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Helicobacter pylori frequency and upper gastrointestinal system endoscopic findings in autoimmune hepatic diseases

Otoimmün karaciğer hastalıklarında *Helicobacter pylori* ve üst gastrointestinal endoskopi bulgularının sıklığı

Elmas KASAP[1], Ufuk DEMİRCİ[2], Tahir BURAN[1], Hakan YÜCEYAR[1]

Departments of [1]Gastroenterology and [2]Internal Medicine, Celal Bayar University School of Medicine, Manisa, Turkey

Background and Aims: *Helicobacter pylori is the main cause of gastric lesions in chronic gastritis, autoimmune gastritis, peptic ulcer disease, and gastric cancer. Autoimmune liver disease is associated with various upper gastrointestinal mucosal lesions, which are not linked to the severity of the disease. The aim of this study was to retrospectively investigate upper gastrointestinal mucosal lesions in relation to the prevalence of Helicobacter pylori infection in autoimmune liver disease.* ***Materials and Methods:*** *This study included 99 patients with autoimmune liver disease and 110 dyspeptic patients as the control group. Endoscopy was performed in all patients, with biopsy specimens taken from the antrum and gastric body for histological examination and Helicobacter pylori detection. Patients were excluded if they had a history of acid suppression therapy, antibiotic or non-steroidal anti-inflammatory drug treatment, or if antrum and gastric body biopsy specimens could not be taken.* ***Results:*** *Helicobacter pylori was detected in 60% of autoimmune hepatitis cases, 57% of primary biliary cirrhosis cases, and 63% of controls. There was no statistically significant difference between the three groups. Abnormal findings during upper gastrointestinal endoscopy were found in 45% of autoimmune hepatitis cases, 52% primary biliary cirrhosis cases, and 43% of dyspeptic controls.* ***Conclusion:*** *Helicobacter pylori was detected in autoimmune liver disease cases at a similar frequency as in the control group. Endoscopic antral gastritis was more prevalent in autoimmune hepatitis than in primary biliary cirrhosis, but autoimmune liver disease was not significantly characterized by more upper gastrointestinal mucosal lesions than in dyspeptic controls.*

Key words: *Autoimmune liver disease, autoimmune hepatitis, primary biliary cirrhosis, Helicobacter pylori, gastric lesions*

Giriş ve Amaç: *Helicobacter pylori birçok gastrik hastalığın nedenidir. Otoimmün karaciğer hastalıklarına diğer hastalıklar ile ilişkisiz olan çeşitli üst gastrointestinal sistem mukozal bulguları eşlik edebilir. Çalışmamızdaki amacımız retrospektif olarak otoimmun karaciğer hastalıklarında üst gastrointestinal endoskopi bulgularını taramak ve Helicobacter pylori ile ilişkisini araştırmaktır.* ***Gereç ve Yöntem:*** *Bu çalışmaya 99 otoimmün karaciğer hastası ve 110 kontrol grubu hastası dahil edilmiştir. Her hastanın antrumdan ve gastrik yüzeyden alınan endoskopik biyopsileri incelenmiş ve Helicobacter pylori varlığı değerlendirilmiştir. Hastalar daha öncesinde asit süpresyon, antibiyotik ya da steroid dışı inflamatuvar baskılayıcı ajan tedavisi almış ise ve veya çeşitli nedenler ile gastrik biyopsi alınmamış ise çalışmaya dahil edilmedi.* ***Bulgular:*** *Helicobacter pylori otoimmün hepatit hastalarında %60, primer biliyer siroz hastalarında %57 ve kontrol grubunda %63 saptandı. Üç grup arasında belirgin bir farklılık yoktu. Patolojik endoskopik bulgular otoimmün hepatit hastalarında %45, primer biliyer siroz hastalarında %52 ve kontrol grubunda %43 saptandı.* ***Sonuç:*** *Helicobacter pylori otoimmün hastalar ile kontrol grubu arasında benzer bulundu. Endoskopik antral gastrit otoimmün hepatit hastalarında yüksek saptansa da otoimmün karaciğer hastalarında dispeptik gruba göre belirgin bir endoskopik bulgu farklılığı saptanmadı.*

Anahtar kelimeler: *Otoimmün karaciğer hastalığı, otoimmün hepatit, primer biliyer siroz, Helicobacter pylori, gastrik lezyon*

INTRODUCTION

Immune system dysregulation causes the clinical manifestations seen in autoimmune disorders. While there are several underlying causes, the most common are bacterial and viral infections, particularly in individuals with a susceptible genetic disposition. Environmental factors and infections can also contribute to the clinical manifestations (1). Autoimmune hepatic diseases include autoimmune hepatitis (AH), primary biliary cirrhosis (PBC), and primary sclerosing cholangitis. These diseases are all associated with intestinal inflammation, although several other autoimmune diseases often coexist (2).

The role of *Helicobacter pylori* (*H. pylori*) in non-hepatic autoimmune disorders has been clearly demonstrated to involve immune system dysregulation (e.g., immune thrombocytopenic purpura and atrophic gastritis) (3). *H. pylori* causes several upper gastrointestinal system pathologies, including gastric ulcers, duodenal ulcers, gastric adenocarcinoma, autoimmune gastritis, and malt lymphoma. The role of *H. pylori* in these disorders has been the subject of many studies (4). The seroprevalence of *H. pylori* is significantly higher in autoimmune disorders such as Graves's disease and Hashimoto's disease than in control groups, with detection of the CagA antigen in most patients positive for *H. pylori* (5). Although previous studies have investigated the prevalence of *H. pylori* in autoimmune hepatic diseases, its prevalence in the upper gastrointestinal system has not been previously investigated

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Correspondence: Ufuk DEMİRCİ
Department of Gastroenterology, Celal Bayar University School of Medicine, 45100, Yunusemre, Manisa, Turkey
E-mail: ufukdemirci3232@gmail.com
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(6). Therefore, in this study, we aimed to determine the prevalence of *H. pylori* in gastrointestinal pathologies resulting from autoimmune hepatic diseases in comparison to controls with functional dyspepsia.

MATERIAL and METHODS

Our retrospective study included 99 patients diagnosed with autoimmune hepatic disease based on liver biopsy or laboratory measurement (antinuclear antibody, anti-mitochondrial antibody, anti-smooth muscle cell antibody or anti-liver kidney antibody) who presented at the Gastroenterology Clinic of Celal Bayar University between 2013 and 2015. Patients were excluded from the study if (i) an upper gastrointestinal endoscopy could not be performed; (ii) they refused a biopsy; (iii) biopsies from the antrum and corpus areas could not be taken with an endoscopy; (iv) they had received acid suppression treatment during the biopsy procedure; (v) they had received *H. pylori* eradication therapy previously; or (vi) they had received antibiotics or non-steroidal anti-inflammatory treatment during the endoscopy. Additionally, this study included 110 functional dyspepsia patients as the control group, diagnosed based on Roma III criteria (Table 1) (7).

Ethics board approval for the study (dated March 23, 2015: no. 144) was received from the Clinical Trials Assessment Committee of the Medical Faculty of Celal Bayar University.

Statistical measurements were performed using the Statistical Package for the Social Sciences (SPSS) 15.0 software. Analyses were performed using chi-square and Student's t-tests. Statistical significance was set at $P < 0.05$.

RESULTS

Of the 99 patients in the autoimmune hepatic disease group, 71 had AH and 28 had PBC. The AH patients, PBC patients and control subjects had mean ages of 51.2±10.2 years, 49.1±11.3 years, and 53.4±9.8 years, respectively. No significant difference was noted between the autoimmune hepatic disease and control groups with respect to gender (Table 2). The AH, PBC, and control groups did not differ significantly for *H. pylori* positivity, with *H. pylori* detected in 60%, 57%, and 63% of subjects, respectively (Table 2).

Pathology was determined based on upper gastrointestinal endoscopy in 45% of patients with AH, 52% of patients with PBCs and 43% of the controls, with no statistically significant difference between the groups. Endoscopic pathologies included oesophagitis, endoscopic antral and pangastritis, gastric ulcers, bulbar ulcers, and oesophageal varices. The prevalence of endoscopic antral gastritis was higher in AH patients than in PBC patients ($P < 0.06$). Oesophageal varices had a greater prevalence in AH and PBC patients than in control group ($P < 0.07$–0.012) (Table 3).

Table 1. Functional dyspepsia diagnostic criteria

Functional Dyspepsia Diagnostic Criteria (Rome III)
1) Presence of one or more of the following symptoms is required (in the last 3 months)
Additionally, symptom or symptoms should have started 6 months previously
•Epigastric pain
•Epigastric burning
•Postprandial fullness
•Easy satiety
2) Absence of an organic disease to explain the symptoms (includes gastroscopic examination)

Table 2. Patient and control group characteristics and *H. Pylori* assessment

	***Helicobacter Pylori* Frequency in Autoimmune Hepatic Disease**					
	Autoimmune Hepatitis (1)	**Primary Biliary Cirrhosis (2)**	**Dyspepsia (3)**	**p (1-2)**	**p (1-3)**	**p (2-3)**
Age (years)	51.2±10.2	49.1±11.3	53.4±9.8	NA	NA	NA
Male	42 (59%)	17 (61%)	64 (58%)	NA	NA	NA
Female	29 (41%)	11 (39%)	46 (42%)	NA	NA	NA
***H. Pylori* (+)**	43 (60%)	16 (57%)	70 (63%)	NA	NA	NA
***H. Pylori* (-)**	28 (40%)	12 (43%)	40 (37%)	NA	NA	NA

Table 3. Endoscopic assessment of patient and control groups

Endoscopic Findings in Autoimmune Hepatic Disease						
	Autoimmune Hepatitis (1)	Primary Biliary Cirrhosis (2)	Dyspepsia (3)	p (1-2)	p (1-3)	p (2-3)
Normal	32 (45%)	13 (48%)	63 (57%)	NA	NA	NA
Esophagitis	1 (2%)	2 (6%)	5 (4%)	NA	NA	NA
Endoscopic antral gastritis	22 (30%)	4 (14%)	20 (19%)	0.06	NA	NA
Endoscopy pangastritis	11 (14%)	5 (17%)	16 (16%)	NA	NA	NA
Gastric Ulcer	1 (2%)	2 (6%)	4 (3%)	NA	NA	NA
Bulbar Ulcer	0 (0%)	1 (3%)	1 (1%)	NA	NA	NA
Oesophageal varices	4 (7%)	2 (6%)	0	NA	0.07	0.012

DISCUSSION

When the etiopathogenesss of autoimmune disorders are examineds it often appears that such disorders have multiple causes, with the principle cause being unclear. Although it is believed that an underlying background of genetic susceptibility is often involved, these disorders also have a shared pathogenesis involving the loss of self-tolerance. The coexistence of autoimmune diseases that have common etiopathogenetic features is often expected (1,3).

AH, PBC, and primary sclerosing cholangitis all represent autoimmune hepatic diseases. Intestinal inflammation frequently accompanies these conditions. AH and primary sclerosing cholangitis are often observed along with inflammatory bowel diseases and patients with PBC often have celiac disease. T helper 17 and memory lymphocytes are frequently blamed for this comorbidity, supporting the notion of coexisting autoimmune disorders (2).

It is believed that several triggers lead to the loss of self-tolerance in patients, a principal example being environmental factors such as bacterial or viral infections (6). Infections in individuals who have genetic susceptibility can trigger several mechanisms, including molecular similarity, epitope spread, polyclonal activation, immune complex formation, MHC-II activation in non-immune cells, proinflammatory cytokine releases and direct inflammatory damage, which can all contribute to the development of autoimmune diseases (6,8).

H. pylori infection has been studied for 30 years. Although found in many regions of the world, it is believed that stomach-dwelling H. pylori first infected people during the migration from East Africa 58,000 years ago (9). More than half of the worldwide population carries *H. pylori*. Based on data from the TURHEP study, a recent urea breath test study and the largest study performed in Turkey to date, the prevalence of *H. pylori* in Turkish adults is 82.5% (10).

No relationship has been established linking AH and *H. pylori* prevalence and previous evidence regarding a possible link between PBC and *H. pylori* was found to be subject to variation (6). In a retrospective analysis by Shapira et al. of 69 patients with PBC, the frequency of *H. pylori* positivity was significantly higher than that of the control group (51% in patients with PBC and 31% in the control group) (11). Ram et al also found a similar anti-HP antibody ratio in patients with autoimmune diseases. 54.4% of 68 patients with PBC were positive for anti-HP antibodies (versus 38.9% in the control group) (12). On the other hand, an analysis of 149 patients with PBC found similar seroprevalence rates between the patient and control groups (13). In a meta-analysis of 21 studies on cirrhosis, *H. Pylori* prevalence in cirrhotic patients in Europe was 88.9%, while it was much less in Asia (31.8%). In the same study, according to data on Europeans when compared to Asians, *H. pylori* prevalence was significantly higher than that of the control group. Differences between these studies may be due to the use of different methods or a significantly higher *H. Pylori* prevalence in patients versus control groups in some studies (14). We found *H. Pylori*-positive rates of 60%, 57%, and 63% in patients with AH, PBC, and functional dyspepsia, respectively, with no statistically significant difference between the three groups. The lower *H. pylori* prevalence seen in our data compared to that seen in the previously mentioned community-based study may be attributed to the hypothesis that autoimmune hepatic diseases may reduce *H. pylori* prevalence via gastric acid levels. Moreover, gastric acid levels may be affected by currently unexplained mechanisms resulting from immune processes. It has been shown that gastrin levels may decline because of pentagastrin stimulation; thus, gastric acid levels may be low in patients with portal fibrosis or portal hypertension associated with hepatic cirrhosis (15). It has also been suggested that peptic ulcer occurrence in liver diseases is associated

with other reasons because of low *H. pylori* prevalence in this population compared with the overall population (16).

According to previous studies, the prevalence of peptic ulcers in cirrhotic patients (5–20%) is higher than that in the general population (2-4%). In some studies, this high prevalence is dedicated to increase of *H. pylori* prevalence. Kim et al found a similar high peptic ulcer prevalence (24.3%) as other studies in 288 cirrhotic patients. However, in this study, we did not find that *H. pylori* played a major role. In a study by Nam et al investigating the effect of *H. pylori* on gastric pH in cirrhotic patients, gastric pH was found to be higher in cirrhotic patients, similar to the results of the study by Kim et al. In that study, most of the cirrhotic patients had hypochloridi. There was no connection between *H. pylori* and blood or gastric NH3 ratio (18). Our data demonstrated no significant differences compared with the control group when peptic ulcer frequency (2–6%) was examined in patients with autoimmune disorders.

With a high worldwide prevalence, *H. pylori* is known to play an important role in several diseases of the gastrointestinal system, including peptic ulcers, non-cardiac stomach cancer, malt lymphoma, and some autoimmune diseases (immune thrombocytopenic purpura, Hashimoto's thyroid, and atrophic gastritis) (3,19,20).

Our data, in support of many previous studies, does not establish a clear relationship between *H. pylori* and autoimmune liver disease. In addition, when compared to control patients with functional dyspepsia, the pathogenesis of the upper gastrointestinal system does not appear to be different. Future studies are needed to elucidate the relationship and etiopathogenesis between autoimmune liver diseases and *H. pylori*.

REFERENCES

1. Hasni S, Ippolito A, Illei GG. Helicobacter pylori and autoimmune diseases. Oral Dis 2011;17:621-7.
2. Trivedi PJ, Adams HD. Mucosal immunity in liver autoimmunity. A comprehensive review. J Autoimmun 2013;46:97-111.
3. Hasni S. Role of Helicobacter pylori infection in autoimmune diseases. Curr Opin Rheumatol 2012;24:429-34.
4. Helicobacter pylori In: Feldman M, Friedman LS and Brandt LJ, Editors. Sleisenger and Fordtran's Gastrointestinal and Liver Diseases, 9 rd ed. 2010; 833-41.
5. Bassi V, Marino G, Iengo A, et al. Autoimmune thyroid diseases and Helicobacter pylori. The correlation is present only in Graves's disease. World J Gastroenterol 2012;18:1093-7.
6. Daniel SS, Koutsoumpa AL, Mytilinaiou MG, et al. Helicobacter pylori and autoimmune disease: Cause or bystander. World J Gastroenterol 2014; 20:613-29.
7. Brun R, Kuo K. Functional dyspepsia. Therap Adv Gastroenterol 2010;3:145-64.
8. Radic M. Role of Helicobacter pylori infection in autoimmune systemic rheumatic disease. World J Gastroenterol 2014;20:12839-46.
9. Linz B, Balloux F, Moodley Y, et al. An African origin for the intimate association between humans and Helicobacter pylori. Nature 2007;445:915-8.
10. Ozaydın N, Turkyilmaz SA, Cali S. Prevalence and risk factors of helicobacter pylori in Turkey: a nationally-representative, cross-sectional, screening with the 13C-Urea breath test. BMC Public Health 2013;13:1215.
11. Shapira Y, Agmon N, Renaudineau Y, et al. Serum markers of infections in patients with primary biliary cirrhosis: evidence of infection burden. Exp Mol Pathol 2012;93:386-90.
12. Ram M, Barzilai O, Shapira Y, et al. Helicobacter pylori serology in autoimmune diseases - fact or fiction? Clin Chem Lab Med 2013;51:1075-82.
13. Durazzo M, Rosina F, Premoli A, et al. Lack of association between seroprevalence of Helicobacter pylori infection and primary biliary cirrhosis. World J Gastroenterol 2004;10:3179-81.
14. Feng H1, Zhou X, Zhang G. Association between cirrhosis and Helicobacter pylori infection: a meta-analysis. Eur J Gastroenterol Hepatol 2014;26:1309-19.
15. Kitano S, Dolgor B. Does portal hypertension contribute to the pathogenesis of gastric ulcer associated with liver cirrhosis? Journal of Gastroenterology 2000;35:79-86.
16. Kim DJ, Kim HY, Kim SJ, et al. Helicobacter pylori infection and peptic ulcer disease in patients with liver cirrhosis. Korean J Intern Med 2008;23:16-21..
17. Calvet X, Navarro M, Gil M, et al. Epidemiology of peptic ulcer disease in cirrhotic patients: role of Helicobacter pylori infection. Am J Gastroenterol 1998;93:2501-7.
18. Nam YJ, Kim SJ, Shin WC, et al. Gastric pH and Helicobacter pylori infection in patients with liver cirrhosis. Korean J Hepatol 2004;10:216-22.
19. Bulajic M, Panic N, Löhr JM. Helicobacter pylori and pancreatic diseases. World J Gastrointest Pathophysiol 2014;5:380-3.
20. Aghili R, Jafarzadeh F, Ghorbani R, et al. The association of Helicobacter pylori infection with Hashimoto's thyroiditis. Acta Medica Iranica 2013;51:293-6.