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Research Article

CELIAC DISEASE IN EGYPTIAN PATIENTS WITH CLINICALLY DIAGNOSED IRRITABLE BOWEL SYNDROME

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ABSTRACT

Background and Aim: There is a definite relation between irritable bowel syndrome (IBS) and celiac disease (CD), also, IBS patients have sensitivity to certain dietary components. This study aimed to reveal the prevalence of celiac disease among Egyptian patients with IBSusing anti-endomysial Ab IgA.

Patients and Methods: This study included 80 Egyptian patients who were diagnosed as IBS according to Rome III criteria. All participants were subjected to: complete clinical evaluation, routine laboratory investigations, serological tests (total IgA and anti-endomysial antibody IgA), and upper gastrointestinal endoscopy with 4 biopsies from second part of duodenum. Video capsule endoscopy (VCE) was performed only to proven cases with CD.

Results: All included patients (100%) presented with abdominal pain, 72 patients (90%) had bloating, and 12(15%) had diarrhea. Eight patients (10%) had positive anti-endomysial antibody. Among them, only two patients had confirmed CD by histopathological examination of duodenal biopsy; one of them matched March Grade II and the other one matched March Grade IIIc. Among patients with negative anti-endomysial antibody (n=72), one patient was proved to have CD by histopathological examination of duodenal biopsy corresponding to March Grade II. Thus, the prevalence of CD in the current study was 3.75% (3 out of 80 patients). VCE showed associated distal enteropathy in one patient with March Grade IIIc criteria. Anti-endomysial antibody showed sensitivity, specificity, positive predictive and negative predictive values of 66.7%, 92.2%, 25% and 98.6% respectively in the diagnosis of CD.

Conclusion: Screening for CD among Egyptian patients with IBS by anti-endomysial antibody alone is not enough as it showed relatively low sensitivity and positive predictive value. Other more sensitive serological markers as anti-tissue transglutaminase (anti-tTG) Ab together with VCE may be beneficial in this setting.

INTRODUCTION

Irritable bowel syndrome (IBS) is defined according to Rome III criteria as a clinical syndrome characterized by presence of abdominal pain or discomfort, at least 3 days per month in the last 3 months. In addition to two or more other symptom features: improvement with defecation, association with a change in stool frequency and association with a change in stool form or appearance. Other symptoms, such as bloating and distension, are also considered to be consistent with the diagnosis of IBS (**Longstreth *et al*., 2006**).

The etiology of IBS remains unclear. Theories have ranged from purely psychologic to more recent proposals about post-infectious alterations in GI tract neuromuscular function. IBS may best be viewed as a biopsychosocial disorder in which altered GI motility, GI hypersensitivity, and psychosocial factors all interact to predispose someone to the syndrome (**Mayer, 1999**).

Celiac disease (CD) is an immune-based reaction to dietary gluten (storage protein for wheat, barley, and rye) that primarily affects the small intestine in those with a genetic predisposition and resolves with exclusion of gluten from the diet. There has been a substantial increase in the prevalence of celiac disease over the last 50 years and an increase in the rate of diagnosis in the last 10 years. It can present with many symptoms, including typical gastrointestinal symptoms (e.g.,

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diarrhea, steatorrhea, weight loss, bloating, flatulence, abdominal pain) and also non-gastrointestinal abnormalities (e.g., abnormal liver function tests, iron deficiency anemia, bone disease or skin disorders) **(Rubio-Tapia*et al*., 2013).**

Patients with IBS and CD exhibit similar gastrointestinal and extra gastrointestinal symptoms. Application of symptom-based diagnostic criteria such as the Rome III criteria could result in diagnosing patients with CD as having IBS. However, it has been suggested that these conditions overlap **(Aziz and Sanders, 2012 and Boettcher and Crowe, 2013).**

A systemic review and meta-analysis has concluded that CD, as diagnosed by positive serology and positive biopsy, was four folds more prevalent among patients with a clinical presentation of IBS than in non-IBS populations **(Ford *et al*., 2008).**

This study aimed to determine the prevalence of celiac disease in clinically diagnosed IBS Egyptian patientsusing anti-endomysial Ab IgA.

Patients and Methods

This cross sectional study included 80 Egyptian patients who were diagnosed as irritable bowel syndrome (IBS), according to Rome III criteria which were fulfilled during the last 3 months with symptom onset at least 6 months prior to diagnosis. They were presented to Internal Medicine and Tropical Medicine Departments, and outpatient clinics at Ain Shams University Hospital, in the period from January 2015 to February 2016.

Patients above 60 years or below 18 years, diabetic patients, those with thyroid dysfunctions, bloody diarrhea, significant weight loss, congestive heart failure, prolonged fever or giardiasis infection were excluded.

Informed written consent was obtained from each patient prior to inclusion. The study protocol was approved by the Research Ethical Committee of Faculty of Medicine, Ain Shams University according to the ethical guidelines of the 1975 Declaration of Helsinki.

All included patients were subjected to the following:

1. Complete clinical evaluation.
2. Routine laboratory investigations: Complete blood count (CBC) using coulter counter (Coulter LH 750 analyzer), erythrocyte sedimentation rate (ESR; in mm/hour) was determined in the first hour by the Westergren method, stool analysis, C-reactive protein, renal profile, liver profile, fasting and two hours post prandial blood sugar, thyroid stimulating hormone (TSH) were measured on Synchron CX-9 autoanalyzer (Beckman Instruments Inc.; Scientific Insturments Division, Fullerton, CA92634, 3100, USA).
3. Serological examination:
   - Assessment of Total IgA: by nephelometric method using Minineph™ human IgA kit (Binding site Group Ltd, Birmingham, UK). (For exclusion of IgA deficiency). Normal range: 61-356 mg/dL.
   - Assessment of Anti-Endomysial antibody (EMA)(IgA): by ELISA kit supplied from Glory Science Co., Ltd.USA (detection range of positive EMA =2.5-50ng/ml, kit sensitivity = 0.1 ng/ml and negative EMA < 2.5 ng/ml).
4. Upper gastrointestinal endoscopy: using the Pentax video endoscope EG 3440. Multiple duodenal biopsies (at least four)were taken from second part of the duodenum and were sectioned and stained with Hematoxylin and Eosin then examined under the microscope to detect the classic pathological changes of CD. Lesions were classified histopathologically according to the Modified Marsh classification **(Marsh, 1992 and Rostami *et al*., 1999)** into:

(Grade 0): Normal or chronic inflammation with no increased lymphocytes,

(Grade I): Increased intra-epithelial lymphocytic infiltration,
(Grade II): Crypt hyperplasia,
(Grade IIIa): Partial villous atrophy,
(Grade IIIb): Subtotal villous atrophy,
(Grade IIIc): Total villous atrophy.

Histopathological examination was done by gastrointestinal-oriented pathologist who was blinded about the serological tests of the patients.

5 **Video Capsule endoscpopy (VCE):** was performed only to proven cases with CD to diagnose distal enteropathy. It was done in EL-KafrawyIntestinal Capsule Unit in Gastroenterology Department, Ain Shams University Hospital, by the OMOM CE (Jinshan Science and Technology Company, Chongqing, China). VCE was considered to be consistent with CD if at least one of the following was detected: reduced duodenal folds, scalloping, mucosal fissures, grooves or mosaic pattern.

Statistical Methods

Collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 22.0.

Descriptive statistics were done as minimum& maximum of the range and mean±SD (standard deviation) for quantitative parametric data, while number and percentage was done for qualitative data, and 95.0% confidence interval (CI) for both data.

Inferential analyses were done for quantitative variables using independent t-test.For qualitative data, Fisher's Exact test was used for variables with small expected numbers. Correlations were done using Pearson's Correlation for numerical parametric data.P value < 0.05 was considered statistically significant & P< 0.01 as highly significant.

Diagnostic characteristics were calculated as follows:

- ***Sensitivity:*** probability that a test result will be positive when the disease is present (true positive rate). It was calculated as: (True positive test / Total positive golden) x 100

- ***Specificity:*** probability that a test result will be negative when the disease is not present (true negative rate). It was calculated as: (True negative test / Total negative golden) x 100
- ***Positive predictive value:*** probability that the disease is present when the test is positive. It was calculated as: (True positive test / Total positive test) x 100
- ***Negative predictive value:*** probability that the disease is not present when the test is negative. It was calculated as: (True negative test / Total negative test) x 100

RESULTS

This study included 80 Egyptian patients diagnosed as IBS according to Rome III criteria. Their mean age was40.3±5.6 years (ranged from 21 to 54 years), 31 of them were males (38.75%) and 49 (61.25%) were females. All included patients (100%) presented with abdominal pain, 72 patients (90%) had bloating, and 12 (15%) had diarrhea.

Among the studied 80 patients, eight patients (10%) had positive anti-endomysial antibody; all of them (100%) presented with abdominal pain, six of them (75%)had bloating, and two (25%) had diarrhea.

Among the eight patients with positive anti-endomysial antibody, only two patients had confirmed CD by histopathological examination of duodenal biopsy; one of them matched March Grade II criteria and the other one matched March Grade IIIc criteria.

Among patients with negative anti-endomysial antibody (n=72), one patient was proved to have CD by histopathological examination of duodenal biopsy corresponding to March Grade II. Thus, the prevalence of CD in the current study was 3.75% (3 out of the studied 80 patients).

The three cases with proven CD underwent examination by Video Capsule Endoscopy (VCE) which revealed associated distal enteropathy in one patient who was fulfilling March Grade IIIc criteria.

In the current study, anti-endomysial antibody showed sensitivity, specificity, positive predictive and negative predictive values of 66.7%, 92.2%, 25% and 98.6% respectively in the diagnosis of CD.

Table (1) shows laboratory investigations of the studied cases.

Table 1 Laboratory investigations of the studied patients (80 cases)

Lab	Mean±SD	Range	95% CI
Hb (g/dL)	13.1±1.1	11–14.9	12.8–13.4
Albumim (g/dL)	3.7±0.3	2.8–4.0	3.7–3.8
ALT (IU/L)	19.4±6.2	10.0–30.0	17.9–20.9
PT (Seconds)	11.5±0.3	11.0–12.0	11.4–11.6
Creatinine (mg/dL)	0.9±0.1	0.7–1.0	0.8–0.9
ESR (mm/hr)	11.5±10.0	6.0–49.0	9.0–14.0
CRP (mg/L)	5.2±1.2	4.0–11.0	4.9–5.5
Total IgA (mg/dL)	218.6±85.1	84.0–506.0	197.6–239.7
Anti-endomysial antibody (ng/mL)	2.2±3.2	0.9–19.9	1.4–3.0

CI: Confidence interval

Table (2) shows non-significant correlation between positive anti-endomysial antibody (EMA) and different studied parameters.

Table 2 Correlation between positive anti-endomysial antibody (EMA) and different parameters.

Parameters	R	p
Age (years)	0.170	0.176
Hb (g/dL)	0.036	0.779
Albumim(g/dL)	0.121	0.336
ALT (Iu/L)	-0.005	0.968
PT (seconds)	0.064	0.615
Creatinine (mg/dL)	0.143	0.257
ESR (mm/hr)	-0.085	0.500
CRP (mg/L)	0.019	0.879
Total IgA (mg/dL)	-0.073	0.566

Pearson's correlation test

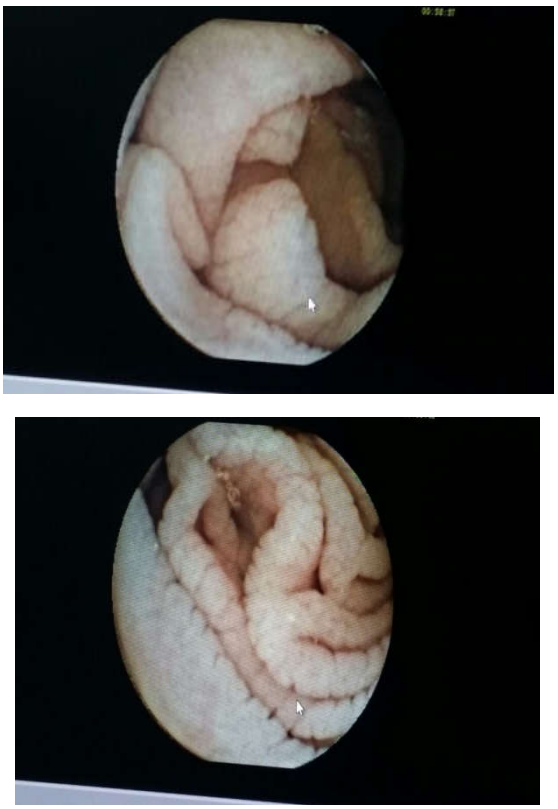

Fig 1 Video capsule endoscopy showing associated distal enteropathy in one patient proved to have celiac disease corresponding to March Grade IIIc criteria.

DISCUSSION

There is an overlap of symptoms between celiac disease (CD) and functional GI diseases such as IBS. While it has been reported that up to 4% of the patients with IBS have CD, and almost 30% of patients with CD have symptoms that are sufficient to make a diagnosis of IBS. Furthermore, even patients with CD on gluten-free diet (GFD) continue to have symptoms of IBS (**Ford *et al*., 2009 and Sainsbury *et al*., 2013**). On the other hand, symptoms attributed to IBS seem to have a different etiology, and it has been reported that many patients fulfilling the criteria for IBS have, in fact, some sensitivity to one nutrient component (**Thompson *et al*., 2000).** This study aimed to determine the prevalence of celiac disease in clinically diagnosed IBS Egyptian patients using anti-endomysial Ab IgA. The study included 80 patients fulfilling

Rome III criteria of IBS, 8 of them (10%) showed positive serology (anti-endomysial antibody); Among them, only two patients had confirmed CD by histopathological examination of duodenal biopsy; one of them matched March Grade II and the other one matched March Grade IIIc.

Among patients with negative anti-endomysial antibody (n=72), one patient was proved to have CD by histopathological examination of duodenal biopsy corresponding to March Grade II. Thus, the prevalence of CD in the current study was 3.75% (3 out of 80 patients).

These results were consistent with ***Hin et al. (1999)*** to some extent, who screened 1000 IBS patients in primary care setting by using anti-endomysial antibody; 30 of them had positive anti-endomysial antibody and all showed histopathological confirmation on duodenal biopsies.

Many previous studies showed variable prevalence of celiac disease in IBS patients by using different screening methods. In the study of ***Berti et al. (2006)***, by testing for anti-tTG (anti-tissue transglutaminase) IgA antibody in primary care patients, only three of 367 adults with IBS (0.8%) found to have CD. ***Korkut et al. (2010)*** screened 100 IBS patients fulfilling Rome III criteria; two of them were found to have elevated levels of serum antigliadin IgA and IgG, and anti-tissue transglutaminase IgA antibodies, with histological evidence of celiac disease on examination of duodenal biopsy.

Sharma et al. (2015) studied 362 IBS patients, 22 patients (6.1%) had positive anti-tTG antibody, among them 3 patients (0.8%) had proven CD by histopathological examination.

In a recent study, ***Sánchez-Vargas et al. (2016)*** investigated 400 IBS patients. In their study, 18 patients were positive for anti-human tissue transglutaminase (h-tTG IgA) and /or DGP (deaminated gliadin peptide)-II IgG. Histopathological confirmation of CD was proven in 2.5% of IBS patients.

In the current study, among the eight patients with positive anti-endomysial antibody, only two patients had confirmed CD by histopathological examination of duodenal biopsy (true positive cases) and the remaining 6 patients were false positive.Anti-endomysial antibody showed sensitivity, specificity, positive predictive and negative predictive values of 66.7%, 92.2%, 25% and 98.6% respectively in the diagnosis of CD among patients with IBS.

False positivity for anti-endomysial antibody in different studies may result from the tendency of these antibodies to have a high predictive value only in the presence of severe mucosal lesion. Thus, the false positivity rate will drop as the percentage of cases with severe mucosal lesion increases **(Rossi *et al*., 1988 and Rostami *et al*., 1999).**

It is not uncommon for patients with CD who consume a gluten-free diet (GFD) and suffer from IBS symptoms to present at the clinic. Reportedly 20–23.3 % of treated CD patients fulfill the symptom-based Rome criteria for IBS. Despite adhering to a GFD, patients with CD who exhibit IBS symptoms have a reduced quality of life as compared with those who do not **(O'Leary *et al*., 2002 and Hauser *et al*., 2007).** It is possible that CD and IBS coexist in some patients; however, it is more likely that the inflammation in CD does not subside completely in some patients after implementation of a GFD, and a low-grade inflammation similar to that seen in post-infectious IBS may exist **(El-Salhy, 2012).**

The three cases with proven CD underwent examination by Video Capsule Endoscopy (VCE) which revealed associated distal enteropathy in one patient who was fulfilling March Grade IIIc criteria. Those patients started gluten free diet and planned for follow up according to their clinical response.

CONCLUSION

Screening for CD among Egyptian patients with IBS by anti-endomysial antibody alone is not enough as it showed relatively low sensitivity and positive predictive value. Other more sensitive serological markers as anti-tissue transglutaminase (anti-tTG) Ab together with video capsule endoscopy (VCE) may be beneficial in this setting.

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