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RAPID COMMUNICATION

Levels of serologic markers of celiac disease in patients with reflux esophagitis

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Abstract

AIM: To investigate the prevalence of celiac disease serologic markers (antigliadin IgA, IgG, and anti-endomysial IgA) in patients with reflux esophagitis and to detect the relationship between reflux esophagitis and celiac disease (CD).

METHODS: This study was performed prospectively between January 2003 and January 2004. Sixty-eight adult reflux esophagitis patients and 40 people as control group for symptoms related with gastrointestinal system were enrolled in this study. The diagnostic work-up included an accurate medical history with gastrointestinal symptoms, routine laboratory measurements, the detection of antibodies against gliadin (IgA and IgG) and endomysium (IgA), and an upper endoscopy with postbulbar biopsy.

RESULTS: IgA-AGA and IgG-AGA were positive at 8.8% and 10.3% in patients with reflux esophagitis. In control group, it was found that 10% people had positive IgA-AGA, and 7.5% people had positive IgG-AGA. There was no significant relationship between patients and control group regarding positive IgA-AGA and IgG-AGA. The patients and persons in control group had no positive IgA-EMA. On postbulbar biopsies, no finding was detected concerning celiac disease. There were no symptoms and signs for gluten enteropathy in patients and control group.

CONCLUSION: This review supports that an association does not exist between celiac disease and reflux esophagitis. We think these diseases exist independently from each other.

Key words: Celiac disease; Reflux; Esophagitis

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INTRODUCTION

Celiac disease (CD) is a chronic inflammatory disorder characterized by damage of the mucosa of the small intestine[1,2]. CD is induced in sensitive individuals by the ingestion of gluten and may range from overt malabsorption to few or no symptoms when only malabsorption of selective nutrients present[3,4]. Clinical manifestations of CD vary markedly with the age of the patient, the duration and extent of disease[1,5]. Clinical and histological improvement occurs with withdrawal of gluten from the diet[6]. The diagnostic criteria of CD are based on the finding of small intestinal mucosal villous atrophy with crypt hyperplasia. Small intestinal histology is the current gold-standard diagnostic test for celiac disease[7].

Subtle and atypical symptoms often make the diagnosis difficult, and, therefore serological screening tests have proved essential in the diagnostic approach[8]. Serological studies currently in clinical use include IgA endomysial antibody (IgA-EMA), IgA tissue transglutaminase antibody (IgA-tTG) and antigliadin antibodies IgA and IgG (AGA). Serology has a limited value in diagnostic procedures and a negative result does not rule out the diagnosis of CD[9].

CD patients have been demonstrated to be associated with a number of motor abnormalities of upper gastrointestinal tract[10-14]. The patients with untreated CD show a significant decrease in low esophageal sphincter (LOS) pressure[13]. However, whether adult celiac patients are more susceptible to reflux esophagitis is still unknown. A few reports support that patients with CD are more susceptible to reflux esophagitis, whereas others do not support this connection[16,17].

So far, no data are available on the relationship between reflux esophagitis and CD. Therefore, we aimed in this study to investigate the prevalence of celiac disease serologic markers (antigliadin IgA, IgG, and antiendomisyum IgA) in patients with reflux esophagitis and to detect the relationship between these two gastrointestinal pathologies.

MATERIALS AND METHODS

This study was performed prospectively in Gastroenterology Department of Gulhane Military Medical Academy between January 2003 and January 2004. Sixty-eight adult reflux esophagitis patients (20 women and 48 men, median age 41 years, range 20-77) were enrolled in this study (Table 1). The diagnostic work-up included an accurate medical history with gastrointestinal symptoms (heart burn, abdominal pain, regurgitation, dysphagia, odynophagia, pulmonary symptoms, diarrhea, meteorism), routine laboratory measurements, the detection of antibodies against gliadin (IgA and IgG) and endomysium, and an upper endoscopy with postbulbar biopsy (Table 2). Upper gastrointestinal endoscopy was performed in the standard way, after a 6-h fast. The severity of esophagitis was assessed according to the Los Angeles Criteria[18].

Forty people (12 women and 28 men, median age 38 years, range 20-68) formed the control group for symptoms related with gastrointestinal system. The control groups comprised patients suffering from dyspepsia and no evidence of gastro-oesophageal reflux disease. The other exclusion criteria were age < 20 or > 80 years and use of any drugs. CD was eliminated by small-intestinal biopsy in all controls. There was no statistical difference of the gender between the two groups.

Small intestinal biopsy specimens were taken from each patient, and the diagnosis of celiac disease was made based on the findings of total or subtotal small intestinal mucosal villous atrophy, crypt hyperplasia, and lymphoplasmacellular infiltration[7]. Enzyme-linked immunosorbent assay (ELISA) technique was used for the detection of serum level of antigliadin IgA and IgG. Serum IgA endomysial antibodies were fixed by indirect immunofluorescence.

The aim of this study was explained to all patients and control subjects and informed consent form was obtained from all. The study was applied according to the principles of the Declaration of Helsinki and was approved by the Ethical Committee of Gulhane Military Medical Academy.

Statistical analysis

All of the statistical analyses were performed using statistical software package SPSS 11.5 (SPSS Inc., Chicago, IL, USA). The results were shown as the median (min-max). Odds ratios and their 95% confidence intervals were calculated, also. Relationships between the controls and patients were investigated with Chi-square test. *P* values less than or equal to 0.05 were considered as statistically significant.

Table 1 Demographic data of patients and controls

Demographic data	Patients	Controls
Gender (M/F)	20/48	12/28
Median age (min-max)	41 (20-77)	38 (20-68)
Esophagitis		
Grade A	80.90%	-
Grade B	14.70%	-
Grade C	4.40%	-
Grade D	-	-

Table 2 Esophageal symptoms in patients with reflux disease (*n* = 68)

Symptoms	*n* (%)
Heartburn	48 (70.6)
Chest pain	40 (58.8)
Regurgitation	48 (70.6)
Bleeding	5 (7.4)
Dysphagia	3 (4.4)
Odynophagia	2 (3.0)
Pulmonary symptoms	10 (14.7)
Others (diarrhea…)	11 (16.2)

Table 3 Prevalence of positive serologic markers for coeliac disease according to the esophagitis grade (*n* = 68)

Grades	Antigliadin IgA		Antigliadin IgG		Antiendomysium IgA	
	n	%	*n*	%	*n*	%
Grade A (*n* = 55)	4	7.2	3	5.4	-	-
Grade B (*n* = 10)	1	10	2	20	-	-
Grade C (*n* = 3)	1	33.3	2	66.6	-	-

Table 4 Prevalence of positive serologic markers for coeliac disease in control subjects (*n* = 40)

Serologic markers	Control subjects (*n* = 40)	
	n	%
Antigliadin IgA	4	10
Antigliadin IgG	3	7.5
Antiendomysium IgA	-	-

RESULTS

Antigliadin IgA (IgA-AGA) was found positive in 6/68 (8.8%) patients with reflux esophagitis. Four of 6 patients were grade A (4/55, 7.2%), one was grade B (1/10, 10%) and one was grade C (1/3, 33.3%). Seven (7/68, 10.3%) patients had positive antigliadin IgG (IgG-AGA); 3/55 (5.4%) were grade A, 2/10 (20%) grade B, and 2/3 (66.6%) grade C (Table 3). No patient had positive antiendomysium IgA (IgA-EMA) and in addition, there were no patients with both positive IgA-AGA and positive IgG-AGA.

On endoscopy in control cases, the macroscopic appearance of the esophageal mucosa was normal. In control group, it was found that 4 (10%) people had positive IgA-AGA, and 3 (7.5%) people had positive IgG-AGA (Table 4), while none in control group had positive IgA-EMA.

On postbulbar biopsies, no finding was detected

concerning celiac disease. In 3 of 6 patients with positive IgA-AGA, histologically slightly chronic non-specific duodenitis was seen and the others had normal duodenal mucosa. The number of moderate chronic nonspecific duodenitis, slightly chronic nonspecific duodenitis, and normal duodenal mucosa were 2, 2, and 3, respectively, in 7 patients with positive IgG-AGA. All other patients had normal duodenal mucosa on histology.

There was no statistically significant relationship between controls and patients for IgA-AGA ($\chi^2 = 0.041$; $P = 0.839$; OR = 0.871, 0.230-3.294). The similar result was obtained for IgG-AGA ($\chi^2 = 0.234$; $P = 0.629$; OR = 1.415, 0.345-5.813).

DISCUSSION

Gastroesophageal reflux disease (GERD) is a motor disorder involving lower esophageal sphincter (LES) and esophageal peristalsis. The mean basal pressure of the LES and peristaltic waves are significantly lower in patients with GERD. These abnormalities are responsible for an ineffective removal of refluxed contents, longer contact of acid with the esophageal mucosa, and possibly esophagitis[19].

The increased frequency of reflux esophagitis in CD was reported in some studies[13,15]. In our study, CD was not seen in patients suffering from reflux esophagitis and in control group suffering from unspecific upper gastrointestinal symptoms. Epidemiological studies using serological tests with biopsy verification have revealed higher prevalence of 1:300 to 1:500 for CD in most countries[20]. In primary care practice it is not recommended that cases with reflux esophagitis must be searched for CD. Moreover, the diagnosis depending GERD is difficult and invasive procedures are needed, including endoscopy, biopsy and pathology. Investigations available include flexible oesophagoscopy (with biopsy), ambulatory or static pH manometry, and radiological assessment. A perfect method for diagnosing reflux disease does not yet exist. For this reason, finding a specific marker for reflux esophagitis is necessary.

The results of our study are apparently in contrast with those of Iovino *et al* who suggested that celiac patients with steatorrhea present a higher prevalence of esophageal symptoms and a lowered esophageal sphincter pressure compared with celiac patients without steatorrhea and control subjects[13]. Cuomo *et al* found a twofold increase in the prevalence of endoscopic esophagitis in adult patients who had been diagnosed with CD compared with control non-celiac subjects[15]. All patients in our study were investigated in primary-care setting and all of them were reflux esophagitis patients. None of our patients had severe esophagitis. The most important finding was that none of the patients had CD. The apparent discrepancy with our study might be due to the fact that subjects enrolled in those studies had CD.

Recently, Collin *et al* evaluated the occurrence of esophagitis in CD. In this study, 0.9% of patients with esophagitis and 0.6% of those with esophageal reflux symptoms had CD[17]. They interpreted that the association between these two conditions was weak. This supports our findings and makes weak the claims that CD may play a role in the pathogenesis of GERD.

The abnormalities in LES and esophageal peristalsis associated with GERD are the important factors in the presence of reflux esophagitis. Some gastrointestinal hormones appear contributing to these dysfunctions. One of these, plasma enteroglucagon, which decreases LES pressure and delays gastric emptying was significantly higher in CD patients than controls[21,22]. Despite of this finding supporting the association between reflux esophagitis and CD, we believe that it needs further clarification.

It is known that reflux esophagitis can be seen in celiac patients, but reflux esophagitis is not accepted as a basic finding in CD. This review suggests that an association does not exist between CD and reflux esophagitis. We think these two diseases exist independently from each other. The negative results are possibly due to the small sample size. Since the correlation between celiac disease and reflux esophagitis may be very weak, much bigger sample size is needed to support the null hypothesis.

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