Relationship Between Helicobacter Pylori, Atrophic Gastritis, Autoimmunity and Intestinal Metaplasia

HELİCOBACTER PYLORİ İLE ATROFİK GASTRİT, OTOİMMÜNİTE VE İNTESTİNAL METAPLAZİ ARASINDAKİ İLİŞKİ

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Summary

Purpose: We aimed to investigate relationship between Helicobacter pylori (Hp), atrophic gastritis, autoimmune phenomena, and intestinal metaplasia.

Materials and Methods: A total of 73 patients underwent upper gastrointestinal endoscopic examination were included. Five gastric biopsy specimens from each patient were obtained. Sera of these patients were screened for anti-parietal cell antibodies (APCA) using an immunofluorescence technique.

Results: Fifty-six of 73 patients (76.7%) were positive for Hp, and 17 of 73 (23.3%) were negative. Eight of the Hp (+) patients (14.2%) and 3 of the Hp (-) patients (17.6%) were positive for APCA. Atrophic changes were observed in 30 of 73 patients, most in lesser curvature-mid antrum. Twenty of the patients with atrophic changes (66.6%) were Hp (+). Hp positivity was significantly higher in patients with atrophy of the antrum than with the atrophy of the corpus ($p=0.003$, $x^2=7.98$). There was no correlation between age and atrophy. Twenty-nine of the 73 patients were having intestinal metaplasia. Twenty-five of the patients with intestinal metaplasia (86.2%) were Hp (+).

Conclusions: There were no significant relationship between Hp positivity and development of atrophy, APCA positivity and intestinal metaplasia ($p>0.05$). But the relationship between intestinal metaplasia and atrophy was significant. Further investigations are needed to confirm these results.

Key Words: Helicobacter pylori, Atrophic gastritis, Autoimmunity, İntestinal metaplasia

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Özet

Giriş ve Amaç: Çalışmamızda Helicobacter pylori enfeksiyonu ile atrofik gastrit, otoimmünite ve intestinal metaplazi arasındaki ilişkiyi araştırmayı amaçladık.

Materyal ve Metodlar: Klinik olarak endoskopi endikasyonu konan 73 hastaya üst gastrointestinal sistem endoskopisi yapıldı. Her hastanın midesinden beşer biyopsi alındı. Tüm hastalardan alınan serum örnekleri klasik antiparietal hücre antikorları bakımından immünfloresan tekniği ile test edildi.

Sonuçlar: Çalışmaya alınan 73 hastanın 56'sında (%76.7) Helicobacter pylori pozitif, 17'sinde (%23.3) ise negatifti. Helicobacter pylori pozitif hastaların 8'inde (%14.2) ve negatif hastaların 3'ünde (%17.6) APCA pozitif bulundu. 73 hastanın 30'unda belli alanlarda -en sık küçük kurvatur mid-antrum-atrofik değişiklikler vardı. Atrofi gözlenen hastaların 20'sinde (%66.6) Helicobacter pylori pozitif idi. Bölgelere dağılımda, antral atrofide Helicobacter pylori pozitifliği oranı, corpus atrofisindekinden anlamlı olarak daha yüksekti ($p=0.003$; $x^2=7.98$). Yaş ile atrofi arasında istatistiksel olarak anlamlı bir korelasyon yoktu. Yine 73 hastanın 29'unda-en sık incisura angulariste olmak üzere-intestinal metaplazi vardı. İntestinal metaplazililerin 25'inde (%86.2) Helicobacter pylori pozitifti.

Tartışma: Atrofi gelişimi, APCA pozitifliği ve intestinal metaplazi açısından Helicobacter pylori varlığı ile yokluğu arasında istatistiksel olarak anlamlı bir fark yoktu ($p>0.05$). Ancak intestinal metaplazi ile atrofi arasında istatistiksel olarak anlamlı korelasyon vardı. Bu sonuçları doğrulamak için ileri çalışmalara gereksinim vardır.

Anahtar Kelimeler: Helicobacter pylori, Atrofik gastrit, Otoimmünite, İntestinal metaplazi

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However Helicobacter pylori (Hp) was identified nearly a century ago, its relationship with development of gastritis was begun to discuss in 1970s. Hp, although is non-invasive, stimulates the immune system and inflammatory response very strongly.

Hp infection always goes along with inflammation of the stomach and submucosal PMNL infiltration of the stomach is characteristic for Hp infection (1). Atrophic gastritis is characterized by lose of the specialized gastric cells and glands, partly or completely. This loss leads to gradual metaplasic differentiation resulting in intestinal metaplasia. The first type of atrophy is relatively rare, includes mainly the body of the stomach and has not relationship with Hp infection. This type of gastritis named as autoimmune gastritis. The second type of atrophy is localized in the antrum, partly in the body, mainly in the incisura angularis and named as multifocal atrophic gastritis. In a great study, the risk of development of multifocal atrophic gastritis found nine-fold higher in Hp (+) patients (2). Hp infection may result in stimulation of antibody production against to parietal cell canaliculi, and presence of these antibodies may be associated with development of gastric atrophy. Presence of epitopes cross-reacting with both Hp and gastric mucosal cells may suggest immunologic pathogenesis of gastric damage (3). It is known that autoantibodies recognize gastric H^+-K^+ ATPase epitope, and there is a relationship between these antibodies and development of gastritis and gastric atrophy in gastric corpus.

Hp is detected in almost all cases of gastritis and inflammation disappears by the time Hp eradicated. As atrophy develops in much of the gastric mucosa, gastric acid secretion diminishes, resulting in difficulty of colonization and finally spontaneous disappearance of Hp. Gastric atrophy does not develop in all gastritis cases infected with Hp. Development of atrophy is related to host characteristics, and Hp strain (3).

In this study, we aimed to investigate clinical and histological parameters of Hp infection and their relationship with APCA, and development of gastric atrophy and intestinal metaplasia.

Materials and Methods

Seventy-three patients underwent upper gastrointestinal endoscopic examination were included to the study. We performed endoscopic examination to our patients who were suffering from variable dyspeptic symptoms. But there was not any significant medication or digestive disease history among them in the far past.

Gastric biopsies were obtained and evaluated according to "The Updated Sydney Classification System"

The sites of biopsies were as follow:

A1: Lesser curvature of the mid-antrum

A2: Greater curvature of the mid-antrum

IA: Incisura angularis

B1: Lesser curvature of the mid-corpus

B2: Greater curvature of the mid-corpus

Biopsy specimens placed into 10% formaldehyde solution for fixation. After fixation period each specimen embedded into paraffin and 4μm sections obtained. Histopathological examination was performed in sections stained with hematoxylin-eosin, and identification of Hp was evaluated in sections stained with toluidin blue using light microscope. The test for Hp was accepted positive when bacillus was seen in the mucus beside the epithelium at least one of five biopsies.

Four mL venous blood sample were obtained from each patient, and serum samples were studied for detection of APCA (APCA kit by Bio-Systems S.A.) by immunofluorescent technique. The examination was performed by using immunofluorescent microscope.

Statistical analysis was performed using SPSS for Windows 7.5. Chi-square test was used for analyzing the data. Correlation between variables was determined using Spearman's rho test. A p value < 0.05 was considered to be statistically significant.

Results

Forty-seven female (64.4%) and 26 male (35.6%) patients were included to the study. Mean age was 45.4 years for women and 47.2 years for men. Hp positivity detected in 56 of 73 patients (76.7%), and the remainder 17 patients (23.3%) were negative. Thirty-eight of Hp-positive patients (67.8%) were women and 18 were men (32.2%), and mean age was 43.4 and 40.9 respectively. In the control group (Hp-negative group) there were

10 women (58.8%) and 7 men (41.2%), and mean age was 50.4 and 56.2 respectively.

Hp positivity was detected in 33 patients (58%) in A1 site, in 40 patients (71%) in A2 site, in 45 patients (80%) in IA site, in 31 patients (55%) in B1 site, and in 30 patients (53%) in B2 site. APCA was positive in 8 Hp (+) patients (14.2%) and 3 Hp (-) patients (17.6%) (Table 1). There was no significant difference between Hp (+) and Hp (-) patients in means of APCA positivity ($p>0.05$). There was no significant correlation between Hp positivity and APCA (Spearman's R test, $p>0.05$) (Table 2).

Atrophy was detected in 30 of 73 patients (41%). Distribution of atrophic changes detected sites were as follows: 17 patients (31%) in A1, 15 patients (27%) in A2, 11 patients (20%) in IA, 8 patients (14%) in B1, and 4 patients (7%) in B2. Twenty patients with atrophy were Hp-positive (66.6%), and 10 patients were Hp-negative (33.4%) (Table 3). In Hp-positive group, the degree of atrophy was mild in %80 and moderate in %20 of the patients. In Hp-negative group, the degree of atrophy was mild in all the patients .

Distribution of atrophic sites among Hp-positive patients was as follows: 46 sites with atrophy were detected, 14 of 46 (30.4%) in A1, 11 of 46 (23.9%) in A2, 11 (23.9%) in IA, 7 (15.2%) in B1, and 3 (6.5%) in B2 site. Besides 6 of APCA-positive patients were having atrophy at some degree. There was no significant difference between Hp (+) and Hp (-) groups in means of development of atrophy ($p>0.05$). There was no significant correlation between age and development of atrophy ($p>0.05$). Hp positivity was significantly higher in patients with atrophy of the antrum than the patients with atrophy of the corpus ($p=0.003$, $x^2=7.98$). There was no statistically significant correlation between APCA positivity and mucosal atrophy ($p>0.05$) (Table 4).

Intestinal metaplasia was detected in 29 of 73 patients (39.7%). Distribution of the intestinal metaplasia detected sites was as follows: 8 (16.6%) in A1, 10 (20.8%) in A2, 14 (29.1%) in IA, 10 (20.8%) in B1, and 6 (12.5%) in B2 site. Twenty-five of 29 patients with intestinal metaplasia (86.2%) were positive for Hp. Although this seems to be a high ratio, we have to emphasize that Hp positive results were obtained from non-metaplasic areas of the stomach. There was a correlation between intestinal metaplasia and atrophy (Shearman's rho test, $r=0.38$; $p=0.001$) (Table 5).

Table 1. Characteristics of the Hp-positive and Hp-negative Patients

	HP		
SEX	Positive (n)	Negative (n)	Total (n)
Male	18	7	25
Female	38	10	48
Total	56	17	73

n: Number
APCA: Anti-parietal cell antibody

Table 2. Characteristics of the Hp-positive and Hp-negative patients

	HP		
APCA	Positive (n)	Negative (n)	Total (n)
Positive	8	3	11
Negative	48	14	62
Total	56	17	73

Table 3. The relationship between atrophy and Hp

	ATROPHY		
H. pylori	Positive (n)	Negative (n)	Total (n)
Positive	20	36	56
Negative	10	7	17
Total	30	43	73

Table 4. The Relationship Between Atrophy and APCA

	ATROPHY		
APCA	Positive (n)	Negative (n)	Total (n)
Positive	7	4	11
Negative	25	37	62
Total	32	41	73

Table 5. The relationship between atrophy and intestinal metaplasia

	ATROPHY		
IM	Positive (n)	Negative (n)	Total (n)
Positive	20	10	30
Negative	12	31	43
Total	32	41	73

IM: Intestinal metaplasia

Table 6. The relationship between intestinal metaplasia and Hp

	Intestinal metaplasia		
H.pylori	Positive (n)	Negative (n)	Total (n)
Positive	25	31	56
Negative	4	13	17
Total	29	44	73

There was no significant correlation either between age and intestinal metaplasia ($p>0.05$) or between intestinal metaplasia and Hp positivity ($p>0.05$) (Table 6). The relationship between Hp positivity and degree of the inflammation was not significant ($p>0.05$).

Discussion

Relationship between Hp and gastritis is being discussed since 1970s. Although being non-invasive, Hp may strongly stimulate immune and inflammatory response.

Although there seems to be a close relationship between Hp and atrophic gastritis, atrophy does not develop in all infected patients. The risk of atrophic gastritis in the presence of infection is dependent upon the severity of the gastritis. The severity of the gastritis is dependent upon the host characteristics and Hp strain. Hp infection was reported to play a major role in development of atrophy (4), As the extension of gastric atrophy increased, loss of gastric glands and diminished gastric acid secretion may impair bacterial colonization of Hp. In our study, 30 of 73 patients were representing in some regions some degree of atrophy. Twenty of 30 were Hp-positive while 10 of 30 were negative. The degree of atrophy was 'mild' in the most of Hp-positive and Hp-negative patients. Atrophy was most encountered in A1 site (30.4%). Hp positivity was significantly higher in patients with atrophy of the antrum than the patients with atrophy of the corpus ($p=0.003$; $x^2=7.98$). We believe that Hp has a role in development of atrophy of the antrum. According to our results, the presence of Hp has no significant effect on development of atrophy ($p>0.05$).

In elderly population, retrospective studies have shown that no correlation between presence of Hp and atrophy. Nevertheless atrophic gastritis develops as a result of Hp infection rather than physiological aging process (5). According to our results, there was no correlation between age and development atrophy ($p>0.05$).

The mechanism of development of gastric atrophy is not clear yet, and probably is multifactorial. There are some reports emphasizing the relationship between Hp infection and development of autoantibodies against epitopes on canalicular structures within parietal cells (5-10). In some studies, APCA was found positive in 30% of the Hp-positive patients (9,11). In this study, APCA was positive in 14.2% of Hp-positive patients (8/56), and in 17.6% of Hp-negative patients (3/17). There was no significant difference between these two groups in means of APCA positivity (Spearman's rho test, $p>0.005$). In Hp-positive patients, there was no correlation between age and APCA positivity.

In course of chronic gastritis, it may result in development intestinal metaplasia. This is a result of defense mechanism of the gastric epithelium saving itself from the gastric acid. Another interesting observation is that once intestinal metaplasia develops, colonization of Hp becomes impossible. Because Hp can only colonizes in case it penetrates gastric epithelium (12). In a previous study, the APCA positivity was reported higher in patients with intestinal metaplasia (%90) than without metaplasia (%50) in patients who had Hp infection formerly (10). This suggests Hp infection may play a role in production of APCA, and consequently development of chronic persistent gastritis and intestinal metaplasia.

In our study, intestinal metaplasia was detected in 29 of 73 patients. Metaplasia was most encountered in IA region (%29). There was no significant correlation between age and metaplasia ($p>0.05$). Nevertheless, according to our data we could not find a significant correlation between APCA positivity and intestinal metaplasia ($p>0.05$), as it was not between Hp positivity and intestinal metaplasia.

We found a positive correlation between intestinal metaplasia and atrophy in our study (Spearman's rho test, $r=0.38$; $p=0.001$). This result confirms the cascade we mentioned that leading the atrophy to intestinal metaplasia.

Hp found positive in 86.2% of the patients with intestinal metaplasia. But Hp positive results were obtained from non-metaplasic areas of the stomach in our study. We have not enough information about their previous health conditions. The reason why no correlation is found between Hp positivity and intestinal metaplasia may be due to the difficulty of the colonization of Hp in a region metaplasia developed. Perhaps all patients with intestinal metaplasia have had Hp infection previously.

In the light of these various results, we conclude that further investigations are needed to show the relationship between Hp, autoimmune phenomena, and atrophic gastritis.

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