Original paper

Prevalence of Celiac Disease in Dyspeptic Patients

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Abstract

Background: Celiac disease (CD) is a disorder of small bowel malabsorption, occur upon exposure to gluten, CD appears to represent a spectrum of presentations: ranging from classical type (most commonly describe), to atypical form found in the setting of another presentation e.g.: iron deficiency, osteoporosis (most patients have it). The diagnosis of CD in adults is classically made on clinical suspicion but firm diagnosis can only be established by small intestinal biopsies and serologic markers
Objectives: to estimate the prevalence of celiac disease in patients with dyspepsia **Methods:** Any patient had dyspepsia, older than 15 years were tested for anti-tissue transglutaminase antibody and underwent upper gastroduodenoscopy.Four endoscopic biopsies were taken from each patient and sent for histopathological examination and classified according to modified Marsh's classification**.**
Results: Among 157 patients who enrolled in study, 17 patients were labeled as celiac disease: 16 of them has histopathologic changes (Marsh II and above) and 1 patient was normal mucosa, 15 patients from them were positive for tTG antibody and 2 patients were negative.
Conclusions: any patients diagnosed with functional dyspepsia and sent for endoscopy, should routinely had biopsy of the descending duodenum. Particular attention to females with dysmotility or indeterminate dyspepsia.
Keywords: celiac disease, gastrointestinal, gluten free diet, tissue transglutaminase, endomysial antibodies.

Introduction

Celiac disease(CD)is a disorder of small bowel malabsorption characterized by mucosal inflammation, villous atrophy, and crypt hyperplasia, which occur upon exposure to gluten, clinical and histological improvement with withdrawal of gluten from the diet.[1,2,3,4]CD is thought to result from the activation of cell-mediated (T-cell) and humoral (B-cell) immune response upon exposure to the glutens (prolamins and glutenins) of wheat, barley, rye, and oats, in a genetically susceptible person.[5, 6] More recent evidence suggests that the presence of auto-antibodies to a connective tissue element surrounding smooth muscle called endomysium is highly specific for CD. The target of this autoantibody is an enzyme called tissue transglutaminase (tTG) which play a prominent role in the pathogenesis of CD by modifying gliadin, resulting in a greater proliferative response of gliadin specific T-cells, which contributes to mucosal inflammation and further B-cell activation.[7, 8] The true prevalence of CD is difficult to estimate because of the variable presentation of the disease, particularly since many patients can have little or no symptoms, there are approximately 7-9 undiagnosed subjects for each known CD patients. Furthermore, approximately 9% of first degree relatives also have CD[9]. CD can affect persons of many ethnic backgrounds, but rarely affect persons of

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purely Chinese, Japanese, or Afro-Caribbean decent.[8]The diagnosis of CD in adults is classically made on the basis of clinical suspicion compatible with a duodenal biopsy while taking a gluten-containing diet, followed by clinical and histological improvement following commencement of a glutean free diet (GFD).[2,5] Firm diagnosis of CD can only be established after small intestinal biopsies confirming a flat mucosa with absence of normal intestinal villi[10].Histological examination further demonstrates a cellular infiltrate of lamina propria with plasma cells and lymphocytes[1]. The number of intraepithelial lymphocytes (IEL) is markedly increasing (> 30 IEL/100 epithelial cells). Small intestinal changes can vary from a nearly normal mucosa with increase IEL to a completely flat mucosa.[11]These histologic findings are characteristic but not specific; their presence permits a presumptive diagnosis of CD and initiation of a gluten-free diet. Indeed, CD is not the only cause of villous atrophy[12]. However, several serologic markers have become available that have altered the classic diagnostic pathway. The sensitivity of IgA anti-gliadin antibodies (AGA) is (70 to 85 %), and the specificity (70 to 90 %). IgA anti-endomysial (EMA) and anti-tissue transglutaminase (tTG) antibodies have sensitivities in excess of 90 percent and specificities of over 95 percent[13]. The titers of endomysial antibodies and anti–tTG correlate with the degree of mucosal damage[14]as a result, the sensitivity of these antibody tests declines when a greater number of patients with lesser degrees of villous atrophy are included in studies[15, 16] Significant variability seems to exist in the reported values among the different studies, these IgA-based tests can be negative in IgA-deficient patients. The sensitivity and specificity of the anti-EMA and anti-tTG antibodies, along with the perceived under diagnosis of CD, has led to suggestions of using these tests for population screening, The IgA and IgG antigliadin antibody tests have lower diagnostic accuracy with frequent false positive results ,sonot recommended for initial diagnostic evaluation or screening[17].The major complications of CD include intestinal and extra intestinal malignancies, ulcerative jejunoileitis, and collagenous sprue. Unlike most gastrointestinal (GI) lymphomas that are typically of B-cell origin, in CD lymphoma most commonly of T-cell origin [8]. There is a growing data suggests that early diagnosis and treatment can prevent complications of CD including lymphoma, diabetes mellitus, cerebral calcification with epilepsy, osteopenia, and infertility.[16, 18] The mortality rate almost twice that of the general population, mostly due to lymphoproliferative disease.[19, 20]CD has been associated with a variety of other diseases: up to 6% have an IgA deficiency, 5% are diabetic (control improves with a gluten-free diet), 5% have thyroid disease[21], and 10% have dermatitis herpetiformis[22]. It also associated with primary biliary cirrhosis and autoimmune hepatitis[23].Dyspepsia is defined as pain or discomfort centered in upper abdomen according to Rome II criteria [24], discomfort may be characterized by or associated with upper abdomen fullness, early satiety, bloating or nausea.[25, 26] It is established that dyspepsia is a common problem worldwide. In the United States, the point prevalence is approximately 25%, excluding those having typical GERDsymptoms[27]. Uppergastrointes-tinal endoscopy is currently the main diagnostic modality in the work-up of dyspeptic patients. It is known that CD may have such atypical forms as functional dyspepsia and irritable bowel syndrome apart from conventional symptoms such as anemia, diarrhea and weight loss [28,29,30].It has been reported that about 20-40% of the patients with CD have dyspepsia [31]. Due to atypical symptoms, CD may be overlooked, especially in patients with dyspepsia [32, 33].

Objectives: to estimate the prevalence of celiac disease in patients with dyspepsia.

Patients and methods

The present study was conducted in Al-Basra health directory, Al-Sadr Teaching Hospital, endoscopic unit from January 1st 2008- June 30th 2009. The patients were choose from inpatient and outpatient attainders, complaining of dyspeptic symptoms (chronic or recurrent pain or discomfort centered in the upper area of the abdomen) According to the Rome II criteria. Room II criteria:

At least 12 weeks (which need not be consecutive), within the

Preceding 12 months, of the following:

- Persistent or recurrent pain or discomfort centered in the Upper abdomen;
- No evidence of organic disease (including upper endoscopy)
- No evidence that the dyspepsia is exclusively relieved by defecation or associated with the onset of a change in stool frequency or stool form (i.e., not irritable bowel syndrome)25

Exclusion criteria include:

1- Patients younger than 15 years.

2-those undergoing clinical workup foran upper GI tract disease suggested by previous radiographicor ultrasonographic findings;

3-those referred for malabsorption, suspected celiac disease, or iron deficiency anemia;

4-those receiving regular follow-up for a known disease (eg, peptic ulcer);

All the patients submitted to serological and endoscopical tests.

Serology: All the patients were tested for IgA anti-tTG ELISA (EUROIMMUN®) after endoscopic procedure, and the result were recorded as either positive or negative.

Endoscopical features and small bowel biopsy: All patients underwent gastroduodenoscopy with fiber optic endoscope (GIF type 2T200, model Olympus) after an overnight fasting under local xylocain spray. The stomach examined carefully and omit any patients with gastric abnormality (erosions, ulcer, growth, etc.). The duodenum was closely inspected for the appearance and the number of mucosal folds by two observers and was noted to be either normal or abnormal and the biopsy taken despite mucosa normal or abnormal.

Four biopsies were pinched from the second part of duodenum and fixed in a tube containing 10% formaldehyde solution. All specimens were routinely processed and embedded on edge in paraffin wax. Sections 4 to 5 micrometer thick were taken, and examined under light microscope by a pathologist unaware of the pattern of endoscopic mucosal changes in patients, nor the serology markers. The changes were graded according to modified Marsh classification.

The patients were classified as having CD positive if both antitTG and histopathologic changes (Marsh II and above) were positive.

Appropriate statistical methods were used with the help of SPSS program version 15.0.

Results

157 of 243 patients attend the endoscopic unit of Al-Sadr Teaching Hospital, Al-Basra health directory were enrolled in the study, all of them age 15 years and more and complain of dyspepsia subjected to various investigations for diagnosis of celiac disease (gastroduodenoscopy, serology and histopathology).

Only 21.0% (33) of the studied group were males and 79% (124) were females. The ages of the studied patients were divided into 3 groups 52.9% of them between 15 - 35 years old.

16 patient (10.2%) of those involved show positive histopathological result (corresponding to marsh II AND above) table 5, while 15 of them (9.6%) tested positive serological test table 6

Table1. Marsh's classification of small-intestinal lesions

Stage 0	Preinfiltrative mucosa.
Stage I	Increase in the number of intraepithelial lymphocytes (IELs) to more than 30 per 100 enterocytes.
Stage II	Crypt hyperplasia. In addition to the increased IELs, there is an increase in crypt depth without a reduction in villus height.
Stage III	Villous atrophy; A partial, B subtotal, C total. This is the classical celiac lesion.
Stage IV	Total villous atrophy. This can be considered the end-stage lesion in a very small group of patients who are unresponsive to gluten withdrawal and may develop malignant complications. There can be deposition of collagen in the mucosa and submucosa (collagenous sprue, a disorder that may be related to CD).
*OMGE Practice Guidline Celiac disease Feb 2005	

Table 2. Frequency of patient with gender

Gender	frequency	Percentage
Male	33	(21.0%)
Female	124	(79.0%)
Total	157	(100.0%)

Table 3. Frequency of patient with Age groups

Agegroups	frequency	Percentage
(15-35)years	83	(52.9%)
(36-60)years	55	(35.0%)
(>61)years	19	(12.1%)
Total	157	(100.0%)

Table 5. Frequency of patient with Biopsy

Biopsy (Marsh II and above)	Frequency	percentage
-ve	141	(89.8%)
+ve	16	(10.2%)
Total	157	(100.0%)

Table 6. Frequency of patient with serology

Serology(anti - tTG)	Frequency	percentage
-ve	142	(90.4%)
+ve	15	(9.6%)
Total	157	(100.0%)

Out of 33 males, 2(6.1%) of them were +ve by biopsy and from 124 females 14 (11.3%) were +ve biopsy, so total of16 (10.2%) had positive biopsy result table 7.

The serological study show that 2 of 33 males (6.1%) and 13 of 124 females (10.5%) involved in the study tested positive, so total of 15 (9.6%) had positive serology.

According to the age group 10 (12.0%) of the 83 aging (15-35) years, and 4 (7.3%) of 55 aging (36-60) years, and 2(10.5%) of 19 age group (>61) years show positive histopathological test table 9.

Result of serological test according to the aging group are shown in the table 10.

Discussion

In this study 17 (10.8%) of 157 involved patients all of them were dyspeptic labeled as celiac disease, this more than what found by Bardella MT, et al (2000) [29]. were they found 5 patients with celiac disease from 517 studied patients, and also more than what found by Lima VM, et al (2005) [30] were they found 4 patients with celiac disease from 142 studied ,this difference

could be ascribed to the fact that the disease is less common in Italy or Brazil where these studies performed respectively, and more common in our locality CD is very prevalent in people from the middle east and these data are not surprising as they inhabit countries included in the "Fertile Crescent" such as Anatolia (South of Turkey), Lebanon, Syria, Palestine and Iraq.[34,35]

Table 7. Relation of gender with histopathological examination (Marsh II and above)

gender		Biopsy(Mash II and above)		Total
		-ve	+ve	
	Male	31(93.9%)	2(6.1%)	33(100.0%)
	Female	110(88.7%)	14(11.3%)	124(100.0%)
Total		141(89.8%)	16(10.2%)	157(100.0%)

Table 8. Relation of gender with serology (anti tTG)

gender		Serology(anti tTG)		Total
		-ve	+ve	
	Male	31(93.3%)	2(6.1%)	33(100.0%)
	Female	111(89.5%)	13(10.5%)	124(100.0%)
Total		142(90.4%)	15(9.6%)	157(100.0%)

Table 9.Relation of age with histopathological examination Marsh II and above

Agegroups		Biopsy(Marsh II and above)		Total
		-ve	+ve	
	(15-35)years	73(88.0%)	10(12.0%)	83(100.0%)
	(36-60)years	51(92.7%)	4(7.3%)	55(100.0%)
	(>61)years	17(89.5%)	2(10.5%)	19(100.0%)
Total		141(89.8%)	16(10.2%)	157(100.0%)

Table 10. Relation of age with serology (anti tTG)

Agegroups		Serology(anti - tTG)		Total
		-ve	+ve	
	(15-35)years	72(86.7%)	11(13.3%)	83(100.0%)
	(36-60)years	51(92.7%)	4(7.3%)	55(100.0%)
	(>61)years	19(100.0%)	0(0%)	19(100.0%)
Total		142(90.4%)	15(9.6%)	157(100.0%)

16 (10.2%) patients have positive biopsy (Marsh II and above), and one of them had negative biopsy but positive anti-tTG, which could be explained by either one of the following reason:

1- The histopathological changes has not established yet. [11]

2- Patchy involvement of small bowel lesion in CD[11,36]

15 (9.6%) patients have positive anti-tTG, and two patients has negative serology but positive biopsy this could be explained by:

1- These patients might have other causes for the mucosal lesions. [37]

2- Selective IgA deficiency which occurs 10 - 15 times more commonly among people with celiac disease compared to the general population [38]. UnfortunatlyIgG anti-tTG was not available at the time of this study.

3- Some of these patients might have seronegative CD: Anti-tTG titers correlate with the severity of mucosal damage, as a result, in the presence of minor mucosal damage of histopathology, the antibody may be negative [39,40]. The age distribution of patients with celiac disease in our study is more common in the third and fourth decade, this age was similar to what found by Bardella MT et al (2000) [29], and also similar to Feighery C. Fortnightly review[41], Ciclitira PJ et al (2001) [42], Maki M et al (1997) .[43], and slightly differ from what found by Ferrell R.J et al (2002) [44] who found two peaks of age one in early childhood around the age of 2 years and the second around the age of 50 years.

This difference is probably related to the differences in the age of the participants in the studies, in the current study, the referral cases were adult, middle age and elderly patients. It is known that celiac disease has a wide spectrum of clinical manifestations; dyspepsia may be one of its symptoms.[31]Our data clearly indicate that patients with dyspepsia are at definite risk for CD. Interestingly, the subgroup of dyspeptic patients at the highest risk comprised young women[31]. As all our patient were having normal looking mucosa, The greater prevalence of CD among patients who reported dysmotility or indeterminate dyspesia may be related to autoimmune damage of the extrinsic autonomic system[45],and/or to an increase in neurotensin and enteroglucagon plasma levels which inhibit the motility of the upper gastrointestinal tract[46], moreover a delayed oro-cecal transit time and a post-prandial decrease in gallbladder emptying rate have been found in untreated CD patients with normalization of oro-cecal transit time after gluten withdrawal using a hydrogen lactulose breath test[45]. Patients who are younger than 45 years and who show no signs or symptoms of anunderlying organic disorder should be serologically examined for CD before empirical treatment is begun. This approach seems to be particularly appropriate for females[29]. In view of the consequences of untreated CD, the large contingency of dyspeptics patients without proper diagnosis, and the high prevalence of this disease among these patients, it is particularly important for endoscopists to be attentive for presence of endoscopic evidences of villous atrophy, thus possibly identifying unsuspected CD. Furthermore, the inclusion of serological CD assays in routine testing for dyspepsia should be strongly recommended. This approach would allow the identification of negative endoscopic CD markers, as well as provide reasonable indications for a duodenal biopsy[30]. The early diagnosis of CD is advisable because of the high prevalence of the disease and the beneficial effect of a gluten-free diet in improving symptoms and decreasing the risk of intestinal lymphoma and other complications.[47]

Recommendations

1. Larger study with larger sample size and multiple centers to confirm this study, and to find how much it is significant.
2. To increase awareness of physician about this relation between celiac disease and dyspepsia.

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