Journal of Physiology and Pathophysiology Vol. 2(1), pp. 1-5, February 2011
Available online http://www.academicjournals.org/jpap
ISSN 2I41-260X ©2011 Academic Journals

Full length Research paper

Frequency of celiac disease in Egyptian patients with chronic diarrhea: Endoscopic, histopathologic and immunologic evaluation

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Accepted 4 January, 2011

Chronic diarrhea is one of the major presenting features of celiac disease (CD), the frequency of CD in patients with chronic diarrhea in Egypt remains unknown. The aim of this study is to determine the frequency of CD among Egyptian patients with chronic diarrhea. This study included 113 adult patients with chronic non-bloody diarrhea that attended the Tropical Medicine and Gastroenterology Department, Assiut University Hospital. All patients were subjected to full history taking, clinical examination, blood picture, serum urea and creatinine, blood glucose, liver function tests, thyroid function test, serum K, Ca and Na, anti-gliadin antibodies (AGA) IgA and IgG and tissue transglutaminase antibody IgA (anti-tTG IgA), abdominal ultrasonography, oesphagogastroduodenoscopy and duodenal biobsy for histopathology and colonoscopy. Sixteen (14.2%) out of 113 adult patients with chronic non-bloody diarrhea was diagnosed CD (positive IgA anti-tTG, histpathology and response to gluten free diet). Endoscopic findings suggesting CD were in 12 patients (75%). All diagnosed CD patients had small intestinal pathological changes of different grades according to modified Marsh classification. CD is one of the relatively frequent causes of chronic non – bloody diarrhea in Egyptian patients. Testing for CD should be indicated in those patients.

Key words: Chronic diarrhea, celiac disease, tissue transglutaminase.

INTRODUCTION

Celiac disease (CD) is an autoimmune gastrointestinal disease caused by intolerance to gluten and dietary proteins present in wheat, rye, and barley. The disease usually manifests in childhood, and symptoms include diarrhea, abdominal pain, and failure to thrive. Symptoms in adulthood include anemia, fatigue, weight loss, diarrhea, constipation, and neurological symptoms (Sollid, 2000; Neuhausen et al., 2002). The diagnosis of CD is based up on histological findings in duodenal or jejunal biopsies, which may present in various forms. At one end of the spectrum is a mucosa with normal architecture and an increase in intraepithelial lymphocytes and at the other end, the classic flat mucosa, villous atrophy and crypt hyperplasia (Oberhuber, 2000). Among different serological tests for screening of CD, such as anti-gliadin antibodies (AGA) and endomysial IgA antibody (EMA), the tissue transglutaminase antibodies (tTGA) has proved to be a very specific indicator to identify patients with CD (Rossi, 2004). In several studies, the sensitivity and specificity of these tests compared with biopsy-proven disease were 94 to 98% (Dieterikh et al., 2000; Sulkanen et al., 1998; Rossi and Tjota, 1998).

Although CD was once thought to be a rare disease (Davidson and Fountain, 1950), recent screening studies indicate that CD is one of the more frequent genetically based diseases, occurring in 1 in 130 to 300 Europeans (Kolho et al., 1998; Catassi et al., 1996). The frequency in finnish school-aged children is 1 in 99 (Maki et al., 2003). In Cairo City, Egypt, Abu-Zekry and Coworkers published that CD is a frequent disorder among Egyptian

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Table 1. Modified Mash classification (Mash, 1992).

Histopathologic finding	Grade
Normal or chronic inflammation with no increased lymphocytes	0
Increased intra-epithelial lymphocytic (IEL) infiltration	I
Crypt hyperplasia	II
Partial villous atrophy	IIIa
Subtotal villous atrophy	IIIb
Total villous atrophy	IIIc

children in the general population (1 in 187), in children with failure to thrive (4.7%) and in children with type1 diabetes (6.4%) (Abu-Zekry et al., 2008).

It is well known that clinical CD represents the tip of the iceberg and diarrhea is the main presenting feature of CD in adults (Ciclitira et al., 2001). In a study in Kuwait, CD accounted for 18.5% of cases of chronic diarrhea in children (Shaltout et al., 1989). Shahbazkhani et al. (2004b) reported that CD is the most common cause of adult chronic non-bloody diarrhea in Tehran. Another, Russian study recorded that the frequency of CD in patients with chronic diarrhea is equal to 16.9% (Sabel´nikova et al., 2004). Little is known about the prevalence of CD in adults with chronic diarrhea in Egypt. So, our study was a trial to know the frequency of CD in Egyptian patients with chronic non-bloody diarrhea.

PATIENTS AND METHODS

From June 2007 to Janurary 2010 we studied a total of 113 consecutive patients with chronic non-bloody diarrhea attending the Tropical Medicine and Gastroenterology Department, Assiut University Hospital, Assiut, Egypt. Patients with bloody diarrhea were excluded. Our study was in accordance with the ethical standards for human experimentation and approved by the Ethics Committee of The Faculty of Medicine, Assiut University. The patients subjected to full history taking with stress on onset, course and duration of chronic diarrhea and any associated gastrointestinal and non gastrointestinal symptoms. Complete physical examination with stress on body weight, pallor, skin examination for any skin lesion, abdominal examination, neurological examination and examination of the loco-motor system. Abdominal ultrasonography was done for all patients. Laboratory investigations involving: full blood picture (serum iron for patients with anemia), serum urea and creatinine, blood glucose, liver function tests (HCV Ab and HBsAg in patients with elevated transaminases levels), thyroid function tests (in suspected patients), serum electrolytes (K, Ca and Na).

All patients subjected to upper gastrointestinal endoscopic examination, and 4 biobsy samples from the second portion of the duodenum were taken, also they subjected to lower endoscopic examination and multiple biopsies were taken. The samples were evaluated by expert pathologist and duodenal biopsies were graded using modified Marsh classification (Table 1). Then 10 ml venous blood was collected from each patient. Samples were centrifuged and the serum was separated, divided into two aliquots and immediately stored at -20℃ (till analyzed in Germany). Tissue transglutaminase antibody (Celiky tTG-IgA) and deaminated gliadin peptides (GliadinDP) IgA and IgG (Pharmacia Diagnostics, Freiburg, Germany) were done for all patients in the Laboratory for Allergy and Immune Diagnosis, Department of Dermatology, University Hospital Freiburg (Director: Prof. Dr. med. Thilo Jakob) that is certified according to DIN EN ISO 15189. Results were considered negative when tTGA levels were < 2.6, equivocal between 2.6 to 3.5 and positive > 3,5. Antigliadin IgA antibodies (AGA-IgA) and (AGA-IgG) were considered negative when levels were < 7, equivocal between 7 - 10 and positively > 10.

Statistical analysis

The Statistical Package for Social Science (SPSS), version 10, was used for the statistical analysis. Simple statistics such as frequency, mean and standard deviation were used. Also, chi-square, t-test and Mann-Whitney U test were used for comparison. The results were considered statistically significant when the P values were <0.05.

RESULTS

A total of 113 patients (71 males, 42 females) were included in this study, suffering from chronic non bloody diarrhea for 4 weeks or more. The mean age of the patients was 29.3 ± 7.6 years range (15 to 45 years). Sixteen patients (14.2%) were diagnosed celiac disease (10 males and 6 females) with mean age (26.6 ± 8.9) based up on increase of antibody levels to IgA tissue transglutaminase (positive when > 3.5), response to gluten free diet (GFD), gluten challenge test and histopathological changes (according to modified marsh classification). tTG-Ab IgA was positive in 16 patients, AGA-IgA and AGA-IgG were positive in 8 (50%) of them. Other symptoms of patients with CD included abdominal pain, weight loss, vomiting, abdominal distension and one patient (6.3%) of them had epilepsy (Table 2). Laboratory findings revealed iron deficiency anemia in 6/16 (37.5%), thrombocytosis in 2/16 (12.5%) and elevated serum transaminases levels in 2/16 (12.5%). Twelve of the diagnosed CD patients (75%) had endoscopic findings suggesting of CD (two had absent or reduced duodenal folds, 5 had scalloping of folds and 5 had visible vessels with fishers or cracks) (Table 3). All of them had histopathological changes (one had grade II, 4 had grade IIIa, 9 had grade IIIb and 2 had grade IIIc) (Table 4). All of them respond to GFD. Other organic causes of chronic diarrhea in our study were tuberculosis in 12 (10.6%) patients, giardiasis in 7 (6.2%) patients and unexpectedly capillariasis also in 7 patients.

Table 2. Signs and symptoms in patients with chronic diarrhea caused by CD compared to patients without CD.

Clinical	Celiac (n = 16)		Non-celiac (n = 97)	
	No.	%	No.	%
Abdominal pain	3	18.8	28	28.8
Vomiting	2	12.5	10	10.3
Weight loss	12	75.0	23	23.7
Lower limb edema	1	6.3	11	11.3
Abdominal distension	6	37.5	17	17.5
Generalized abdominal tenderness	1	6.3	15	15.5
Pallor	9	56.3	23	23.7
Convulsions*	1	6.3	0	0.0
Response to gluten free diet	16	100.0	0	0.0

*Epilepsy.

Table 3. Macroscopic findings at endoscopy in CD and non-CD patients.

Variable	Celiac (n = 16)		Non-celiac (n = 97)		P-value
	No.	%	No.	%	
Endoscopy					
Negative	4	25.0	69	71.1	0.000*
Positive	12	75.0	28	28.9	
Endoscopic findings					
Reduced or absent duodenal folds	2	16.7	19	67.9	
Scalloping of folds	5	41.7	1	3.6	-
Mosaic appearance of mucosa	0	0.0	8	28.6	
Visible vessels with mucosal fisher or cracks	5	41.7	0	0.0	

Table 4. Histopatholgical changes in CD and non-CD patients.

Variable	Celiac (n = 16)		Non-celiac (n = 97)		P-value
	No.	%	No.	%	
Pathological changes					
Negative	0	0.0	80	82.5	0.000*
Positive	16	100.0	17	17.5	
Pathological grades					
Grade I (Increase lymphocyte infiltration)	0	0.0	6	35.4	
Grade II (Crypt Hyperplasia)	1	6.3	3	17.6	
Grade III a (Partial villous atrophy)	4	25.0	4	23.5	--
Grade III b (Subtotal villous atrophy)	9	56.2	3	17.6	
Grade III c (Total villous atrophy)	2	12.5	1	5.9	

DISCUSSION

Although CD was once thought to be a rare disease (Davidson and Fountain, 1950), recent screening studies indicate that CD is one of the more frequent genetically based diseases, occurring in 1 in 130 to 300 Europeans (Catassi et al., 1995; Kolho et al., 1998). The frequency in Finnish school-aged children is 1 in 99 (Farrell and Kelly, 2002). In Cairo City, Egypt, Abu-Zekry et al. published that CD is a frequent disorder among Egyptian

children, both in the general population (1 in 187) and in at-risk groups (4.7% in children with failure to thrive and 6.4% in children with type 1 diabetes) (Abu-Zekry et al., 2008).The disease usually manifests in childhood, and symptoms include diarrhea, abdominal pain, and growth failure. Symptoms in adulthood include anemia, fatigue, weight loss, diarrhea, constipation, and neurological symptoms (Sollid, 2000; Neuhausen et al., 2002). It is well known that clinical CD represents the tip of the iceberg and diarrhea is the main presenting feature of CD in adults (Ciclitira et al., 2001). Chronic diarrhea is one of the most common reasons for referral to a gastroenterology clinic (Thomas et al., 2003). The differential diagnosis is complex, and variety of tests must be done for those patients (Fine and Schiller, 1999).

In this study, we assessed the frequency of CD among 113 adult Egyptian patients with chronic non bloody diarrhea based up on increase of antibody levels to IgA tissue transglutaminase (positive when > 3.5), response to GFD, gluten challenge test and histopthological changes (modified marsh classification). In an adult population, the pooled estimates of the sensitivity and specificity of IgA tTGA-HU were 95.1 and 98.3%, respectively (Rostom et al., 2004). The frequency of CD in the studied patients with chronic diarrhea was 14.2%. Our results were within the average ranges of the previous studies. In Egypt, Soliman et al. (2001) studied 40 cases of chronic diarrhea over a period of 18 months by using push enteroscope and celiac like pattern was seen histopathologically in 4 cases (10%). In another study in Egypt, CD was diagnosed in 22.4% out of 73 patients with chronic diarrhea (Bamekhlah et al., 2006). In Iraq, Al-Bayatti (2002) studied 50 adult patients with diarrhea for 4 weeks or more, CD was diagnosed in (20%) of patients (Al-Bayati, 2002). Shahbazkhani et al. (2004b) reported that, CD is the most common cause of adult chronic non-bloody diarrhea in Tehran, where CD was diagnosed in (19%) of patients. Another study in Russia recorded that, the frequency of CD in patients with chronic diarrhea is equal to 16.9% (Sabel´nikova et al., 2004). Shaltout et al. reported a prevalence of 18.5% for CD among Kuwaiti children with chronic diarrhea (Shaltout et al., 1989).

Our study also showed that GFD can eliminate or reduce the severity of diarrhea in most patients with CD.

Four endoscopic markers suggestive of villous atrophy have been described in CD; loss or reduction in duodenal Kerkring's folds, mosaic mucosal pattern, scalloped configuration of duodenal folds and micronodular pattern of the mucosa (Brocchi et al., 2002; Tursi et al., 2002).

Sensitivity of these markers for the diagnosis of CD ranges between 47 and 100% (Brocchi et al., 2002; Dickey and Hughes, 1999; Oxentenko et al., 2002). Overalls endoscopic markers have a wide range in sensitivity mainly in case of minor degrees of villous atrophy. Therefore, endoscopic evaluation without biopsies is considered not sensitive enough for diagnosis and inadequate to confirm or to exclude CD (Cammarota et al., 2005).

In our study, endoscopic findings suggesting CD were in 12/16 (75%) of patients with chronic diarrhea diagnosed CD, so normal endoscopic findings do not exclude CD and further histopathological examination of the duodenal biopsies and immunological assay especially tTG-antibodies is important. In our study, tuberculosis (endemic disease in Egypt), capillarisis which unexpectedly diagnosed by finding eggs of capillaria in stool and sometimes finding parts of capillaria worm during histopathological examination of duodenal biopsies and giardiasis which diagnosed by finding giardia lamblia cysts in stool were organic causes of chronic diarrhea in some cases, so those causes should be taken in consideration and must be in mind as an organic causes of chronic non bloody diarrhea in Egypt.

Our study showed that 2/16 (12.5%) of patients with chronic diarrhea diagnosed CD previously diagnosed Irritable Bowel Syndrome (IBS). Also, Jadallah and Khader (2009) revealed that the prevalence of CD in Jordan patients with diarrhea predominant IBS was (6.8%). Further evaluation for frequency of CD in Egyptian patients with IBS is recommended.

Conclusion

Celiac disease is one of the relatively frequent causes of chronic non–bloody diarrhea in Egyptian patients, so, testing for CD may be indicated in all patients being evaluated for chronic diarrhea.

More studies on large number of patients in different medical centers in Egypt are needed to confirm our suggestion.

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