Can Irritable Bowel Syndrome Hide An Organic Disease?

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Abstract: ***Introduction:*** Consensus diagnostic Rome criteria based on symptoms have been established to aid irritable bowel syndrome (IBS) diagnosis. Many items in the Rome criteria are also seen in celiac patients. Furthermore, tests for celiac disease are not routinely performed on patients believed to have IBS, thus patients with celiac disease may easily be misdiagnosed as IBS. ***Objective of this work***: was to assess the association of celiac disease with IBS. ***Subjects and methods:*** The current study included 60 IBS patients and 40 healthy subjects. All subjects were investigated for celiac disease by analysis of serum anti-tissue transglutaminase antibody (tTG). Patients with positive antibody results were offered duodenal biopsy to confirm the possibility of celiac disease. ***Results:*** The proportion of celiac disease in IBS cases was (5/60→8.3%) while was (0/40→0%) in controls. Six patients with IBS (10%) had positive antibody results of whom five cases were confirmed to have celiac disease by biopsy and the last one refused endoscopy. While, none of the controls diagnosed as celiac disease. ***Conclusion:*** Celiac disease seems to be un-recognized and under-investigated in IBS patients, so it is recommended to add Anti-tTG antibody as a screening test for celiac disease to the diagnostic Rome criteria for IBS to offer better prognosis to those patients simply by gluten free diet.

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Key Words: Celiac disease • gluten-free diet • irritable bowel syndrome.

Introduction:

Irritable bowel syndrome (IBS) is one of the commonest conditions seen by gastroenterologists. [1]IBS is not really a disease nor does it have confirmatory diagnostic tests. Rather, it's diagnosis based on a constellation of symptoms (Rome criteria) and the absence of other diagnoses. [2]Manifestations of celiac disease ranges from (a) ***Typical fully expressed enteropathy***(intestinal symptoms) e.g. chronic diarrhea, weight loss, failure to thrive in children and evidence of overt nutritional deficiencies and abdominal distention,(b) ***Atypical fully expressed enteropathy*** (extra-intestinal manifestations) e.g. iron deficiency, short stature and osteoporosis, (c) ***Silent fully expressed enteropathy*** e.g. minimal complaints or symptom-free (occasionally discovered by serological screening) and finally (d) ***Latent minimal changes enteropathy*** or normal small intestinal mucosa sometimes symptomatic. [3] Many items in the Rome criteria are also seen in celiac patients. Furthermore, tests for celiac disease are not routinely performed on patients believed to have IBS. [1]Many studies indicate that a large proportion of celiac remain undiagnosed; this is due to many clinicians being unfamiliar with the condition and many cases misdiagnosed as IBS. [4] As the management of patients with IBS is frequently unsatisfactory and if we can find definite treatment for even a small group of these patients, it would be important progress.

The aim of this study:

The aim of this study was to assess the association of celiac disease with irritable bowel syndrome in patients fulfilling Rome III criteria.

Subjects and Methods:

Subjects:

We applied the Rome III criteria for IBS to ***60 new patients*** presented to Ain Shams university hospital gastroenterology clinic. None of the patients had their condition investigated previously, they were 33 females and 27 males; they ranged in age from 18 to 48 with mean age 30 year. (patients excluded if they did not fulfill Rome III criteria or had sinister symptoms such as weight loss, rectal bleeding, nocturnal diarrhea or anemia) and ***40 Control healthy subjects*** without IBS, they were 18 males and 22 females with mean age of 28.4 and range (18-42) year matched to case subjects by age and sex and questioned in the same fashion as the case subjects. Written informed consent was obtained from all participants.

Methods:

All case and control subjects underwent **(A):** A

wide range of baseline investigations, including full blood count, erythrocyte sedimentation rate, fasting and 2 hours postprandial blood glucose, blood urea nitrogen, serum electrolyte levels, liver profile, stool analysis, ECG and abdominal U/S. **(B):** They were investigated for celiac disease by analysis of serum anti-tissue transglutaminase antibody (tTG) (serum specimens were stored at -20 °C). It was detected by ELISA. Dilutions of patients and controls' serum and calibrants (1:100) were added and plates incubated at room temperature for 60 min, then reading the optical density and calculating the results at 450 nm. Bi-chromatic measurement with a reference at 600-690 nm is recommended. The developed color is stable for at least 30 minutes. Anti tTG (IgG) greater than 10 U/ml was considered positive. The lower detection limit for Anti tTG (IgG) has been determined at 1.0 U/ml. The Anti tTG (IgG) test kit recognizes only IgG class auto antibodies specific for tTG. [5]

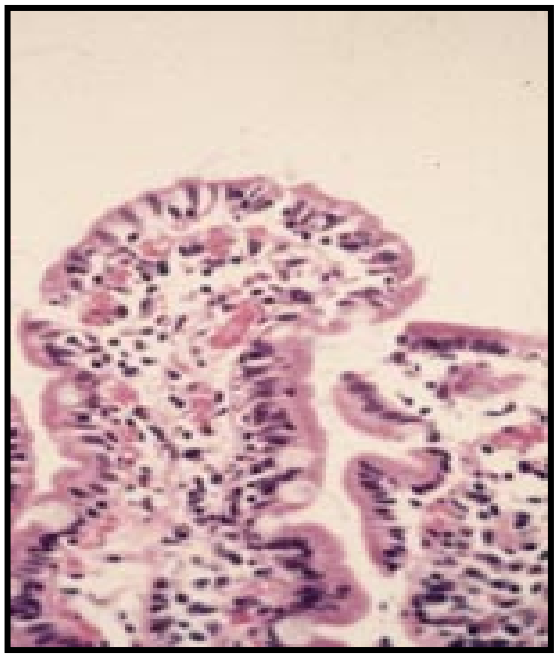
(c): Patients who tested positive for anti tTG were invited for upper endoscopy four to eight specimens were taken from the third part of the duodenum, obtained with biopsy forceps. **(d):** Pathological examination: Duodenal biopsies were initially stored in 10% formalin; thereafter they were embedded in paraffin wax cut on micro tomes at 4 µm and stained with haematoxlyin and eosin. The classic pathology changes of celiac disease in the small bowel are categorized by the "Marsh classification. [6] ***Marsh stage* 0*:*** Normal mucosa. ***Marsh stage* 1*:*** Increased number of intra-epithelial lymphocytes, usually exceeding 20 per 100 enterocytes. ***Marsh stage* 2*:*** Proliferation of the crypts of Lieberkuhn. ***Marsh stage 3:*** Partial or complete villous atrophy. ***Marsh stage 4:*** Hypoplasia of the small bowel architecture. [7]

Patients found to have positive serological tests, if confirmed by histological findings were considered to have celiac disease. To confirm that their symptoms were caused by celiac disease not co-existing IBS. (E): These patients advised to adhere to a gluten-free diet and their symptoms were re-evaluated after six months. ***An excellent response*** was defined as complete elimination of all symptoms. Partial elimination or improvement of some symptoms was considered a ***good response***. [1]

(f): Statistical analysis: All the collected data were analyzed by using SPSS version 13 and were expressed as mean ± SD. Chi square test was used two compare two quantitative groups. P › 0.05 was considered non significant, P ‹ 0.05 was considered significant and P ‹ 0.01 was considered highly significant.

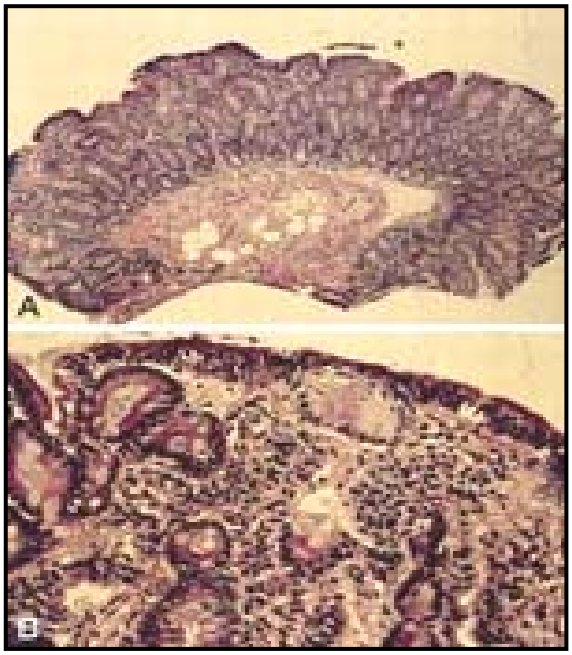
Results:

Among the 60 IBS patients 34 (56.7%) were diarrhea-predominant, 26(43.3%) were constipation-predominant .All patients and controls had within normal laboratory investigations and unremarkable findings in abdominal ultrasound. There was no statistically significant difference between cases and controls as regard Anti tTG (6.83±6.9 u/ml vs. 4.77 ±2.1 u/ml) p value > 0.05. The proportion of celiac disease in IBS cases was (5/60→8.3%) while was (0/40→0%) in controls, as six patients with IBS (10%) had positive antibody results (2 males and 4 females, mean age 31.8 range 24-42 year) of whom five cases had celiac disease; their biopsies were compatible with the histo pathological criteria of celiac disease. Two of them (40%) had increased number of intra-epithelial lymphocytes (corresponded to marsh stage I) while the other three cases (60%) had proliferation of crypts of Lieberkuhen with partial or complete villous atrophy (corresponded to marsh stage III) as shown in figure 1 and 2. The last one refused duodenal biopsy, while none of the controls diagnosed as celiac disease.



Figure(1):Duodenal biopsy in celiac disease with Marsh Type I lesion: The villus is unremarkable except for a modest increase in intraepithelial lymphocytes, particularly at the villous tip

Celiac disease patients had a significantly higher anti- tTG antibody than the controls (28.75±8.5 u/ml vs. 4.77 ±2.1 u/ml) p<0.01 as shown in table (1).



Figure(2): Duodenal biopsy in celiac disease Marsh Type III lesion.**A:** at low power, there is virtually complete villous blunting associated with crypt hyperplasia.**B:** at higher power, the increased number of surface intraepithelial lymphocytes and the damage to enterocytes are evident.

Table (1): Comparison between cases and controls as regard anti (tTG).

Parameter	Patients(5)	Controls(40)	T	P
Anti- tTG	28.75±8.5	4.77±2.1	14.7	<0.01

No particular symptom was more indicative of celiac disease as it was found that 1/25(4%) of constipation predominant IBS and 4/34(11%) of diarrhea predominant IBS proved to have celiac disease p value <0.05. Constipation was the presenting symptom in 20%, while diarrhea was the representing symptom in 80% of celiac disease patients.

A clinical response to a gluten-free diet for the five patients with celiac disease revealed excellent response in two patients and three patients showed a good response.

DISCUSSION:

The current study was carried out on 60 IBS patients fulfilling Rome III criteria and 40 healthy subjects. All subjects' hematological and biochemical results were within the normal ranges with no statistical difference between celiac disease and IBS patients (P > 0.05), this was in agreement with ***Sanders et al.*** [8] who found that IBS patients had normal hematological and biochemical profiles, so we can not detect celiac disease patients who were misdiagnosed as IBS on the basis of hematological or biochemical assays. Hence, the importance of diagnostic markers beside endoscopy and biopsy.

In the current study there was (5/60) IBS patients (8.3%) diagnosed as celiac disease by serological test using anti- tTG antibody and confirmed by duodenal biopsies while none of the controls diagnosed as celiac disease.

Sanders et al. [8] found that 66/300(22%)IBS patients tested positive for (IgA, IgG antibodies against gliadin and antibodies against endomysium(EMA)) and 14(4.7%) of them had active celiac disease (confirmed by duodenal biopsy), 43 had normal duodenal mucosa, and 9 were lost to follow-up or declined biopsy as compared with 2/300 (0.66%) of the controls had celiac disease and were positive for EMA, and 1 control had only IgA antigliadin and a normal duodenal biopsy. IBS cases had a significantly higher proportion of celiac disease than controls. ***Shahbazkhani et al.*** [1] found 12 of 105 cases of IBS (11.4%) diagnosed as celiac disease where they are tested positive for antibodies against endomysium and all these patients had compatible histological findings.

On contradiction to the previous results ***Richard et al.*** [9] found that there was no increase in the prevalence of celiac disease among the subjects with IBS, their study had been done on 150 subjects IBS and dyspepsia. Among those with symptoms 50 subjects met the criteria for IBS and the positive serology for celiac disease by tTG was identified in 2 subjects with irritable bowel syndrome (4.0%), although a percentage of the study population had positive tTG- IgA antibodies, none of these subjects were confirmed to have celiac disease by positive EMA. However, in the current study the results were confirmed by histopathology. Moreover, ***Van der Wooden et al.*** [10] found that the prevalence of celiac disease in patients with IBS is low and that screening may be ineffective. As they tested 152 patients with IBS fulfilling Rome II criteria for celiac disease using IgA endomyseal antibodies and total IgA level and there were no cases of celiac disease diagnosed (prevalence 0%), this disagreement could be explained by the fact that the endomyseal antibody (EMA) negative celiac disease patients is well recognized and so it is possible that some cases of celiac disease could have been missed [11]. So that, anti-tTG antibodies were used during the current study as a screening test because sensitivity and specificity of anti endomyseal and anti tTG antibodies are 87-95% and 95-100% versus 90 - 100% and 94-100% respectively. [12]

Celiac disease has traditionally been thought of as a diarrheal illness. Indeed, many patients with long-

standing, undiagnosed celiac disease regarded their bowel movements as normal or even as typical of constipation[8]. In the current study celiac disease patients were presented by either constipation (one patient (20%)) or diarrhea (four patients (80%)) and no particular symptoms was more indicative of celiac disease as 1/25(%) of constipation predominant and 3/34 of diarrhea predominant IBS patients confirmed to have celiac disease P value >0.05.

Shahbazkhani et al. [1] found that of the 12 celiac disease patients 3 presented with diarrhea(25%) 4 patients presented with constipation(33%) and 5 patients with intermittent diarrhea and constipation(42%). ***Sanders et al.*** [8] stated that of the 14 celiac disease patients (4) patients were diarrhea predominant (28.6%), (2) patients were constipation predominant (14.3%) and (8) patients were intermittent diarrhea and constipation (57.1%). ***Häuser et al.*** [13] found 96/412 (23.3%) celiac patients with reported biopsy-proven diagnosis fulfilled the modified Rome I criteria for IBS. So the frequent misdiagnosis of IBS in patients with celiac disease may in part be due to a low degree of suspicion for celiac disease, but it may also be attributable to that most doctors are unaware that celiac disease may present in adults and be associated with constipation.

In this study a clinical response to a gluten-free diet for the five celiac disease patients revealed excellent response in two patients and three patients showed a good response ,also in the study **of *Shahbazkhani et al.*** [1] 11 of 12 Celiac disease patients follow a gluten free diet for 6 months 3 showed excellent response and 8 showed good response.

Conclusion:

Celiac disease seems to be un-recognized and under-investigated in patients with symptoms of IBS, as it is clear from the current study, there was a significant number of celiac disease patients were misdiagnosed as IBS.

So, it is recommended to add Anti- tTG antibody as a screening test for celiac disease to the diagnostic Rome criteria for IBS to offer better prognosis to those patients simply by gluten free diet.

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