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Helicobacter pylori and histopathological findings in patients with dyspepsia

Cansel TÜRKAY[1], Mustafa ERBAYRAK[1], Nükhet BAVBEK[2], Sibel YENİDÜNYA[3], Elife ERASLAN[1], Benan KASAPOĞLU[2]

Departments of [1]Gastroenterology, [2]Internal Medicine and [3]Pathalogy, Fatih University, School of Medicine, Ankara

Background/aims: *Although Helicobacter pylori infection has been reported to be more frequent in patients with dyspepsia, whether it should be treated in dyspepsia remains controversial. This study was carried out to compare the histopathological changes in Helicobacter pylori- positive and -negative dyspepsia patients.* ***Methods:*** *A total of 461 patients with Helicobacter pylori-positive dyspepsia seen in our institution were enrolled in the study. The control group was formed from 100 Helicobacter pylori-negative dyspepsia patients. Subjects underwent an upper gastrointestinal endoscopy, and biopsy specimens were taken from the gastric antrum and corpus. All of the cases were evaluated according to the Sydney classification, and the relation of Helicobacter pylori with chronic inflammation, atrophy, intestinal metaplasia, and activity was investigated by two pathologists.* ***Results:*** *Activity, inflammation and intestinal metaplasia were found in 10 (10%), 70 (70%) and 10 (10%) of Helicobacter pylori (-) patients, respectively, and the numbers increased with increasing Helicobacter pylori intensity when compared with Helicobacter pylori (+) patients ($p<0.01$, $p<0.01$ and $p<0.05$, respectively). Atrophy was found in 27 (5.5%) of all cases (in 10 Helicobacter pylori (-) patients and in 17 Helicobacter pylori (+) patients), but no significant relation was found with increasing Helicobacter pylori intensity ($p>0.05$). There was no significant difference between corpus alone or antrum alone Helicobacter pylori (+) and both corpus/antrum (+) patients in regards to the presence of activity, inflammation, intestinal metaplasia, and atrophy ($p>0.05$).* ***Conclusions:*** *Determination of the degree of morphological changes accompanying Helicobacter pylori infection in dyspepsia is important in the follow-up and treatment of patients. As activity, inflammation and intestinal metaplasia increase with increasing Helicobacter pylori intensity in dyspepsia patients, Helicobacter pylori eradication treatment can be recommended in these patients.*

Key words: Dyspepsia, *Helicobacter pylori,* histopathology

Helikobakter pilori ve dispeptik hastalarda histopatolojik bulgular

Amaç: *Helikobakter pilori enfeksiyonu dispepsili hastalarda daha sık bildirilse de dispepside Helikobakter pilori tedavisine gerek olup olmadığı tartışmalıdır. Bu çalışmada Helikobakter pilori pozitif ve negatif olan dispepsili vakalarda histopatolojik verilerin karşılaştırılması amaçlanmıştır.* ***Yöntem:*** *Helikobakter pilori pozitif 461 dispepsili vaka çalışma grubu olarak, Helikobakter pilori negatif 100 dispepsili vaka ise kontrol grubu olarak alınmıştır. Tüm vakalara üst gastrointestinal sistem endoskopisi yapılmış ve gastrik antrum ve korpustan biyopsiler alınmıştır. Tüm biyopsiler Sydney klasifikasyonuna göre değerlendirilmiş ve Helikobakter pilori ile kronik inflamasyon, atrofi ve aktivite 2 farklı patolog tarafından değerlendirilmiştir.* ***Bulgular:*** *Helikobakter pilori pozitif dispeptik şikayetleri olan 461 hasta çalışmaya dahil edildi. Kontrol grubu da Helikobakter pilori negatif 74 kadın ve 26 erkekten oluşmaktaydı. Aktivite, inflamasyon ve intestinal metaplazi sırası ile kontrol grubu hastalarının %10, %70 ve %10'unda tespit edildi ve bu oranlar Helikobakter pilori yoğunluğu arttıça istatistiksel anlamlı olacak şekilde artmaktaydı. Aktivite, inflamasyon ve intestinal metaplazi Helikobakter pilori yoğunluğu arttıkça artmaktaydı fakat atrofi ile Helikobakter pilori arasında herhangi bir ilişki saptanmadı.* ***Sonuç:*** *Sonuç olarak dispepsili hastalarda Helikobakter pilori'ye eşlik eden morfolojik değişikliklerin belirlenmesi hastaların takip ve tedavisinde önemlidir. Aktivite, inflamasyon ve intestinal metaplazinin Helikobakter pilori yoğunluğu ile artması nedeniyle dispepsili hastalara Helikobakter pilori eradikasyonu önerilebilir.*

Anahtar kelimeler: Dispepsi, *Helicobacter pilori,* histopatoloji

Address for correspondence: Cansel TÜRKAY
Department of Gastroenterology, Fatih University, School of Medicine
Ankara, Turkey
Phone: + 90 312 203 51 00
E-mail: canselturkay@gmail.com

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INTRODUCTION

Dyspepsia is chronic and recurrent pain or discomfort centered in the epigastrium. The most common cause of dyspepsia is functional dyspepsia, which is also called idiopathic dyspepsia. Functional dyspepsia is diagnosed when no structural or biochemical explanation for a patient's symptoms is identified after appropriate investigations (1,2). The cause of nonulcer dyspepsia is unclear but is thought to be heterogeneous (3-5).

Helicobacter pylori (*Hp*) infection is the most common bacterial infection worldwide (6), and has a role in the etiology of chronic active gastritis, duodenal and gastric ulcer, gastric cancer, and mucosa-associated lymphoid tissue (MALT)-lymphoma. The bacteria that are ingested penetrate along the gastric mucus layer and begin to multiply by adhering to the epithelial cells lining the gastric mucosa, frequently causing different degrees of inflammation (7). *Hp* infection always exists with inflammation in the stomach and leads to chronic gastritis. It is assumed that the sequence of events in gastric cancer is as follows: chronic gastritis, atrophy, intestinal metaplasia (IM), dysplasia, and carcinoma. It is also known that *Hp* can be involved in the chain of these chronic phenomena.

Although *Hp* infection has been reported to be more frequent in patients with dyspepsia, its relationship with gastric cancer and whether or not it should be treated in dyspepsia are still controversial (8-15). In an effort to resolve these questions, we studied the histopathological changes in *Hp*-positive and -negative dyspepsia patients.

MATERIALS AND METHODS

Subjects

From January 2005 to January 2007, 461 patients with *Hp*-positive dyspepsia seen at the Gastroenterology Outpatient Clinic, Fatih University Medical School Hospital, Ankara, Turkey, were enrolled in the study. The control group was formed from 100 *Hp*-negative dyspepsia patients. Patients were excluded if they had received nonsteroidal anti-inflammatory drugs, bismuth compounds, proton pump inhibitors, oral anticoagulants, or antibiotics known to be active against *Hp* within the previous three months. The diagnosis of dyspepsia was based on Rome II criteria (Rome II: The Functional Gastrointestinal Disorders, 2nd Edition, D. A. Drossman, MD, University of North Carolina, USA).

Endoscopy

Subjects underwent an upper gastrointestinal endoscopy, and biopsy specimens were taken from the gastric antrum and corpus. Endoscopy was performed under sedation with 0.07-0.1 mg/kg of intravenous midazolam. A flexible gastroscope (Olympus Optical Company Ltd., Tokyo, Japan) was used. To determine the status of *Hp* infection, biopsy specimens were taken from the antrum (within 2 cm of the pylorus, 2 for histopathology), and corpus (half-way along the greater curvature, 2 for histopathology).

Histology

Biopsy specimens were placed in formaldehyde solution for histopathologic examination and sent to the laboratory. Tissues were routinely processed, embedded in paraffin and cut into 5-µm sections. All sections were stained with hematoxylin-eosin (HE) plus toluidine O stains. All of the cases were evaluated according to the Sydney classification, and the relation of *Hp* with chronic inflammation, atrophy, IM, and activity was investigated by two pathologists (16) (Table 1).

Statistical Analysis

SPSS 11.5 for Windows was used for statistical analysis. Chi-square and Spearman correlation tests were used, with the level of significance set at $p<0.05$.

Table 1. Updated Sydney system

Histologic Properties	Definition	Grade		
		Mild	Moderate	Severe
Chronic inflammation	Lymphocyte and plasma cell in lamina propria	+	++	+++
Neutrophil activation	Neutrophil infiltration in lamina propria or superficial epithelium	<1/3	1/3-2/3	>2/3
Glandular atrophy	Loss of corpus and antral glands	+	++	+++
Intestinal metaplasia	Intestinal metaplasia in mucosal epithelium	<1/3	1/3-2/3	>2/3
Hp	*Hp* intensity	+	++	+++

RESULTS

Four hundred sixty-one *Hp*-positive dyspepsia patients with a mean age of 47.30±13.5 years (17-80 years) were randomly enrolled in the study. There were 277 women (70.1%) and 118 men (29.9%). *Hp* was found in the antrum alone in 361 (78.3%) cases, while it was found in the corpus alone in 34 (7.4%) cases; the remaining 66 (14.3%) patients were *Hp*-positive in both the antrum and corpus. The control patients consisted of 74 women (74%) and 26 men (26%), with a mean age of 49.76±17.01 years (16-90 years), who were *Hp*-negative. There was no significant difference between the groups with respect to age or gender (p>0.05).

Activity, inflammation and IM were found in 10 (10%), 70 (70%) and 10 (10%) of *Hp* (-) patients, respectively, and the numbers increased with increasing *Hp* intensity when compared with *Hp* (+) patients (p<0.01, p<0.01 and p<0.05 respectively). Atrophy was found in 27 (5.45%) of all cases (in 10 *Hp* (-) patients and in 17 *Hp* (+) patients), but no significant relation was found with increasing *Hp* intensity (p>0.05) (Table 2). There was no significant difference between the corpus alone or antrum alone *Hp* (+) and both corpus/antrum (+) patients with regards to the presence of activity, inflammation, IM, and atrophy (p>0.05).

Among the patients, *Hp* positivity was present in the antrum in 361 patients and in the corpus in 34 patients. When they were compared with control patients, a statistically significant relationship between intensity of *Hp* and the degree of chronic inflammation was determined (p<0.01, x^2=19.05) (Table 3).

Although there was no activation in 90% of *Hp* (-) patients, there was a statistically significant association between increasing *Hp* intensity and the degree of inflammation (p<0.001, x^2=13.65) (Table 3). However, no relationship was found between *Hp* intensity and the degree of activation and atrophy (p>0.05) (Tables 4, 5).

DISCUSSION

Helicobacter pylori plays a major role in the pathogenesis of gastric and duodenal ulcers. The rate of peptic ulcer disease throughout life in *Hp*-infected patients is about 3% in the United States and 25% in Japan (19). Eradication of *Hp* lowers the recurrence of peptic ulcer (20). *Hp* also causes chronic active gastritis, gastric cancer and MALT lymphoma (21-25).

The prevalence of *Hp* infection in adults varies in different countries depending on the social and economic status of the population (26). While the prevalence among the middle-aged population in developing countries is about 80%, it is only 20-50% in developed countries. Although *Hp* infection has been reported to be more frequent in patients with dyspepsia than controls, the role of *Hp* in dyspepsia remains controversial (8). In one study, despite *Hp* eradication, only 9% of patients with dyspepsia have been reported to have a symptomatic improvement (27). Therefore, the role of *Hp* in the pathogenesis of dyspepsia and the possible

Table 2. The relation of *Hp* intensity with activation, atrophy, inflammation and intestinal metaplasia

	***Hp* (-)**	***Hp* (+)**	***Hp* (++)**	***Hp* (+++)**	**p**
Activation (%)	10 (10%)	68 (57.1%)	136 (88.9%)	82 (92.1%)	<0.01
Atrophy (%)	10 (10%)	5 (4.2%)	9 (5.9%)	3 (3.4%)	>0.05
Inflammation (%)	70 (70%)	117 (98.3%)	152 (99.3%)	89 (100%)	<0.01
Intestinal metaplasia (%)	10 (10%)	19 (16%)	6 (3.9%)	15 (16.9%)	<0.05
Total	100	119	153	89	

Table 3. The relation of *Hp* intensity with degree of chronic inflammation (x^2=19.05, p<0.01)

	***Hp* (-)**	***Hp* (+)**	***Hp* (++)**	***Hp* (+++)**	**Total**
No inflammation (%)	30 (30%)	2 (1.7%)	1 (0.7%)	0	33
Mild inflammation (%)	42 (42%)	51 (42.9%)	17 (11.1%)	5 (5.6%)	115
Moderate inflammation (%)	28 (28%)	55 (46.2%)	105 (68.6%)	38 (42.7%)	226
Severe inflammation (%)	0	11 (9.2%)	30 (19.6%)	46 (51.7%)	87
Total	100	119	153	89	461

Table 4. The relation of *Hp* intensity with degree of activation (x^2=13.65, p<0.001)

	***Hp* (-)**	***Hp* (+)**	***Hp* (++)**	***Hp* (+++)**	**Total**
No activation (%)	90 (90%)	51 (42.9%)	17 (11.1%)	7 (7.9%)	165
Mild activation (%)	2 (2%)	41 (34.5%)	55 (35.9%)	15 (16.9%)	113
Moderate activation (%)	8 (8%)	20 (16.8%)	70 (45.8%)	45 (50.6%)	143
Severe activation (%)	0	7 (5.9)	11 (7.2%)	22 (24.7%)	40
Total	100	119	153	89	461

Table 5. The relation of *Hp* intensity with degree of atrophy (p>0.05)

	***Hp* (-)**	***Hp* (+)**	***Hp* (++)**	***Hp* (+++)**	**Total**
No atrophy (%)	90 (90%)	114 (95%)	144 (94.1%)	86 (96.6%)	434
Mild atrophy (%)	8 (8%)	3 (2.5%)	8 (5.2%)	2 (2.2%)	21
Moderate atrophy (%)	2 (2%)	2 (1.7%)	1 (0.7%)	1 (1.1%)	6
Severe atrophy (%)	0	0	0	0	0
Total	100	119	153	89	461

effect of eradication therapy on the outcome of the disease remain to be determined.

The mucosal destructive mechanism of *Hp* is not precisely known. The bacteria destroy the gastric mucus, which is glycoprotein in structure, by forming protease, and cause acid in gastric juice to irritate the mucosa by passing the mucus bicarbonate layer (28-31). *Hp* increases ammonia production in the gastric lumen by its urease activity. Ammonia causes cell destruction by its direct toxic effect and also disintegrates cell permeability and active transport (31,32). In addition, *Hp* secretes cytokines and chemotactic factors, which have a direct cytopathic effect or initiate the inflammation. Although neutrophil infiltration in the lamina propria is generally accepted to be the unanimous finding of *Hp* gastritis, there are conflicting results in studies about *Hp* abundance and the intensity of inflammatory activity. In some studies, no relation between *Hp* and inflammatory activity has been reported (33,34), but in others, a significant relation was reported (35,36). In our study, when *Hp* (+) and (-) dyspepsia patients were compared, inflammation increased with increasing *Hp* intensity.

The response of surface epithelium to *Hp* infection is mucus depletion, desquamation of the epithelium and regenerative change. Loss of the glands in the gastric mucosa is known as atrophy. Corporal atrophy induced by free oxygen radicals released from neutrophils is closely related to the suppression of acid secretion and IM and also increases the risk of gastric carcinoma development (28).

Ohkuma et al. (37) reported a direct relation between *Hp* infection and the degree of gastritis, atrophy and IM. Asaka et al. (38) studied the relation of *Hp* with atrophic gastritis and IM. They found the rate of atrophic gastritis as 82.9% in the *Hp*-infected group and as 9.8% in the non-infected group. Similarly, the rates of IM were 43.1% and 6.2% in the infected and non-infected groups, respectively (37,38). Topal et al. (39) showed that the greater the intensity of *Hp*, the greater the degree of chronic gastritis and atrophy; a statistically significant positive correlation was defined between them. These studies were not done in dyspepsia patients. In our study, in dyspepsia patients, no significant relation was found with increasing *Hp* intensity. The reason might be that atrophy is unfavorable for *Hp* growth; therefore, *Hp* might have decreased gradually, as the bacteria multiply by adhering to the epithelial cells.

As to the distribution of *Hp* and inflammation in the stomach, Genta et al. (40) reported that *Hp* was distributed evenly throughout the stomach. Zhang et al. (41) reported higher rates in the corpus. In our study, 78.3% of patients had *Hp* positivity in the antrum, 7.4% had positivity in the corpus and 14.3% were positive in both the antrum and corpus. As *Hp* infection is frequent in Turkey (with a prevalence of 84.05% in men, 81.6% in women and 82.75% overall) (42), many patients are infected in the childhood period. In our study, adults had *Hp* positivity mostly in the antrum as an indicator of a long-term infection.

In conclusion, determination of the degree of

morphological changes accompanying *Hp* infection in dyspepsia is important in the follow-up and treatment of patients. As activity, inflammation and IM increase with increasing *Hp* intensity in dyspepsia patients, *Hp* eradication treatment can be recommended in these patients. However, these results should be evaluated in prospective studies with larger numbers of patients.

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