, 1 patient (0.68%) had melanosis coli and 105 patients (72.41%) had normal colonoscopy findings.

D2 biopsy was done in 138 patients. Complete villous atrophy was seen in one patient (0.7%), marked villous atrophy was seen in one patient (0.7%), mild villous atrophy was seen in eleven patients (7.8%), mild intra epithelial lymphocytosis was seen in four patients (2.8%), two patients (1.4%) had marked villous atrophy with giardiasis, fifteen patients (10.9%) had changes of duodenitis and 104 patients (75.9%) had normal D2 biopsy (Table 5).

Table 5 D2 Biopsy findings

D2 BIOPSY	Frequency	Percentage
Duodenitis	15	10.9%
Complete Villous Atrophy With IEL (Marsh 3c)	1	0.7%
Marked Villous Atrophy With Gairdiasis	2	1.4%
Marked Villous Atrophy With IEL (Marsh 3b)	1	0.7%
Mild IEL (Marsh 1)	4	2.8%
Mild Villous Atrophy With IEL (Marsh 3a)	11	7.8%
Normal	104	75.9%
Total	**138**	**100%**

DISCUSSION

Globally IBS is twice more common in women than in men but in India, IBS is more common in men [6]. In the present study men were more commonly affected than women (M: F – 1.2:1) which is in agreement with the other study [6]. Approximately 50% of people with IBS report symptoms beginning before 35 years of age. The mean age of presentation of IBS in the present study was 41.8 years.

In the present study IBS-C was the commonest subtype of IBS noted in our study population affecting 122 (48.2%) out of 253 patients which is not in agreement with other study by Makharia *et al*[15] in which IBS-M is more common. Patients of IBS-D are more likely to have CeD [12]. In the present study also 2 patients who were positive for IgA anti tTG had features of IBS-D thus in agreement with the other study [12].
In the present study the seroprevalence of CeD in IBS patients was 0.8% which is in agreement with other studies [11,12]. Two patients were positive for IgA anti tTG antibody. Out of the two patients one had histological changes of CeD. The prevalence of CeD [IgA anti tTG antibody (+) and biopsy changes (+)] was 0.4%, which is less when compared with other studies [15,16,17]. Although the prevalence of CeD is higher in northern India, the present study did not agree with this. Possible explanation for lower prevalence of CeD in the present study can be the cohort of patients. The ethnicity of the cohort in the present study was mixed with patients being from different parts of the country and the world thus altering the prevalence of CeD. As the health care insurance is not a norm and the institute is a corporate one, many people from the rural and poor socio-economic background prefer a cheaper government run hospitals, thus decreasing the prevalence of the disease in the present study.

El-Salhy *et al* [11] screened 968 IBS patients (Rome III criteria) and found that four patients were positive for IgA anti tTG. D2 biopsies of these 4 patients were also consistent with the features seen in CeD. Out of these four patients, one patient had Marsh type 3b and three patients had Marsh type 1 changes on D2 biopsy. All the four patients had diarrhoea predominant IBS. The prevalence of CeD was reported as 0.4%. In the present study as well the prevalence of celiac disease in IBS patients was 0.4% and both the patients who were IgA anti tTG positive had diarrhoea predominant IBS.
Study conducted by Holt *et al* screened 138 patients of IBS (Rome I criteria) and found that only one patient for positive (Anti EMA) [16]. However histologically all the patients had normal D2 biopsy. In the present study Rome III criteria was used for diagnosing IBS. Since the sensitivity and specificity of IgA anti tTG is higher than Anti EMA [17], former was used for diagnosing seropositivity in CeD. In the present study, two patients were positive for IgA anti tTG, out of which one patient was histologically positive for CeD.

On EGD, majority of the patients, 125 (49.4%) out of 253 had features of gastritis. On colonoscopy majority of patients, 105 (72.41%) out of 145 had no abnormality consistent with the diagnosis of IBS, a functional disease.

Emami *et al* [18] recruited 328 IBS patients (Rome II criteria) in the study to establish the prevalence of CeD in IBS patients. Out of 328 recruited patients no one was positive for IgA anti tTG antibody. Five patients were IgA deficient, however these patients were AGA (anti gliadin antibody) negative. D2 biopsy was taken in 60 patients and pathologic evaluation classifiedfifty-three patients as Marsh 0, three each as Marsh I&Marsh II and one as Marsh IIIa. The study concluded that IgA anti tTG may not be useful in diagnosis of celiac disease which is contradictory to other studies. In the present study only one patient out of 253 patients was positive for both IgA anti tTG and D2 biopsy (Marsh grade 3) for celiac disease. Out of total 138 D2 biopsies, one hundred four patients (75.9%) had normal D2 biopsy; seventeen biopsies had changes of Marsh grade 3, two biopsies revealed giardiasis and fifteen biopsies revealed changes of duodenitis.

HL Wang *et al*screened 578 patients of IBS-D (Rome III criteria) and found seven patients positive for IgA anti tTG and DGP (Deamidatedgliadin peptides) antibody [13]. These patients were put on glutein free diet and followed up for their symptoms and antibody titres. On follow up both symptoms and serological markers improved. The study concluded that IBS-D patients should be screened for celiac disease. In the present study also both the patients who were positive for IgA anti tTG had diarrhoea predominant IBS which is consistent with the findings of the study of HL Wang *et al* [13].

Sharma *et al* screened 362 patients with IBS (Rome III criteria) and found twenty two (6.1%) had positive anti tTG antibody [12].Among these patients, three (0.8%) had D2 biopsy changes consistent with celiac disease (0.8%).They concluded that prevalence of CeD in the study was 0.8% and prevalence of potential celiac disease (Ig A anti tTG positive and D2 biopsy negative) was 5.3% (19 patients). The results of this study were significantly higher as compared to the present study. This can be attributed to the fact that study done by Sharma *et al* was conducted in Delhi and the population was predominantly north Indian where the prevalence of CeD is high [12]. At the centre where the present study was done, the population was mixed i.e. from different parts of country and the world, not truly representing the north Indian patients.

CONCLUSION

From the present study we conclude that although the prevalence of celiac disease in IBS patients at our centrewas 0.4% and that of potential/latent celiac disease wasalso 0.4%, validating the study is not justifiable because of the small sample size.More patients need to be recruited to arrive at a definite conclusion. However, it is stressed that symptoms of CeD and IBS have overlapping symptoms andCeD must be excluded if IBS patients have symptoms suspicious of CeD.

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