Original Article

Clinical and Histological Presentation of *Helicobacter pylori* and Gluten Related Gastroenteropathy

Mohammad Rostami Nejad BS[1], Kamran Rostami MD PhD•[2], Yoshio Yamaoka MD PhD[3], Reza Mashayekhi MD[1], Mahsa Molaei MD[1], Hossein Dabiri PhD[1], David Al Dulaimi MD[4], Dariush Mirsattari MD[1], Homayoun Zojaji MD[1], Mohsen Norouzinia MD[1], Mohammad Reza Zali MD FACG AGAF[1]

Abstract

Background: Celiac disease has been reported to be associated with gastric abnormalities. The aim of this study was to assess the relationship between the prevalence of celiac disease and *Helicobacter pylori* infection in an Iranian population of 250 patients.

Methods: Biopsies were taken from the gastric antrum and duodenum. Morphology and histology were evaluated using the updated Sydney system and modified Marsh criteria, respectively. To simplify the interpretation of gastric lesions we classified gastritis in macroscopic and microscopic stages. Serology for anti-tissue transglutaminase antibody was performed to determine the presence of celiac disease.

Results: Among 250 patients, 232 (93%) had histological evidence of *Helicobacter pylori* infection. Histological abnormalities (Marsh I to IIIc) were present in 24 (10%). Of 24 patients, 20 (83%) with histological abnormalities were infected with *Helicobacter pylori*. Of 250 patients, 25 (10%) had a positive anti-tissue transglutaminase antibody. Of 25 anti-tissue transglutaminase antibody positive patients, 9 (3.6%) had microscopic and macroscopic enteritis (Marsh I to IIIc).

Conclusions: Clinical presentation of celiac disease was not distinguishable from cases infected with *Helicobacter pylori*. Histology, even in patients with positive serology, was non-specific and unhelpful. We found a high prevalence of *Helicobacter pylori* infection and chronic gastritis, but neither was associated with celiac disease, in agreement with studies in Western populations.

Keywords: Celiac disease, *Helicobacter pylori,* macroscopic gastritis, microscopic enteritis, microenteropathy

Introduction

Celiac disease (CD) is frequently associated with abnormalities of gastric histology and gastric function, including gastritis, peptic ulceration and atrophic gastritis.[1–4] Although our knowledge of the pathogenesis of CD is rapidly expanding, the possible role of chronic *Helicobacter pylori* (HP) infection, known to be capable of inducing duodenal ulcers, needs further examination. HP infection could influence the development and evolution of gluten-related enteropathy by modulating inflammatory and immune responses in the small intestine.[4–6]

HP is recognized as a major etiological factor in most patients with non-autoimmune chronic gastritis.[1] HP is also the causative agent in more than 90% of patients with peptic ulcer disease, primary gastric mucosa-associated lymphoid tissue (MALT) lymphoma and gastric cancer.[7,8] Atrophic gastritis is frequently associated with the presence of parietal cell auto-antibodies.[8] In developing countries, the majority of the population is infected with HP, and in Iran more than 90% of the population is reported to be infected with HP.[9–11]

Epidemiological studies have failed to reveal an association between severe gastritis and CD.[4,6] However, previous studies have suggested a close association between CD and HP-related lymphocytic gastritis [12–15] and a causal relationship between HP infection and anemia among patients with CD.[16,17] Recent studies have shown that patients with HP-related gastritis are more likely to have increased numbers of intraepithelial lymphocytes in the duodenal mucosa, and that this can be reversed by the eradication of HP.[18,19] Therefore, more studies are required to clarify the relationship between HP infection and CD.

The purpose of this study was to assess the prevalence of HP infection and CD among Iranian patients receiving diagnostic gastroscopy for dyspeptic symptoms. We investigated the gastroduodenal symptoms, endoscopic and histopathological findings and assessed whether these were related to the presence of HP infection and/or CD.

Authors' affiliations: [1]Research Institute of Gastroenterology and Liver Disease, Shahid Beheshti University, M.C., Tehran, Iran, [2]School of Medicine, University of Birmingham, UK, [3]Department of Medicine-Gastroenterology, Michael E. DeBakey Veterans Affairs Medical Center and Baylor College of Medicine, Houston, Texas 77030, USA, [4]Department of Gastroenterology, Alexandra Hospital, Redditch, UK.
•Corresponding author and reprints: Kamran Rostami MD PhD, School of Medicine, University of Birmingham, UK,
Tel: +44-190-576-3333; E-mail: kamran.rostami@nhs.net
Accepted for publication: 29 September 2010

Materials and Methods

Patients

Between November 2007 and April 2008, 3432 patients aged 15 years or more attended the outpatient Gastroenterology Clinic of Taleghani Hospital, Tehran, Iran. Two hundred and fifty patients (120 male; mean age 36 years, range 16 – 75 years) were recruited in this study. After obtaining written consent, all patients underwent a structured interview including personal information, past medical history, past endoscopic history and gastrointestinal symptoms (such as abdominal pain, constipation, diarrhea, bloating, dyspepsia, nausea and vomiting, weight loss and heartburn), followed by a gastroduodenoscopy to collect gastric and duodenal biopsy specimens. Patients with similar symptoms who had an established diagnosis, such as underlying malignancy, inflammatory bowel disease or pancreatitis, were excluded from the study. The study was approved by the Institutional Ethics Committee of the Research Center for Gastroenterology and Liver Disease, Shaheed Beheshti University M.C.

Histological diagnosis of HP infection and CD

Two biopsy specimens were obtained from the antrum and at least four specimens were obtained from different portions of the duodenum. Biopsy specimens were fixed overnight in buffered formalin, embedded in paraffin, cut to 3 μm thickness and stained with hematoxylin-eosin (H&E) for routine histological evaluation. HP status was evaluated with Giemsa staining. The slides were blindly evaluated by two expert gastrointestinal pathologists.

Macroscopic gastritis

Gastric antral biopsy specimens were evaluated using the five morphological features of the updated Sydney System[20]: chronic inflammation, polymorph nuclear cell (PMN) activity, intestinal metaplasia (IM), glandular atrophy and HP density. Chronic gastritis was divided into "mild," "moderate" and "severe" based on the severity of chronic inflammation. PMN activity, IM and atrophy, when noted in patients, have been mentioned in the Results section. The degree of HP density was determined in all cases, but in the present study we classified it as either positive or negative. To simplify the interpretation of our results gastric lesions were classified as macroscopic (gastritis with normal appearing mucosa) and microscopic or invisible by endoscope (gastritis without normal appearing mucosa).

Duodenal specimens were also stained with H&E. The diagnosis of CD was determined based on the histological findings of increased intra-epithelial lymphocytes, villous atrophy and crypt hyperplasia according to the standard classification proposed by Marsh, [21,22] as modified by Rostami et al.[23]

Diagnosis of CD using serum anti-tissue transglutaminase antibody (tTGA)

Blood samples were obtained on the same day of gastroduodenoscopy, and the serum was stored at -70°C until tested for anti-tTGA levels. Patients who had normal duodenal histology but yielded positive results for tTGA were encouraged to re-perform gastroduodenoscopy and duodenal biopsy in 12 months and the second set of data for these patients were analyzed in this study.

IgA class human anti-tissue transglutaminase (tTG) antibody and total serum IgA values were measured as described previously.[24]

Statistical analysis

Descriptive statistics and frequency tables were used to describe the results. Since the prevalence of HP in GI patients was approximately 80% with regard to 95% confidence and an error of 5%, the sample size calculated 256 cases.

Chi-square test was performed to comparing proportion of binomial variables among groups of patients (with demographic levels). A P value of <0.05 was accepted as statistically significant. All analysis was performed using SPSS software version 13.0 (SPSS Inc. Chicago, Illinois, USA).

Results

Among the 250 patients enrolled in the study, 232 (93%) had histology-based evidence of HP infection. HP-infected patients had various symptoms including abdominal discomfort (80%) and bloating (73%). As expected, most HP-positive patients had macroscopic gastritis (moderate to severe chronic gastritis, 91%), whereas only 6 of 18 (33%) HP-negative patients had moderate or severe chronic gastritis.

Duodenal histology was normal in 164 (66%) patients, while 1 (0.4%) had a hyperplastic polyp, 61 (24%) had duodenitis and 24 (10%) showed histological abnormalities (Marsh I to IIIc). Of the 24 patients with Marsh I-IIIc, 20 (83%) had positive results for HP. Therefore, the prevalence of HP in patients without an abnormality in the small bowel mucosa (94%) was higher than in those patients with Marsh I-IIIc (83%), but this difference was not significant (P=0.06).

Of the 250 patients, 25 (10%) had positive CD serology with detectable tTGA. Of the 250 recruited patients, 5 were IgA deficient and none were positive for IgG tTGA. However, HP was positive only in 20 (80%) of 25 patients with positive tTG. The detailed characteristics of the 25 tTGA positive CD patients are presented in Table 1.

Positive CD serology was associated with microscopic and macroscopic lesions (Marsh I to IIIc) in 9 of the 25 tTGA positive patients (36%; 3 patients with Marsh I, 2 with Marsh II, 1 with Marsh IIIa, 2 with Marsh IIIb and 1 with Marsh IIIc; Table 2). The majority of seropositive cases (16/25) had normal histology. As the sensitivity of the tTGA

Table 1. Characteristics of cases with positive anti-tTGA test.

Subject	Gender Male/ female	Marsh lesions	Age (yr)	*H. pylori*	tTGA level (U/mL)	Gastritis finding	GI Symptoms of CD
Case 1	F	—	27	Positive	44.3	MCG	Abdominal pain , nausea, flatulence
Case 2	M	Marsh II	18	Positive	34.5	ModACG	Abdominal pain, heart burn
Case 3	M	Marsh I	45	Positive	67.2	SACG	Abdominal pain, weight loss, heart burn
Case 4	M	—	25	Positive	111.2	ModCG	Abdominal pain, anorexia, weight loss
Case 5	F	—	68	Positive	53.1	MCG	Bloating
Case 6	F	Marsh I	17	Positive	42.9	ModCG	Abdominal pain, anorexia, weight loss, early satiety, bloating
Case 7	M	—	35	Negative	94.5	MCG	Anorexia, weight loss, nausea
Case 8	M	—	45	Positive	31.2	MCG	Anorexia, weight loss, nausea, bloating
Case 9	M	—	35	Positive	71.8	ModCG	Abdominal pain, heart burn, early satiety, flatulence, bloating
Case 10	F	—	51	Negative	84.3	MCG	Abdominal pain, nausea, heart, early satiety, flatulence, bloating
Case 11	F	Marsh IIIb	24	Positive	42.1	SCG	Abdominal pain, weight loss, heart burn, early satiety, flatulence, bloating
Case 12	F	—	40	Negative	145.6	ModCG	Nausea, heart burn, early satiety, flatulence, bloating
Case 13	F	Marsh I	20	Positive	19.9	ModACG	Abdominal pain, heart burn, early satiety , bloating
Case 14	F	—	25	Negative	25.7	MCG	Anorexia, nausea , heart burn, early satiety, bloating
Case 15	F	Marsh IIIa	29	Positive	93.5	SACG	Abdominal pain, weight loss, heart burn, bloating
Case 16	F	—	47	Positive	67.8	ModCG	Abdominal pain, heart burn, early satiety
Case 17	M	—	30	Positive	194.9	ModCG	Abdominal pain, heart burn, early satiety, flatulence
Case 18	F	—	67	Positive	69.3	SCG	Abdominal pain, anorexia, weight loss
Case 19	F	Marsh II	60	Positive	55.6	ModCG	Abdominal pain
Case 20	F	—	50	Positive	79		Early satiety, flatulence, bloating
Case 21	F	Marsh IIIc	21	Negative	64.7	SACG	Abdominal pain, anorexia, weight loss, nausea, heart burn, early satiety, flatulence
Case 22	M	—	55	Positive	18.4	MCG	Abdominal pain, nausea, early satiety, flatulence
Case 23	M	—	24	Positive	81	MCG	Abdominal pain, anorexia, weight loss
Case 24	F	Marsh IIIb	40	Positive	49.5	MCG	Weight loss, heart burn
Case 25	F	—	43	Positive	69.4	MCG	Abdominal pain, weight loss, heart burn

MCG=mild chronic gastritis; ModCG=moderate chronic gastritis; ModACG=moderate active chronic gastritis; SCG=severe chronic gastritis; SACG=severe active chronic gastritis; tTGA=tissue transglutaminase antibody; M=male; F=female

Table 2. Histological findings and serology for tTGA in 24 cases with enteropathy.

		Macroscopic gastritis							
		Total	**MCG**	**ModCG**	**ModACG**	**SCG**	**SACG**	**tTGA**	**HP**
MicE	Marsh I	11	5	3	1	1	1	3/11	9/11
	Marsh II	4	2	1	1	—	—	2/4	3/4
MacE	Marsh IIIa	2	1	1	—	—	—	1/2	2/2
	Marsh IIIb	6	2	2	—	1	1	2/6	5/6
	Marsh IIIc	1	—	—	—	—	1	1/2	1/1
	Total	24	10	7	2	2	3	9	20

MicE= microscopic enteritis; MacE=macroscopic enteritis; MCG=mild chronic gastritis; ModCG=moderate chronic gastritis; ModACG= moderate chronic active gastritis; SCG=severe chronic gastritis; SACG=severe active chronic gastritis (Active= if PMN infiltration was higher than 1); tTGA=tissue transglutaminase antibody; HP= *H. pylori*

Table 3. Features of gastritis in 9 of the 25 patients with positive CD serology and histology.

Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Severe active chronic	Moderate active chronic	Mild chronic	Severe chronic	Moderate chronic	Moderate active chronic	Severe active chronic	Moderate chronic	Severe active chronic

Table 4. Distribution of HP and CD (serology positive) according to sex in the study population.

Disease	Male	Female	*P*-value
HP	107 (46.1%)	125 (53.9%)	$P<0.05$
CD	11 (44%)	14 (56 %)	$P>0.05$

assay is very high, these patients might have microscopic enteritis [25] and are likely to develop severe enteropathy in the future.[26]

As shown in Table 3, gastric biopsies from the 9 tTGA positive patients showed a broad range of inflammations consistent with macroscopic gastritis (13% severe active chronic gastritis, 25% moderate active chronic gastritis and mild chronic gastritis, and 37% severe chronic gastritis). These data suggest no association between gastritis and severity of mucosal damage in CD.

There was a significant statistical correlation between CD and weight loss ($P<0.05$). However, no statistical significant correlations were seen with other GI symptoms, and no significant statistical correlations were seen between HP and studied GI symptoms. CD and HP were more prevalent in females than males but the difference was statistically significant only for HP (Table 4).

Discussion

Dyspeptic symptoms are frequently associated with HP infection. CD can also be associated with dyspeptic symptoms. In this study, we found no relationship between HP infection and histological abnormalities. Approximately 10% of patients with dyspepsia had positive celiac serology. Positive serology correlated with the degree of mucosal abnormalities as assessed by the modified Marsh score,[20] in keeping with previously published results.[8,25,26] Only 9 of 24 patients with enteropathy had positive CD serology. This suggests that, as in Western populations, mucosal abnormalities such as microscopic enteritis (Marsh I-II) are likely due to a wide variety of conditions including HP infection, viral infections, drug therapy and tropical sprue as well as serology negative CD.[27–29]

Whereas atypical presentation is the predominant form of celiac disease[24,30–32] by increasing the identification of atypical CD, strongly positive tTG antibody titers might be sufficient for CD diagnosis. However, because of the different and complex presentations of CD, duodenal biopsy cannot be avoided as a critical component of diagnosis.[33] In the atypical form there is no correlation between the mode of presentation and the degree of mucosal damages.[24]

Although the prevalence of CD seems to be much higher in these dyspeptic patients compared to general population, our study found no association between HP infection and CD. In addition, there were no relationships between the grade of gastritis and the severity of duodenal mucosal damage in CD, and only 80% (20/25) of cases with positive tTG were positive for HP. Nevertheless, dyspepsia seems an essential symptom in HP, HP gastritis and CD. Clinicians investigating dyspeptic symptoms in patient populations similar to that in our study are likely to have a low threshold to perform the CD screening test. In this study, 10% of cases were shown as positive tTGA, and this prevalence is higher than reported for the general population in many studies.[34–36] For example, the prevalence of CD in healthy blood donors in Iran is 0.6% and this prevalence is five times lower than in this study.[36]

Of 25 serology positive patients, 16 showed normal histology and of the 9 with abnormal histology, only 4 presented gastritis with normal-appearing mucosa. These findings suggest that histology alone fails to diagnose CD in the majority of patients. Celiac disease with classical severe malabsorption and severe mucosal changes, where histology is the gold standard for diagnosis, is still a rare condition. The population with the more common atypical presentation has substantial differences with classical CD. In these atypical cases autoantibodies like tTGAs are very specific, and hence we could expect that >95 – 99% of tTGA positive cases might be gluten sensitive. In contrast, a mild enteropathy is clearly not a specific marker for gluten sensitivity.

In conclusion, upper GI symptoms are very common and are reasonably frequently associated with celiac serology (10%), As celiac disease presents predominantly with atypical symptoms undistinguishable from HP despite the lack of association, and given the high prevalence of gluten sensitivity (10%) in this study, we suggest that duodenal biopsies and pertinent laboratory tests should be performed in patients presenting with upper GI symptoms such as dyspepsia.

Conflicts of interest

There are no conflicts of interest.

Acknowledgments

This study was financially supported by the Research Institute of Gastroenterology and Liver Disease (RIGLD), Shahid Beheshti University, M.C., Tehran, Iran.

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