

Is there a relationship between *Helicobacter pylori* and gastric autoimmunity?

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Background/aims: *Helicobacter pylori*-associated corpus atrophy and autoimmune gastric atrophy share similar histopathologic and clinical aspects. In our study, the relation between *Helicobacter pylori* and autoimmune gastritis was investigated. **Methods:** Eighty-two consecutive histologically and serologically *Helicobacter pylori*-positive and 96 *Helicobacter pylori*-negative patients were enrolled in the study. All patients underwent diagnostic upper esophagogastroduodenal endoscopy. Three biopsy specimens from the antrum and corpus greater curvature were obtained for histologic evaluation. Serum samples were collected for detection of anti-parietal cell antibody, anti-*Helicobacter pylori* IgG and vitamin B12. Statistical analyses were determined with Student t-test and chi-square test. Statistical significance was determined with a p-value <0.05. **Results:** Of 82 *Helicobacter pylori*-positive patients, 45 were female and 36 were male, with a mean age 45.1 ± 15.1 . There was no significant difference in age, gender and corpus atrophy between the *Helicobacter pylori*-positive and -negative groups. Eleven *Helicobacter pylori*-positive patients (13.4%) and 14 (14.6%) *Helicobacter pylori*-negative patients were positive for anti-parietal cell antibody; the difference between the two groups was not statistically significant ($p>0.05$). Differences in esophagogastroduodenal endoscopy findings, antrum and corpus inflammation, antrum and corpus atrophy, and vitamin B12 levels were found to be insignificant between parietal cell antibody-positive and -negative groups ($p>0.05$). **Conclusions:** We did not find any relation between *Helicobacter pylori* infection and anti-parietal cell antibody, a marker of autoimmune gastritis. Long-term follow-up of *Helicobacter pylori*-infected patients and also determination of the relation between eradication of *Helicobacter pylori* and autoimmune atrophic gastritis are needed.

Key words: *Helicobacter pylori*, autoantibodies, parietal cells, gastric, gastritis, atrophic, vitamin B12

Helikobakter pilori ile otoimmün gastrit arasında bir ilişki var mıdır?

Amaç: *Helikobakter pilori* ilişkili atrofik gastrit ile klasik otoimmün atrofik gastrit benzer histopatolojik ve klinik bulgular taşımaktadır. Bu çalışmada *Helikobakter pilori* ve otoimmün gastrit arasındaki ilişki araştırılmıştır. **Yöntem:** Histopatolojik ve serolojik olarak *Helikobakter pilori* pozitif ardışık 82 olgu ile histopatolojik ve serolojik olarak *Helikobakter pilori* negatif ardışık 96 olgu çalışmaya dahil edilmiştir. Her hastaya özofagogastroduodenoskopi yapıp gastrik antrum ve korpus büyük krevaturdan histopatolojik inceleme için üçer adet biyopsi alınmıştır. Kandan parietal hücre antikor, *Helikobakter pilori* antikor (Ig G) ve vitamin B12 düzeyleri çalışılmıştır. İstatiksel değerlendirmesinde student t testi ve ki kare testi kullanılmıştır. Testlerde anlamlılık sınırı olarak $p<0,05$ kabul edilmiştir. **Bulgular:** *Helikobakter pilori* pozitif 82 olgunun 46'sı kadın, 36'sı erkek olup yaş ortalaması $45,1 \pm 15,1$ yıl bulunmuştur. *Helikobakter pilori* pozitif vakalar ile kontrol grup arasında yaş, cinsiyet ve korpus atrofi açısından anlamlı bir fark saptanmamıştır. *Helikobakter pilori* pozitif grupta 11 (%13,4) olguda, kontrol grubunda 14 (%14,6) olguda parietal hücre antikor pozitif olup her iki grup arasındaki fark anlamlı bulunmamıştır ($p>0,05$). Parietal hücre antikor pozitif ve negatif gruplar arasında özofagogastroduodenoskopik muayene bulguları, antrum ve korpus inflamasyonu, antrum ve korpus atrofi ve vitamin B12 düzeyleri açısından anlamlı bir fark saptanmamıştır ($p>0,05$). **Sonuç:** *Helikobakter pilori* ile otoimmün gastritin belirteci olan parietal hücre antikoru arasında anlamlı bir ilişki saptanmamıştır. *Helikobakter pilori* enfeksiyonu saptanan hastaların uzun süre takip edildiği ve *Helikobakter pilori* tedavisi ile otoimmün atrofik gastrit arasındaki ilişkinin irdelendiği uzun süreli çalışmalara ihtiyaç vardır.

Anahtar kelimeler: *Helikobakter pilori*, otoantikorlar, parietal hücreler, mide, gastritis, atrofik, vitamin B12.

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INTRODUCTION

Autoimmune gastritis is an autosomal dominant disease seen mostly in Northern Europe. Women are affected three times more than men. Affected people have an increased risk for developing pernicious anemia. Chronic inflammation, leading to mucosal gland atrophy and epithelial metaplasia, correlates with increased serum antibodies to parietal cells and intrinsic factor. This may show an autoimmune origin. In the early stage, focal or diffuse lymphocytic infiltration of oxyntic glands leads eventually to destruction of glands, known as active autoimmune gastritis. In the late stages, metaplastic glands replace oxyntic glands partially or totally. The mucosa thins and may resemble the small intestine. These patients have an increased risk for developing carcinoid tumor and adenocarcinoma. Risk for adenocarcinoma is 3-18 times greater than in the normal population (1,2).

Helicobacter pylori (*Hp*) is a gram-negative bacterium causing persistent infection in nearly 50% of the world population. *Hp* mostly causes asymptomatic gastric infection. Chronic gastritis, peptic ulcer disease, atrophic gastritis, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma are the other spectrum of diseases related with the bacteria (3). *Hp*-related environmental metaplastic atrophic gastritis and autoimmune metaplastic atrophic gastritis demonstrate similar histologic and clinical findings. In some studies, *Hp* prevalence on both pathologic investigation of the gastric mucosa and serology was found low. This suggested that *Hp* was not related with autoimmune gastritis (4-7). Pernicious anemia is more common in countries where *Hp* prevalence is low. This finding also suggests that *Hp* is not related with gastric autoimmunity (4). However, in some studies, it was put forward that in the early phases of autoimmune gastritis, *Hp* infection causes antibodies against parietal cells, and later *Hp* spontaneously disappears with the development of gastric body atrophy and hypoacidity (8,9). A clear relation of *Hp* with gastric autoimmunity is challenging (1). Here, in this case-control study, we aimed to examine the possible role of *Hp* in autoimmune gastritis, and we review the related literature.

MATERIALS AND METHODS

The study was designed as a case-control study. Patients (>18 years) with dyspepsia referring to Başkent University Gastroenterology Department

between December 2004 and April 2005 were enrolled. Eighty-two consecutive histologically and serologically *Hp*-positive and 96 negative control patients were included in the study. Exclusion criteria were use of proton pump inhibitors or antibiotics during the last week and patients with gastric or small bowel surgery. The study was approved by Başkent University, and each patient gave written informed consent. Upper endoscopy was performed in all patients. Three biopsy specimens were taken for each patient from the gastric antrum and body along the greater curvature. Hematoxylin-eosin staining was used for histopathologic investigation according to the Updated Sydney System classification proposed at the International Workshop on the Histopathology of Gastritis (10). All gastric specimens were evaluated for epithelial damage, acute and chronic inflammation and degree of atrophy of the antrum and body under light microscope by two experienced pathologists. Biopsy specimens were also stained with toluidine blue for the presence of *Hp*. Serum samples were taken from all patients shortly before upper endoscopy and collected for serological investigations. Anti-parietal cell antibody was detected by indirect immunofluorescence test using primate stomach with urea pretreatment (EUROIMMUN, Medizinische Labordiagnostika AG, Germany). Positive result was $\geq 1/100$ dilution. Antibodies to *Hp* of the IgG class were determined using a commercial ELISA kit (Immulite, Diagnostic Products Corporation, USA). Vitamin B12 was also determined. Statistical analyses were performed using the Statistical Package for the Social Sciences software program (Version 11.0, SPSS Inc, Chicago, IL, USA). Student *t*-test and chi-square test were used. A *p*-value <0.05 was considered statistically significant.

RESULTS

Forty-six of 82 *Hp*-positive patients were women and 36 were men. The mean age was 45.1 ± 15.1 years. Age and gender were equally distributed between the two groups ($p > 0.05$). Eleven (13.4%) of the *Hp*-positive group and 14 (14.6%) of the control group had anti-parietal cell antibodies. There was no significant statistical difference between the two groups ($p > 0.05$). Seventeen (68%) of 25 anti-parietal cell antibody-positive patients were women and 8 (32%) were men. The mean age was 54.1 ± 15.2 years. Anti-parietal cell antibody-positive patients were older than the negative group ($p = 0.01$) (Table 1).

Table 1. Comparison of age, gender, *H. pylori* status, B12 levels and histological findings of patients with regards to anti-parietal cell antibody status

	Anti-parietal cell antibody-positive (n=25)	Anti-parietal cell antibody-negative (n=153)	P value
Age (year)	54.08 ± 15.14	45.01 ± 16.19	<0.01
Male/Female	2.1 (17/8)	1.2 (86/67)	>0.05
<i>H. pylori</i> -positive patients	11 (44%)	71 (46.4%)	>0.05
Vitamin B12 level (pg/ml)	464.68 ± 273.22	402.98 ± 203.23	>0.05
Acute inflammation of antrum	13 (52.0%)	69 (45.1%)	>0.05
Chronic inflammation of antrum	23 (92.0%)	136 (88.9%)	>0.05
Acute inflammation of corpus	12 (48.0%)	54 (35.3%)	>0.05
Chronic inflammation of corpus	20 (80%)	119 (77.8%)	>0.05
Atrophy of antrum	22 (88.0%)	103 (67.3%)	>0.05
Low	16 (64%)	77 (50.3%)	
Moderate and severe	6 (24%)	26 (17%)	
Atrophy of corpus	4 (16.0%)	23 (15%)	>0.05
Low	2 (8%)	19 (12.4%)	
Moderate and severe	2 (8.0%)	4 (2.6%)	

Upper endoscopic findings of *Hp*-positive patients were as follows: 48 (58.5%) had pangastritis, 13 (15.9%) erosive gastritis, 10 (12.2%) duodenal ulcer, 7 (8.5%) antral gastritis, 2 (2.4%) erosive bulbitis, and 2 (2.4%) gastric ulcer. There was no statistical significance between *Hp*-positive and -negative patients regarding upper endoscopic findings except for duodenal ulcer. Moreover, there was no statistical significance between anti-parietal cell antibody-positive and -negative groups concerning upper endoscopic findings ($p>0.05$).

Differences in antrum and corpus acute and chronic inflammation were statistically significant in the *Hp*-positive group compared to the negative group ($p<0.001$). The two groups were investigated in terms of antrum and corpus atrophy stage (mild, moderate and severe). Only antrum atrophy was found statistically significant in the *Hp*-positive group ($p<0.05$).

No statistically significant difference was determined in acute and chronic inflammation or antrum and corpus atrophy between the anti-parietal cell antibody-positive and -negative groups ($p>0.05$). Mean B12 level was 402.98 ± 203.23 pg/ml in the parietal cell antibody-positive group, and the difference between groups was not statistically significant. Fifty (28.1%) of 178 patients had vitamin B12 level <300 pg/ml, and vitamin B12 level was significantly lower in patients with corpus atrophy (low, mild and severe) than in those without atrophy ($p<0.05$).

DISCUSSION

Autoimmune gastritis is an organ-specific inflammatory disease. In the early stages, most patients have antibodies against parietal cells in the serum and at the gastric level, while in the late stages, severe atrophy and intestinal metaplasia are seen in the gastric corpus. Many environmental factors have been suggested to trigger autoimmunity. However, clinical progression depends on impairment in personal toleration. For an agent to be considered to trigger autoimmunity, it has to provide certain preconditions, like being present in the early phase of disease, being capable of damaging immunotolerance in susceptible persons and being extensive in the population (8). Immunotolerance may be a result of molecular mimicry, antigen secretion or ability of environmental factors to serve as a superagent (11-13). Several studies have been conducted to investigate any possible relation of *Hp* with autoimmune gastritis. In our study, the relation of *Hp* with autoimmune gastritis was investigated.

Eleven (13.4%) *Hp*-positive patients and 14 (14.6%) *Hp*-negative patients had antibody against parietal cells. The mean age of the patients with parietal cell antibody was 54.1 ± 15.2 years, and patients were found statistically significantly older than in the parietal cell antibody-negative group. Like in our study, gastric autoimmunity was found in other studies to increase in conjunction with an increase in age (14). Jassel *et al.* (15) showed that anti-parietal cell antibody and intrin-

sic factor antibody prevalences were 2% in the second decade, whereas the prevalence was 15.9% in the eighth decade.

Corpus atrophy was found in 15.2% of all patients, and there was no significant difference between *Hp*-positive and -negative groups. Annibale et al. (16) found that two-thirds of patients with atrophic gastritis were *Hp*-positive. In this study, *Hp* was detected by serologic tests in 75.3%, whereas 22.6% of patients were *Hp*-positive on histology and had elevated IgG against *Hp*. Histopathologic investigation and rapid urease tests, which are based on histology, do not always yield *Hp* because of scattered or low colonization of bacteria in the mucosa in atrophic gastritis. Serology may be the only means to show active *Hp* infection in atrophic gastritis and histologically negative patients (17,18). In our study, the diagnosis of *Hp* was made utilizing both histologic and serological tests.

Some studies suggest that *Hp* may lead to autoimmune gastritis (8,9,19,20). In one study, *Hp*-positive patients were followed for 32 years, and it was shown that *Hp* disappeared over time as corpus atrophy and anti-parietal cell antibody developed. It was stated that in the early phases of autoimmune gastritis, *Hp* is present in the mucosa, and with the development of atrophy, spontaneous eradication occurs (19). Annibale et al. (20) showed that antibodies against intrinsic factor were lower in the early stages, when *Hp* could be detected by histologic means, than in late stages, when *Hp* can only be detected by serological test. In light of these findings, it was suggested that there was a link between progression of corpus atrophy, *Hp* loss and development of antibody against intrinsic factor. Presotto et al. (8) found that 58% of parietal cell antibody-positive patients had *Hp* infection, whereas 75% of patients with pernicious anemia had atrophic gastritis and 21% had *Hp* infection. These findings showed that with decrease in gastric acid secretion, *Hp* infection also decreases, suggesting that *Hp* plays a role in induction or maintenance of autoimmune gastritis.

In our study, we did not find any significant relation between *Hp* and anti-parietal cell antibody. Similarly, some other studies also found no relation of *Hp* with gastric autoimmunity (5-7). In a study of Okazaki et al. (5), neonatally thymectomized BALB/c mice with autoimmune gastritis were given *Hp* orally. Mice that developed *Hp* infection were shown to have preserved parietal cells and decreased anti-parietal cell antibodies, whereas

parietal cells disappeared in uninfected mice. *Hp* was shown to cause regression in autoimmune gastritis. This was suggested as the reason for the low autoimmune gastritis rate in Japan, where *Hp* prevalence is very high. In another study in Japan, patients with pernicious anemia were examined for *Hp* prevalence, and no statistical difference was found between patient and control groups (4). Dyspeptic patients with and without Sjögren's syndrome were investigated for the presence of *Hp* and antigastric antibodies. *Hp* and antigastric antibodies were found equally prevalent between the two groups (6).

We found anti-parietal antibodies to increase with age, but there was no correlation with atrophy. Autoimmune gastritis results in hypochlorhydria by the loss of parietal cells and pernicious anemia by the inadequate secretion of intrinsic factor (1,2). Although vitamin B12 level was found significantly lower in patients with corpus atrophy in our study, we could not detect any statistically significant difference regarding vitamin B12 level between anti-parietal cell antibody-positive and -negative groups. In our study, the mean age of anti-parietal cell antibody-positive patients was found as 54.1 ± 15.2 years. However, it is known that autoimmune gastritis is seen in the elderly and progresses starting with atrophic gastritis (1,2,8). This may suggest that these patients with anti-parietal cell antibodies are in the early phases and have not yet developed autoimmune gastritis. Similar to our study, Presotto et al. (8) was also unable to find any relation between B12 levels and anti-parietal cell antibodies.

In conclusion, we could not find a significant relation between *Hp* and anti-parietal cell antibody, which is a marker of gastric autoimmunity. To date, no definite relation between *Hp* and gastric autoimmunity has been determined. There are studies suggesting a positive relation and *vice versa*. New studies with long-term follow-up of *Hp*-positive patients and the results of eradication are needed to investigate any possible relation with gastric autoimmunity.

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