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Helicobacter Pylori Relationship in Cases of Coexistence of Gastritis and Gallbladder Disease

Ramazan Uçak[1], Özlem Eryılmaz[1], Ömer Faruk Dilbaz[1], Cemal Kaya[2], Banu Yılmaz Özgüven[3], Emir Çapkınoğlu[4], Fevziye Kabukçuoğlu[1]

[1]Department of Pathology, Health Sciences University, Seyrantepe Hamidiye Etfal Training and Research Hospital, Istanbul, Turkey

[2]Department of General Surgery, Health Sciences University, Seyrantepe Hamidiye Etfal Training and Research Hospital, Istanbul, Turkey

[3]Department of Pathology, Health Sciences University, Cam-Sakura Training and Research Hospital, Istanbul, Turkey

[4]Department of General Surgery, Acibadem Mehmet Ali Aydinlar University, School of Medicine, Istanbul, Turkey

Ramazan UÇAK
Özlem ERYILMAZ
Ömer Faruk DİLBAZ
Cemal KAYA
Banu YILMAZ ÖZGÜVEN
Emir ÇAPKINOĞLU
Fevziye KABUKÇUOĞLU

Correspondence: Emir Çapkınoğlu
Department of General Surgery, Acibadem Mehmet Ali Aydinlar University, School of Medicine, Istanbul, Turkey
Phone: +905326763985
E-mail: emircapkinoglu@gmail.com

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ABSTRACT

Purpose: We aimed to investigate the effect of Helicobacter Pylorii (HP) on the development of gallbladder diseases and cholelithiasis and its relationship with gastritis.

Methods: 282 gastritis cases with follow-up and operated gallbladder material were included in the study. All histomorphological findings, presence of HP and other variables were compared. Active inflammation and presence of HP were examined in the gastritis group. The gallbladder (GB) disease group was evaluated in terms of cholelithiasis, inflammation, cholesterolosis, intestinal and pyloric metaplasia, and the presence of HP.

Results: Gallbladder HP (+) was higher in female patients than in male patients. The presence of HP in the GB was significantly higher in patients with cholelithiasis than patients without cholelithiasis. The incidence of HP in the GB was higher in patients with active gastritis than in patients with inactive gastritis. The presence of HP in the GB was found to be higher in patients with HP on gastric biopsy. HP was found to be less in cases without cholesterolosis in the GB ($p < 0.05$). Acute inflammation in the gallbladder, pyloric and intestinal metaplasia were not associated with the presence of HP. In HP (+) gastritis cases, the rate of stone and HP association in the GB was higher than the patients with HP (-) gastritis ($p < 0.05$). However, the presence or absence of HP in gastritis cases was not found to affect the rate of cholelithiasis or HP status in the group without cholelithiasis.

Conclusion: In our study, correlation with the presence of HP is clearly seen in patients with gastritis and accompanying cholelithiasis. However, there are many parameters affecting the formation of cholelithiasis and other diseases. Therefore, it will be more useful to interpret the effect of HP presence on the GB with prospective studies in series with more cases, using the control group and limiting the number of variables as much as possible.

Keywords: Gastritis, Gallbladder diseases, Helicobacter pylori

Gastrit ve Safra Kesesi hastalığının Birlikte Olduğu Durumların Helicobacter Pylori İlişkisi

ÖZET

Amaç: Bilinen gastrit olgularında, Helicobacter Pylorii'nin (HP) safra kesesi hastalıkları ve kolelitiyazis gelişimi üzerindeki etkisi araştırıldı.

Gereç-Yöntem: Takipli ve opere, safra kesesi materyali olan 282 adet gastrit olgusu çalışmaya dahil edildi. Tüm histomorfolojik bulgular, HP varlığı diğer değişkenler karşılaştırıldı. Gastrit grubunda aktif inflamasyon ve HP varlığı incelendi. Safra kesesi hastalığı grubu, kolelityazis, inflamasyon, kolesterolozis, intestinal ve pilorik metaplazi, HP varlığı açısından değerlendirildi.

Bulgular: Safra kesesi HP (+)'liği, kadın hastalarda erkek hastalara göre daha yüksekti. Safra kesesinde HP varlığı, kolelitiazisli hastalarda, anlamlı olarak daha yüksekti. Safra kesesinde HP görülme sıklığı aktif gastritli hastalarda, inaktif gastritli hastalara göre daha yüksekti. Tüm HP pozitif gastrit olgularında, safra kesesinde HP varlığı daha yüksek bulundu. Safra kesesinde kolesterolozis olmayan olgularda, HP daha az bulundu ($p < 0.05$). Safra kesesinde akut iltihap, pilorik ve intestinal metaplazinin, HP varlığı ile ilişkisi yoktu. HP (+) gastrit olgularında, safra keselerinde taş ve HP birlikteliğinin oranı, HP (-) gastritli olgulardan yüksekti ($p<0.05$). Ancak gastrit olgularındaki HP varlığı ya da yokluğunun safra kesesi taşı olma oranına ya da safra kesesi taşı olmayan gruptaki HP durumuna etkisi bulunamadı.

Sonuç: Çalışmamızda gastrit ve beraberinde safra kesesi taşı olan olgularda, HP varlığı ile korelasyon açıkça görülmektedir. Ancak safra kesesi taşı oluşumunu ve diğer hastalıklarını etkileyen birçok parametre vardır. Bu nedenle, HP varlığının safra kesesindeki etkisi, kontrol grubunu kullanarak ve değişken sayısını mümkün olduğunca sınırlandırarak, daha fazla olgu içeren serilerde, ileriye dönük çalışmalarla yorumlamak daha faydalı olacaktır.

Anahtar Kelimeler: Gastrit, Safra kesesi hastalıkları, Helicobacter pylori

Although, Helicobacter pylori (HP) is especially common in the stomach, it's extra-gastric localization and it's relationship with diseases are evaluated. One of the organs investigated for the HP effect on extra-gastric localization is the gallbladder (GB) and its diseases. In patients with HP positive gastritis, there are few studies evaluating the incidence of GB inflammation and stone, and the presence of HP in the GB, and the results are contradictory. In this study, we aimed to investigate the effect of HP on the development of GB diseases and cholelithiasis and its relationship with gastritis.

In 1982, Marshall (Gastroenterologist) and Warren (Pathologist) isolated gram (-) spiral bacteria in the antral biopsies of gastritis cases. They described it as Campylobacter pyloridis, but it is now called HP. It is a gram negative, small (0.5-3 µm), spiral, curved, motile bacteria with 4-6 flagellas. Reproduces at 37 degrees in micro-aerophilic environment (1).

Although a large variety of helicobacter species have been isolated, the most important pathogen for humans is HP. Today, half of the world's population is considered to be infected with HP (2-4).

HP coexists with various diseases such as gastritis, ulcers and gastric lymphomas. There is a long list of potential effects of HP outside the stomach. It is thought to be associated with neurological, dermatological, hematologic, ocular, cardiovascular, metabolic, allergic, otorhinolaryngiatric, ophthalmologic, endocrinologic disorders, respiratory diseases, pancreatic diseases and hepatobiliary diseases. Epidemiological data are contradictory (2, 4-6).

Chronic cholecystitis and cholelithiasis are a common disease group worldwide. Many etiologic factors play a role in the development of cholelithiasis. Bacterial infection of the GB and bile ducts is recognized as an important risk factor for cholelithiasis (7). Therefore, the effect of HP on GB inflammation and stone formation is being investigated.

Epidemiological evidence that increases the risk of disease associated with HP infection is controversial. Different pathogenic mechanisms such as environmental factors, infectious agents, dietary habits or genetic disposition may be responsible. Most meta-analysis studies show that infection of the GB with Helicobacter pylori is closely associated with an increased risk of chronic cholecystitis and cholelithiasis (7, 8).

Materials and Methods

Resected GB materials and gastric biopsies of 282 cases with known gastritis between 2011 and 2018, were examined retrospectively in our center. These cases were selected from the patients who had close-range gastric biopsy and GB operations as well as patients with gastric and GB complaints at the same time. In the pathological examination of the tissue in biopsy or GB resections, cases with diagnostic clear or correct clinical-pathological records were used.

Patients without clinical follow-up, those who had long intervals between gastritis complaints and treatment and the period of GB operation, and those who had clinical complaints and treatment-free periods between the two diseases and could not establish a clinical connection were excluded from the study.

Preparations of Hematoxylene-Eosine (HE) and Warthin Starry (WS), which belong to all cases, were reexamined separately and blindly by 2 experienced pathologists. All histomorphological findings and HP presence were noted. There were rare cases with contradictions in the data and these were excluded from the study. The patients diagnosed with gastritis and operated for chronic cholecystitis and cholelithiasis were compared for the presence of HP as well as other variables. From the paraffin blocks of gastric biopsy and GB resection materials, 4 micron thick sections were obtained. Staining was performed with HE and WS (DAKO Artisan Warthin-Starry Stain Kit- EN / FR / DE Instructions for Use, Code AR181). Cases were evaluated using routine preparations and histochemical staining method. In the gastritis group, the presence of active inflammation and HP were examined. GB disease group was evaluated for acute / chronic inflammation, cholesterolosis, intestinal and pyloric metaplasia and presence of HP. The presence of stones in the GB was determined from the reports.

Statistical Analysis

SPSS 24.0 packet analysis program, Chi-square and Fisher exact test were used for statistical analysis. Statistical significance level was taken as 0.05 in all tests.

Results

Of the 282 cases, 178 were women. The initial diagnoses of gastric biopsies were active gastritis in 126 cases and inactive gastritis in 156 cases. There were HP (+) gastritis in 178 cases and HP (-) gastritis in 104 cases. There were GB stones in 194 cases. Cholecystitis was detected in all. HP

was detected in 65 (23%) of the 282 GBs. Cholesterolosis (84 cases), acute cholecystitis (22 cases), intestinal metaplasia (10 cases), pyloric metaplasia (6 cases) were detected. 57 of the 84 patients with cholesterolosis had no HP in the GB (68%). GB HP (+) had cholelithiasis in 59 of these 65 cases and active gastritis (47) was noted in the majority of these 65 cases. 126 (45%) of the patients had coexistence of HP (+) gastritis and cholelithiasis, and 50 of them had GB HP (+). In 68 (24%) of the cases, HP (-) gastritis / cholelithiasis coexistence, 9 of them had GB HP (+), while 59 of them had GB HP (-). There were HP (+) gastritis in all of the 6 patients with GB HP (+) without cholelithiasis.

The presence of HP in the GB was not associated with the presence of acute cholecystitis, intestinal metaplasia and pyloric metaplasia (p> 0.05).

GB HP (+) was higher in female patients than in male patients (p <0.05). The presence of HP in the GB was significantly higher in patients with cholelithiasis than patients without cholelithiasis (p <0.05). There was a statistically significant correlation between the absence of cholesterolosis in the GB and the absence of HP. HP was found to be less in cases without cholesterolosis in the GB (p <0.05).

The incidence of HP in the GB was higher in patients with active gastritis than in patients with inactive gastritis (p <0.05). The presence of HP in the GB was found to be higher in patients with HP on gastric biopsy (p <0.05). In other words, HP negativity was also prominent in GB of HP negative gastritis cases. No significant correlation was observed in the presence of cholelithiasis in patients with HP (+) or (-) gastritis (p> 0.05). The findings and statistical values are shown in Tables 1 and 2.

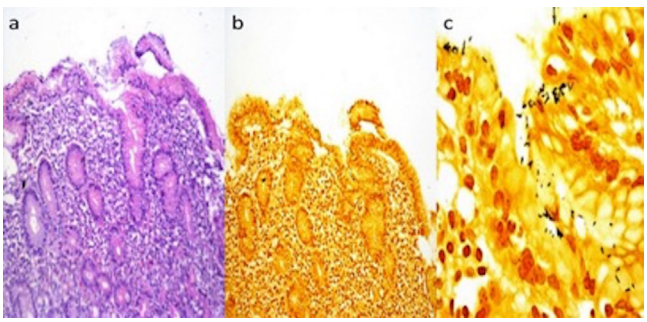

Figure 1: *HP is seen on the epithelial surface of the stomach, HE and WS preparations*
a) HE, X 40 b-c) WS, Histochemistry, X40 and X400

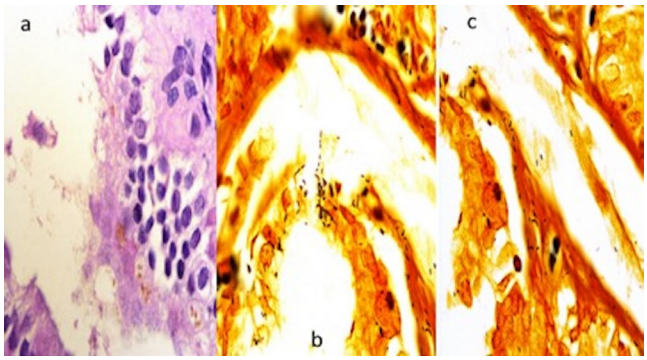

Figure 2: *HP is seen on the epithelial surface of the gallbladder, HE and WS preparations*
a) HE, X 400 b-c) WS, Histochemistry, X 400

Table 1: Comparison of Gallbladder Helicobacter pylorii status with other parameters

		GB HP (+) n (%)	GB HP(-) n (%)	P value
Gender	**Female**	50 (18)	128 (45)	0.008*
	Male	15 (5)	89 (32)	
Cholelithiasis	+	59 (21)	135(48)	0.000*
	-	6 (2)	82 (29)	
Active Cholecystitis	+	6 (2)	16 (6)	0.624*
	-	59 (21)	201 (71)	
Cholesterolosis	+	27 (10)	57 (20)	0.018*
	-	38 (13)	160 (57)	
Intestinal metaplasia	+	3 (1)	7 (2)	0.701#
	-	62 (22)	210 (75)	
Pyloric metaplasia	+	1 (0.3)	5 (0.2)	1.000#
	-	64 (23)	212 (76.5)	
Active gastritis		47 (17)	79 (28)	0.000*
Inactive gastritis		18 (6)	138 (49)	
HP status (Stomach)	+	50 (18)	122 (43)	0.002*
	-	15 (5)	95 (34)	

GB: Gallbladder, HP: Helicobacter pylorii

Table 2: Comparison of the presence of Helicobacter pylorii in the gallbladder with the presence of cholelithiasis in Helicobacter pylorii positive / negative gastritis cases

		HP (+) Gastritis n (%)	HP (-) Gastritis n (%)	P value
Cholelithiasis	+	126 (45)	68 (24)	0.344*
	-	52 (18)	36 (13)	
Cholelithiasis(+), HP status	+	50 (26)	9 (5)	0.000*
	-	76 (39)	59 (30)	
Cholelithiasis(-), HP status	+	6 (7)	0	0.077#
	-	46 (52)	36 (41)	

HP: Helicobacter pylorii

** This test was done with Chi-Square test.*
 # This test was done with the Fisher Exact Test

Discussion

It is being investigated whether HP has effects on many other systems and diseases other than the stomach. Cardiovascular diseases, neurodegenerative diseases, hemathologic disorders, hepatobiliary diseases, autoimmune diseases, respiratory diseases, eye, ear, nose, and throat disorders, dermatological diseases are some of them (2-9).

In many studies and meta-analysis, the possible relationship between HP and hepatobiliary system diseases has been evaluated. Meta-analysis studies report that HP infection correlates with cholelithiasis. In these assessments, the general trend of HP prevalence and cholelithiasis correlation is reported in many countries (7, 8). In addition, similar results have been suggested in Japan, China, Saudi Arabia and Pakistan populations (9-12). In many studies, the presence of HP in the GB was determined and its correlation with cholecystitis and cholelithiasis was shown (12-14). In our study, the correlation between the presence of cholelithiasis and HP was clearly seen. This data suggests us the close association between cholelithiasis and GB HP infection, as in many studies. However, there are investigations suggesting that this correlation is absent or there is insufficient evidence (15-17).

In our cases with HP in the gastric mucosa, there was also a significant correlation between HP infection in the GB and cholelithiasis. This shows similar results with studies involving large numbers of cases and concurrent stomach and GB tissue. As we aimed in our study, many studies also examined the association of GB diseases and HP in patients with gastritis. In many of these studies, the incidence of cholelithiasis and HP is reported to be high in HP-positive patients with gastritis, consistent with our results (18-22) . However, there are studies that suggest no significant correlation (23, 24) . The presence of HP in the GB was more prominent in our patients with active gastritis. This finding is contrary to the declarations (21). As stated in this study, the presence of intestinal metaplasia in the GB did not correlate with the presence of HP in our data. In our cases with pyloric gastric metaplasia in the GB, we did not see a significant difference in terms of HP colonization. However, there is a general approach in terms of HP colonization in GB tissue with areas of gastric metaplasia (25).

Studies questioning the relationship between cholesterolosis and the presence of HP are rare. In a study investigating the presence of HP in the GB of obese patients in the Taiwan population, no correlation was found between all GB diseases (including cholesterolosis) and the presence of HP (26) . Although our data suggest that patients without cholesterolosis have more HP (-), it is clear that more studies are needed in this area. Perhaps, studies that will question the relationship between obesity and the presence of HP indirectly over cholesterolosis can be considered.

As noted in one study (18), we did not see a correlation between acute cholecystitis and the presence of HP. We should note that the number of patients with acute cholecystitis, intestinal and gastric metaplasia was low. In fact, these histopathological changes are less common in the pathological examination of the GB, and the data on the relationship between these changes and HP are very few and contradictory in the literature. However, clearer results will be obtained in studies where the data of multiple and large centers are evaluated together.

As stated in one study (17) , HP infection in the GB was more common in our cases in female gender. In another study (15) , it was suggested that there were no gender differences. However, this correlation may have occurred due to the large number of female patients in our cases. We already know that GB diseases are more common in women.

There are also meta-analysis studies on the correlation of the presence of H. pylori in cirrhosis (27) and biliary tract carcinomas (28). It is also noteworthy that HP infection in the GB is closely associated with changes in tissue such as lymphocytic infiltration, metaplasia and hyperplasia, and there are predictions that this may increase the risk of cancer (29) . In a study conducted in India, studies examining the presence of HP infection and GB diseases in the world are summarized chronologically. In this article, the authors proposed a close association of GB carcinomas, cholelithiasis and HP infection (30) . Therefore, strong evidence that there is a relationship between colelithiasis and HP, which we have determined, can be questioned in terms of the development mechanisms of GB cancers in future studies.

The shortcomings of the study are that it is retrospective and the control group cannot be used. However, since the etiology of GB diseases is multifactorial, a cautious approach to research results is required.

The positive aspects are the large number of cases, the fact that they have clinical follow-ups, the use of routine preparations and histochemical method together for pathological evaluation, which was done blindly by two experienced pathologists.

Conclusion

In our study, the correlation between the presence of HP is clearly seen in patients with gastritis and cholelithiasis. HP infection should be considered not only for stomach diseases but also for GB diseases. Of course, we should not forget many factors that affect the formation of cholelithiasis and GB diseases. Therefore, it may be more useful to comment with prospective studies using the control group and limiting the number of variables as much as possible.

Declarations

Ethical Approval Statement

The study was approved by Sağlık Bilimleri Üniversitesi Şişli Hamidiye Etfal Eğitim ve Araştırma Hastanesi Sağlık Uygulama ve Araştırma Merkezi Klinik Araştırmalar Etik Kurulu (Date: 10.03.2020, Number: 2707).

Authors' contributions

All authors have made substantial contributions to this article being submitted for publications. All authors critically reviewed the manuscript and approved the final form.

Competing interests

No conflict of interest was declared by the authors.

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Availability of data and material

Available.

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