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Specific Coeliac Disease Antibodies and Microenteropathy

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1. Introduction

Coeliac disease and dyspepsia are common conditions, and consume considerable resources in both investigation and treatment. In the last years, considerable changes in epidemiology of Coeliac disease (CD) have been observed. Recently several studies have been published on the prevalence and importance of CD in Iran and showed that 1 out of 166 healthy Iranian blood donors are affected by CD (1).

A marked increase in CD prevalence and incidence especially the gluten sensitivity with milder enteropathy has been reported, (1, 2) which can be at least partially explained by both the development of more sensitive serological tests and a high degree of disease suspicion (3, 4). The variability of in particular clinical (5) and histological aspects of CD may face the clinician often with uncertainty as some of the features might not quite fit in the diagnostic models in current guidelines (2).

Related malabsorptive symptoms, such as weight loss, diarrhea/steatorrhea and abdominal distension may not be necessarily observed in many CD (6). Atypical forms of CD have increased considerably (7) and the presence of dyspepsia as a unique symptom has been frequently attributed to CD (8). In classical CD with prominent malabsorptive features, dyspepsia may be one of the symptoms. It has been reported that the frequency of CD in people with dyspeptic complaints is 1.1-3%, which is two to nine times higher than in the general population around the world (6, 8-12). Anti-endomysial antibodies (EmA) were confirmed to be less sensitive than IgA tTG antibodies, although at present, human recombinant tissue transglutaminase (tTG) antibodies of IgA class are considered the most sensitive marker (8-11). Moreover, a new serological test that is, antibodies to deamidated gliadin peptides (DGP) – has been proposed as a screening test for CD, since many retrospective and perspective studies showed a very high diagnostic accuracy of this immune marker. AGA were the first serological markers routinely used for CD screening, allowing the identification of at-risk-patients for gluten-sensitive enteropathy, but at present their importance is only historical, since their predictive value is quite significantly lower than that of EmA and tTG antibodies. The sensitivity and specificity of tTG IgA is in the 93% to 97% range and, therefore, they represent the first-choice test for screening asymptomatic

people like dyspeptic patients and for ruling out CD in symptomatic patients with a low pretest probability for CD (9).

In the present study we described the prevalence of gluten sensitive enteropathy in dyspeptic patients and compare the value of serology with histology in diagnosing CD.

2. Method

2.1 Patients and methods

Between November 2007 and October 2008, 5732 patients aged 15 years or more attended the Gastroenterology section of the Taleghani Hospital of Tehran, Iran. Four hundred and seven patients (193 men and 214 women) with dyspepsia were prospectively studied. The study was approved by the institutional ethics committees of Research center for gastroenterology and liver disease, Shahid Beheshti University of Medical sciences, and all participants signed a written informed consent.

Individuals were considered dyspeptic if they complained of persistent pain or uneasiness in the upper abdomen. Upper GI endoscopies were performed in these patients to diagnose common causes of dyspepsia including esophagitis, peptic ulcers, duodenitis and cancer. In addition, CD was identified by histological alterations characteristic of gluten sensitive enteropathy and by consistent CD serology.

Gastric biopsies were obtained for *H.pylori* detection and biopsies from the second part of the duodenum for histological processing. Histological diagnosis of CD was based on the presence of intraepithelial lymphocytes, crypts hyperplasia and/or villi atrophy. Biopsy results were classified as absence of CD (Marsh 0) or suggestive of CD (Marsh I to IIIc), according to Marsh criteria (13) and subsequently modified by Rostami et al. (14). The histological specimens were examined by two pathologists who did not know the endoscopic results and clinical history of the patients.

The optical density readings on enzyme-linked immunosorbent assay (ELISA) of 407 patients were analyzed for IgA class human antitissue transglutaminase (tTG) antibody and total serum IgA values according to the manufacturer's instructions (15). Determinations of IgA tTGA antibody were carried out using a commercially available kit (AESKULISA tTG, Germany). According to standardized methods, when a value higher than 15.0 U/ml was recorded, the result was considered positive. Total serum IgA values were measured by an immunoturbidometric assay (Pars Azmoon, Iran) and serum levels below 70 U/L were considered indicative of IgA deficiency. Those with IgA deficiency were tested with Immunoglobulin G (IgG) tTGG by an ELISA method, and using the commercially available kit (AESKULISA tTGG, Germany).

Serological data were correlated to the endoscopic results and to the histological pattern observed in the small intestine. All patients with confirmed CD diagnosis were treated with a gluten free diet and followed.

2.2 Statistical analysis

Statistical analysis was performed using SPSS software, version 13.5. Descriptive variables such as mean, median and standard deviation were determined. Chi-square ($\chi 2$) test was performed to find out the association between CD and risk factors.

3. Results

The mean age of the patients was 36.1 years. The gastroenterology symptoms in the subjects were: 78% abdominal pain, 70% bloating, 58% heart burn, 46% early satiety, 32% nausea, 32% flatulence, 31% weight loss and 22% anorexia. Recurrent abdominal pain, heart burn and bloating were present in 60%, 45% and 31% of the patients respectively.

H.pylori was detected in 90.5% cases. There were 26 cases with enteropathy (12 Marsh I, 4 Marsh II, 2 Marsh IIIa, 6 Marsh IIIb and 2 Marsh IIIc). Four of 407 dyspeptic patients were IgA deficient and all of them were negative for IgG tTG. Thirty three (8.1%) of the 407 patients tested had tTGA level more than 15 u/ml and considered as tTGA positive. Twenty three of 33 seropositive had normal small bowel mucosa.

The demographic, histologic and serologic characteristics of 33 patients with serology positive and 26 with abnormal histology are shown in table 1. In 10 of 33 tTGA positive patients CD was confirmed by histology analysis of the intestinal biopsy samples, giving a prevalence of CD of 2.45%. Five of these 10 coeliac patients were Marsh IIIa-c followed by 3 Marsh I and 2 Marsh II. The highest rate of histological abnormalites and of CD seropositivity was found in the age cathegories of 21-30 years and 10-20 years respectively.

subjects	no. of cases	Mean age	gender		GI symptoms								HP	CD
			M	F	AP	AN	WL	NA	HB	ES	FL	BL		
Abnormal histology patients	26	37.9	11	15	18	6	11	5	14	8	7	12	21	10
Seropositive patients	33	42.6	13	20	25	8	9	9	10	9	7	15	26	10

AP; abdominal discomfort, AN; anorexia, WL; weight loss, NA; nausea, HB; heart burn, Early satiety, FL; flatulence, BL; bloating, HP; *Helicobacter pylori*, CD; Coeliac disease

Table 1. Clinical and laboratory features of seropositive patients

4. Discussion

Dyspepsia is a highly prevalent and heterogeneous disorder (16). We know that damages in gluten sensitivity are not confined to the small intestine (17) and no every gluten sensitive patients develop severe mucosal small bowel abnormality. Several studies have demonstrated that continues exposure to gluten may damage the structure and function of the gastric mucosa in gluten-sensitive patients (18, 19). Other surveys indicate that approximately 20% of patients with dyspeptic symptoms have erosive esophagitis, 20% are estimated to have endoscopy-negative reflux disease, 10% have peptic ulcer, 2% have Barrett esophagus (20) and the results of the present study suggest that at least 2-3% coeliac disease with histology confirmation could be added to the list. However, the proportion of gluten related dyspepsia seems to be even higher (serology >8%) and hence gluten sensitivity might be a major etiology for dyspepsia.

The most important identifiable causes underlying dyspeptic symptoms in our study group were duodenitis (13%), gastritis (12%), esophagitis (9%) and peptic ulcer disease in 10% malignancies of the upper gastrointestinal tract were not found. Approximately 60% of patients with dyspepsia showed no abnormality in their mucosa but the majorities were positive for *H.pylori*.

A significant number (8%) of our cohort with dyspepsia had positive serology for CD. The large number with positive tTG in this study (in total 33 tTG positive which 23/33 had normal histology) would suggest that dyspepsia might represent a cardinal sign and a prevalent mod of presentation for gluten sensitivity. We found that anti-tTG IgA antibodies were highly specific but poorly sensitive for detecting severe villous atrophy in coeliac patients under a gluten free diet.

Immunoglobulin A (IgA), anti-endomysial antibodies (IgA EMA-ab) and IgA anti-tTG antibodies (IgA tTG-ab) are in close correlation in untreated as well as treated coeliac (fig 1) (21, 22). It is important to note that serology (EMA/tTGA) is a far more specific marker for atypical CD compared to microenteropathy (Marsh I-II) which seems to have a non-specific nature (23). In other word the specificity of serology for CD seems to be close to 99% in many studies (24). This is in contrast to histology that would have a non-specific value especially in cases with milder enteropathy (microscopic enteritis, Marsh 0-II). Obviously histology could represent the gold standard for CD diagnosis only in cases with severe mucosal abnormality (Marsh IIIa-c). Since tTG autoantibodies have a far higher specificity (>98-100%) for CD compared to a milder enteropathy, we might consider a higher prevalence (±8%) for CD in dyspeptic patients (25, 26). Testing for tTG antibodies is the cheapest and most accurate option, as the EMA method used to detect endomysial antibodies is subjective and uses expensive tissue of monkey oesophagus or umbilical cord as the substrate. When there is a low suspicion of CD, serological testing should be done as a high-specificity rule-in test, but when there is a high suspicion of CD, HLA typing as a high-sensitivity rule-out test would be useful. This strategy might be helpful in encouraging health professionals to use serology because the index of suspicion is generally low for atypical presentation. Perhaps performing HLA typing in seronegatives would give some more degree of reassurance in ruling it out.

Recent studies has clearly emphasized that, while IgA DGP antibodies do not add anything to the IgA tTG test, but IgG DGP antibodies are a relevant test for CD diagnosis and can identify the CD patients with IgA deficiency (27). In this CD subgroup, IgG DGP antibodies should be preferred to IgG tTG antibodies, whose positivity, as generally acknowledged, is fairly less specific and indicative of CD than that of IgG DGP antibodies (fig 1).

We are aware that there is no a single perfect test to diagnose CD in its own. Histological abnormalities were found in 26 (6.4%) of our patients. Despite high specificity of autoantibodies, this finding would provoke the discussion on seronegative cases and question the sensitivity of serological tests. Although, microenteropathy could be a result of any other intestinal disorder, from previous experience we learned those negative serological tests were less reliable in symptomatic cases presenting with a milder enteropathy (28- 30).

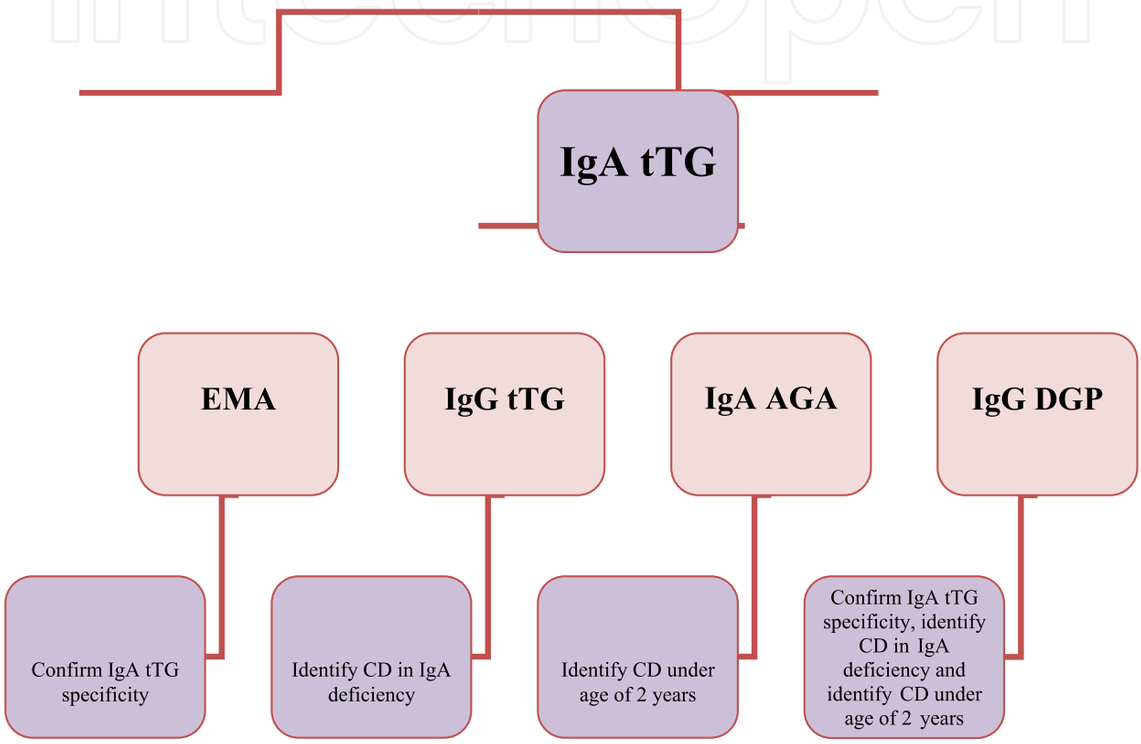


Fig. 1. Comparison between the present and new serological strategy for coeliac disease diagnosis

Based on this evidence if we believe that specificity of serology (tTGA) is beyond 98% and if we also believe that seronegative cases presenting with milder enteropathy exist, we might be able to recognize that an even higher proportion (>8%) of our CD patients might present with dyspepsia. In such cases in contrast to the high diagnostic value of severe enteropathy, microenteropathy obviously fails to represent the gold standard in diagnosis of gluten sensitivity as it is simply unreliable in its own. There is nothing against the fact that histology remains as an important component in diagnosis of GS but not as the gold standard at least in atypical cases with microenteropathy. Coeliac disease with flat mucosa based on which the gold standard was introduced >50 years ago is still a rare condition. It is time to recognize that for a good proportion of gluten sensitive cases histology is non-specific and hence the pathologist is unable to make the definite diagnosis in his own. Therefore, in conclusion, we suggest do not expect too much from histology and concentrate on clinical presentation and presence of autoantibodies as the diamond standard for diagnosis of CD. Future studies would be needed to assess whether dyspeptic patients presenting with positive antibodies and whatever histology would require gluten free diet?

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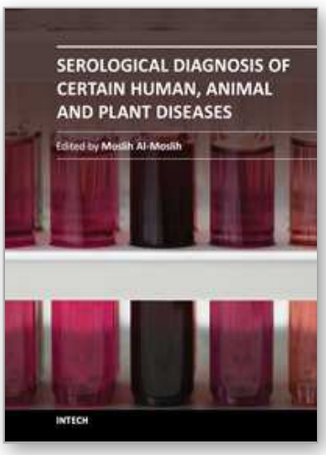
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This book explains the concept of serological methods used in laboratory diagnoses of certain bacteria, mycoplasmas, viruses in humans, animals and plants, certain parasitic agents as well as autoimmune disease. The authors present up-to-date information concerning the serological methods in laboratory diagnosis of such infectious diseases. Section one deals with the serological methods for bacteria. Section 2 deals with serological methods in human, animal and plant viruses. Section 3 is concerned with the serological laboratory diagnosis of echinococcus and human toxocariasis agents. The last section deals with serological laboratory methods in the diagnosis of coeliac disease.

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