Clinical research

Helicobacter pylori rate and histopathological evaluation in HBeAg-negative chronic hepatitis B virus infection

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Abstract

Introduction: Studies of *Helicobacter pylori* (HP) in liver diseases and hepatitis B virus (HBV) infection have been increasingly discussed. Most studies investigating the relationship between HP and HBV have been conducted in patients with cirrhosis and hepatocellular carcinoma (HCC) and usually involving noninvasive tests. The HP frequency in these patients was higher than in healthy controls. No histopathological evaluation was performed in these studies. We investigated the incidence of HP in HBeAg-negative chronic HBV infection (previously termed "inactive carrier") by using invasive gastric biopsies and carried out histopathological evaluation.
Material and methods: We included 90 treatment-naive inactive hepatitis-B carriers as patients. The control group comprised 107 healthy subjects. Biopsies were obtained from the antrum and corpus and were evaluated histopathologically using the Sydney system of classification for gastritis.
Results: The rate of HP in inactive hepatitis-B carriers was significantly higher than the control group (75.6% vs. 53.3%, respectively; $p = 0.001$). There was no difference in incidence of atrophy, intestinal metaplasia, activity, or inflammation ($p > 0.05$). Peptic ulcer was detected in 11 (12.2%) patients in the HBV group and in 7 (6.5%) patients in the control group ($p = 0.360$). The incidence of HP was higher in patients with HBV DNA ≥ 2000 IU/ml than in patients with HBV DNA < 2000 IU/ml, but this difference was not statistically significant (85% vs. 68%, respectively; $p = 0.062$).
Conclusions: Although the HP rate in inactive hepatitis-B carriers was higher than the control group, there were no intergroup differences with respect to atrophy, intestinal metaplasia, activity, inflammation, and peptic ulcer frequency.

Key words: *Helicobacter pylori*, hepatitis B, endoscopy.

Introduction

Helicobacter pylori (HP) is a gram-negative, microaerophilic, spiral, gastric-resistant bacteria that resides in the mucus lining covering the gastric epithelial cells. The microorganism mainly colonizes in the antrum (prepyloric area) [1]. It is also associated with chronic gastritis, peptic ulcer disease, and gastric cancer. It is a commonly occurring pathogen worldwide, especially in developing countries, and more than 50% of the world's population carry HP in their gastrointestinal tracts [2]. HP may cause local and general proinflammatory cytokines to be released, resulting in extragastric organ disturbance leading to hematological dis-

eases, cardiovascular diseases, and especially liver diseases [3, 4]. Some studies have shown that *H. pylori* infection has a detrimental effect on the progression of liver damage, especially fibrosis [5, 6]. Invasive and noninvasive methods are used for HP detection. One of the gold standard diagnostic methods in HP screening is endoscopic biopsy followed by histopathological examination [7].

In a study, 248 million people worldwide were estimated to be carriers of chronic HBV surface antigen (HBsAg) in 2010 [8]. More than half of these patients have HBe antigen negative chronic HBV infection (previously termed "inactive carriers") and these patients are usually followed up without treatment. Over time, some of these patients may develop active disease that progresses to cirrhosis and hepatocellular carcinoma (HCC) [9].

In previous studies, HP prevalence was found to be high in patients with HBV- or hepatitis C virus (HCV)-related cirrhosis and HCC, and it was emphasized that HP could contribute to disease progression [10, 11]. However, the role of HP in the pathogenesis of HBV-related diseases is still unclear [12]. In most studies investigating the relationship of HP in inactive hepatitis B carriers, noninvasive methods of HP diagnosis are typically used, with no histopathological evaluation [12–15]. Herein, we evaluated the HP frequency in inactive HBV carriers using gastric biopsy and investigated the histopathological differences. We also investigated whether there were differences in the group with high HBV DNA (cut-off: 2000 IU/ml).

Material and methods

Patient collection

Ninety patients with HBV (patient group) and 107 healthy subjects (control group) were included in the study. The patient group consisted of those who applied to our clinic between March 2016 and December 2018. The patients with HBV were HBe-Ag negative, treatment-naïve, non-cirrhotic patients who had normal transaminase levels (at least three times in the past year). All patients and controls had dyspeptic symptoms and were older than 18 years. The following exclusion criteria were applicable to both study groups: receipt of antibiotics for HP within the past 1 year; receipt of proton pump inhibitors (PPIs), antibiotics, and non-steroidal anti-inflammatory drug (NSAID) treatment in the last one month; history of gastric surgery or gastrointestinal bleeding; alcohol consumption; any chronic illness; and cirrhotic findings in abdominal ultrasonography. This study was approved by the local ethics committee of our hospital. The research has been in accordance with the Declaration of Helsinki. Written and verbal informed consent was obtained from all patients before the start of the study.

Endoscopy

Endoscopic evaluation was performed after about 10 h of fasting. A flexible gastroscope (Fujinon or Pentax gastroscope) was used. The esophagus, stomach, duodenal bulb, and the second part of the duodenum were evaluated. At least four biopsies (two each from the antrum and corpus) were taken from all patients in the antrum (especially from the prepyloric area) and the corpus (large and small curvature) regions. Esophagitis, ulcers, gastritis, and duodenitis were defined as endoscopic findings.

Histology

The biopsy samples were quickly transferred to formaldehyde solutions and sent to the pathology laboratory. Tissues were routinely processed, embedded in paraffin and cut into 5–6 µm-thick sections. All sections were stained with PAS Alcian blue (for intestinal metaplasia (IM)) and modified Giemsa (for HP). Histopathological evaluation was made according to the updated Sydney classification [16]. Inflammation, HP, activity, atrophy, and IM were interpreted by a pathologist in a double-blind manner.

Serological, biochemical, and HBV DNA assay

Blood samples were collected after a minimum fasting period of 8 h. Complete blood count, biochemical, and other tests were conducted in our laboratory (Beckman Coulter (AU 5800 and AU 680) and Sysmex (XN 9000)). Hepatitis B serology was determined by commercial ELISA kits (Architect; Abbott Diagnostics Laboratories, Irving, Texas, USA)'. Serum HBV-DNA levels were measured using a COBAS TaqMan 48 (Roche Diagnostics, Germany).

Statistical analysis

Mean and standard deviation were used as descriptive statistics relating to continuous parameters. Student's *t*-test was used to determine intergroup differences. The χ^2 test was used to assess the relationship between two categorical variables. Graphs were used for visual presentation of the differences between the groups. $P < 0.05$ was considered statistically significant.

Results

In this study, we evaluated 197 patients (90 patients and 107 controls) (53.8% female; mean age of patients, 48.5 ±12.4 years; mean age of controls, 47.2 ±12.7 years). The average HBV DNA lev-

Table I. Laboratory and demographic data of inactive hepatitis B carriers (patients) and control subjects

Parameter	Patients (n = 90)	Controls (n = 107)	P-value
Female, n (%)	43 (47.8)	63 (58.9)	0.120
Age [years]	48.5 ±12.4	47.2 ±12.7	0.486
BMI [kg/m^2]	23.2 ±4.7	24.2 ±5.1	0.716
Smoking, n (%)	33 (36.7)	40 (37.4)	0.917
Hb [g/dl]	13.8 ±1.48	14.1 ±4.81	0.616
Creatinine [mg/dl]	0.80 ±0.14	0.86 ±0.81	0.475
ALT [U/l]	23.1 ±10.1	22.1 ±11.6	0.565
GGT [U/l]	24.7 ±15.8	28.8 ±24.5	0.174
Albumin [g/dl]	4.33 ±0.36	4.62 ±3.97	0.482
Calcium [mg/dl]	9.30 ±0.39	10.16 ±0.84	0.333
Total bilirubin [mg/dl]	0.63 ±0.32	0.66 ±0.35	0.568
INR	1.05 ±0.09	1.04 ±0.06	0.081
TSH [mU/l]	3.65 ±1.89	1.76 ±1.57	0.305
HBV DNA [× 10^3 IU/ml]	6.83 ±12.67	–	–

Hb – hemoglobin, ALT – alanine transaminase, BMI – body mass index, GGT – γ-glutamyl transpeptidase, TSH – thyroid stimulating hormone.

el was 6.83 ±12.67 × 10^3 IU/ml (range: 15–51.990 IU/ml). There was no difference between groups in terms of gender, smoking, and body mass index (BMI) (p > 0.05). Hemoglobin, alanine transaminase (ALT), γ-glutamyl transpeptidase (GGT), creatinine, albumin, calcium, total bilirubin, and INR were similar in both groups (p > 0.05) (Table I).

The incidence of HP was significantly higher in the inactive hepatitis B carrier group than the control group (75.6% vs. 53.3%, respectively) (p = 0.001). There were no intergroup differences with respect to incidence of inflammation, activity, atrophy, and intestinal metaplasia (p > 0.05) (Figure 1).

HP positivity was evaluated separately in the antrum and corpus and showed significant differences between the two groups (Table II). In the antrum, but not in the corpus, differences were found with respect to severity of HP (Table II). No intergroup differences were found in either the antrum or the corpus with regard to inflammation, activity, atrophy, and intestinal metaplasia severity (p > 0.05) (Figures 2 and 3).

While 12.2% of endoscopically inactive hepatitis B carriers had gastric or duodenal ulcers, this rate was 6.5% in the control group (p = 0.360) (Table III).

When comparing the HP positive (+) versus negative (–) group in the patient group, the HP (+) group was younger (46.2 ±11 vs. 55.8 ±12.1 years, respectively, p = 0.001). Although HBV DNA levels were higher in the HP (+) group, this was not statistically significant (2.63 ±4.63 vs. 8.19 ±14.10 × 10^3 IU/ml) (p = 0.073). Further, inflammation and activity were higher in the HP (+) group, but there was no difference in other histopathological and endoscopic evaluation parameters (Table IV).

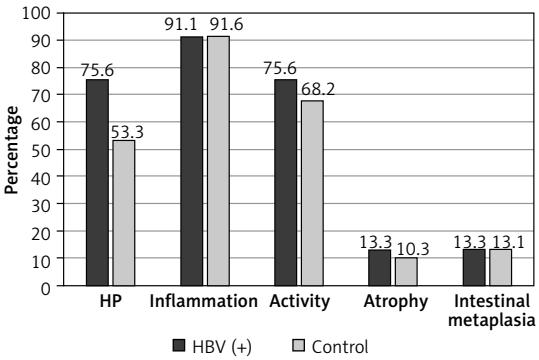

Figure 1. Histopathological evaluation of patients and controls. Only HP frequency showed a significant difference (p = 0.001 for HP, p > 0.05 for others)

We further divided the groups according to the level of HBV DNA. HP was high in the group with HBV DNA ≥ 2,000 IU/ml, but this was not statistically significant (85.0% vs. 68%, respectively) (p = 0.062). Inflammation was significantly higher in the HBV DNA ≥ 2,000 IU/ml group, but there was no difference in other histopathological and endoscopic evaluations (Table V).

Discussion

Helicobacter pylori infection is endemic in the world and is considered to be a group 1 carcinogen

Table II. HP frequency and grade in inactive hepatitis B carriers (patients) and controls

Parameter	Patients (n = 90)	Controls (n = 107)	P-value
HP (–) (antrum (–) and corpus (–), *n* (%)	22 (24.4)	50 (46.7)	0.001
HP (+) (antrum (+) or corpus (+),*n* (%)	68 (75.6)	57 (53.3)	0.001
Antrum HP (+) (+ or ++ or +++), *n* (%)	64 (71.1)	54 (50.5)	0.001
Corpus HP (+) (+ or ++ or +++), *n* (%)	47 (52.2)	44(41.1)	0.015
Antrum HP (–), *n* (%)	26 (28.9)	53 (49.5)	0.012
Antrum HP (+), *n* (%)	25 (27.8)	15 (14.0)	0.027
Antrum HP (++), *n* (%)	32 (35.6)	29 (27.1)	0.043
Antrum HP (+++), *n* (%)	7 (7.8)	10 (9.3)	0.856
Corpus HP (–), *n* (%)	43 (47.8)	63 (58.9)	0.079
Corpus HP (+), *n* (%)	21 (23.3)	12 (11.2)	0.048
Corpus HP (++), *n* (%)	25 (27.8)	28 (26.2)	0.381
Corpus HP (+++), *n* (%)	1 (1.1)	4 (3.7)	0.275

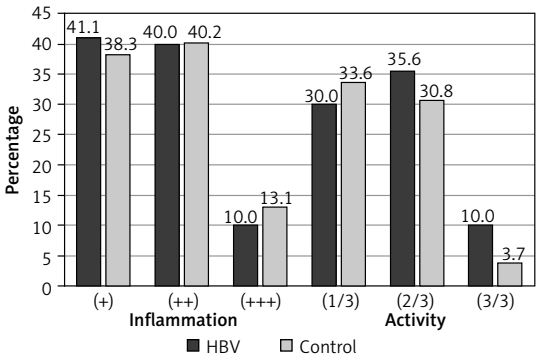

Figure 2. In terms of inflammation and activity, there is no difference between the patient and control groups (p > 0.05)

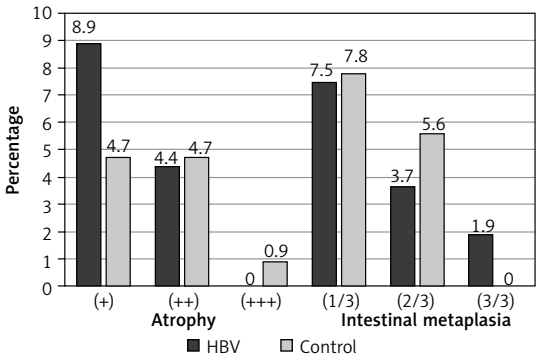

Figure 3. In terms of atrophy and intestinal metaplasia, there is no difference between inactive hepatitis B carriers and control group (p > 0.05)

Table III. Endoscopic findings of patients and controls

Parameter	Patients (n = 90)	Controls (n = 107)	P-value
Peptic ulcer, *n* (%)	11 (12.2)	7 (6.5)	0.360
Gastritis or duodenitis, *n* (%)	78 (86.7)	98 (91.6)	0.593
Esophagitis, *n* (%)	1 (1.1)	2 (1.9)	0.654

for gastric cancer [17]. The relationship between HP and liver diseases has been investigated in previous studies and it has been found that the incidence of HP in HBV-related cirrhosis and HCC patients is higher than in healthy volunteers [12, 18, 19]. *Helicobacter pylori* infection can be diagnosed by various invasive and noninvasive methods. Endoscopic biopsy is one of the gold standard methods. The disadvantage of this method is the heterogeneous distribution of HP in the stomach [12]. Therefore, we addressed this limitation by taking at least two samples from the antrum and corpus.

In our study, we found the HP rate in inactive HBV patients to be significantly higher than the control group (75.6% vs. 53.3% respectively, p = 0.001). Huang and Cui, in their 13-C urea breath study in patients with chronic hepatitis, found that the HP rate was significantly higher than in healthy volunteers (58% vs. 23.3%, respectively; p < 0.05) [12]. In the same study, HP was found to be 79.3% for patients with HBV-related cirrhosis and 68.9% for those with HBV-associated hepatic carcinoma. Fan *et al.* in their serological study compared patients with hepatitis B and

Table IV. Comparison of HP (+) group with HP (-) group in HBV patients

Parameter	HP (–) (*n* = 22)	HP (+) (*n* = 68)	*P*-value
Female, *n* (%)	9 (40.9)	34 (50.0)	0.458
Age [years]	55.8 ±12.1	46.2 ±11.0	0.001
Smoking, *n* (%)	8 (36.4)	25 (36.8)	0.973
HBV DNA [× 10^3 IU/ml]	2.63 ±4.63	8.19 ±14.10	0.073
AFP [µg/l]	3.43 ±2.19	3.67 ±2.66	0.706
Hb [g/dl]	14.1 ±1.55	13.7 ±1.45	0.289
ALT [U/l]	19.5 ±8.8	24.2 ±11.4	0.076
Inflammation (+), *n* (%)	15 (68.2)	67 (98.5)	< 0.001
Activity (+), *n* (%)	4 (18.2)	64 (94.1)	< 0.001
Atrophy (+), *n* (%)	3 (13.6)	9 (13.2)	0.999
Int. Met. (+), *n* (%)	3 (13.6)	9 (13.2)	0.593
Peptic ulcer, *n* (%)	0 (0.0)	11 (16.2)	0.032
Gastritis or duodenitis, *n* (%)	21 (95.5)	57 (83.8)	0.174
Esophagitis, *n* (%)	1 (4.5)	0 (0.0)	–

AFP – α-fetoprotein, Hb – hemoglobin, ALT – alanine transaminase, Int. Met – intestinal metaplasia.

Table V. Assessment according to HBV DNA level (HBV DNA < 2000 IU/ml and HBV DNA ≥ 2000 IU/ml)

Parameter	HBV DNA < 2,000 (*n* = 50)	HBV DNA ≥ 2,000 (*n* = 40)	*P*-value
Female, *n* (%)	25 (50.0)	18 (45.0)	0.637
Age [years]	48.9 ±12.8	48.1 ±12.1	0.760
Smoking, *n* (%)	22 (44.0)	11 (27.5)	0.107
HBV DNA [× 10^3 IU/ml]	0.58 ±0.56	14.65 ±15.91	0.000
AFP [µg/l]	3.26 ±1.75	4.04 ±3.25	0.147
Hb [g/dl]	13.9 ±1.59	13.8 ±1.34	0.854
ALT [U/l]	22.5 ±11.9	23.7 ±9.8	0.621
HP (+), *n* (%)	34 (68.0)	34 (85.0)	0.062
Inflammation (+), *n* (%)	44 (88)	38 (95)	0.013
Activity (+), *n* (%)	34 (68)	34 (85)	0.917
Atrophy (+), *n* (%)	6 (12)	6 (15)	0.762
Int. Met. (+), *n* (%)	5 (10)	7 (17.5)	0.579
Peptic ulcer, *n* (%)	6 (12.0)	5 (12.5)	0.667
Gastritis or duodenitis, *n* (%)	43 (86.0)	35 (87.5)	0.931
Esophagitis, *n* (%)	1 (2.0)	0 (0.0)	–

AFP – α-fetoprotein, Hb – hemoglobin, ALT – alanine transaminase, HP – Helicobacter pylori, Int. Met. – intestinal metaplasia.

healthy controls and found that the former group had a high HP (57.3% vs. 42.3%, respectively, $p < 0.05$) [14]. In another study, the incidence of HP in asymptomatic HBV carriers was similar to the control group (38.67% vs. 35.49%, respectively, $p > 0.05$) [20]. In a meta-analysis conducted in 2016, the rate of HP was 2.44 times in chronic hepatitis B (odds ratio), 4.28-times in HBV-associated cirrhosis, and 6.02-fold higher in HBV-associated HCC as compared to the healthy population

[11]. In a study by Ponzetto *et al.*, the HP-antibody ratio was significantly higher in patients with HBV-related cirrhosis than healthy controls (89% vs. 59%, respectively, $p < 0.05$) [13]. In addition, in a meta-analysis evaluating the relationship between HP and HCV, the rate of HP in HCV patients was 2.93-fold higher than in the control group. In this meta-analysis, HP was found to be high in patients with cirrhosis and HCC due to HCV (odds ratios: 4.48 and 5.45, respectively) [10]. In another study, HP-infected HCV patients were found to have more advanced fibrosis than HCV patients without HP infection [21]. These findings suggest that HP adversely affects the course of hepatotropic viruses. In another study, the HP rate was higher in cirrhosis due to HBV than in cirrhosis due to alcoholism (67.7% vs. 28.6%, respectively) [22]. This suggests that HBV increases the incidence of HP by showing different immunopathology.

The rate of HP in inactive hepatitis B patients was higher than in the control group in our study, but we found no difference in the incidence of atrophy, intestinal metaplasia, activity, inflammation, or peptic ulcers. To our best knowledge, there is no study yet that has evaluated histopathology in patients who are inactive hepatitis B carriers. In a previous study, the ratio of chronic gastritis and glandular metaplasia had been found in cirrhotic patients as follows: 15.6% of patients of Child-Pugh A, 70% of Child-Pugh B, and 100% of Child-Pugh C [23]. In a Turkish study on patients with dyspepsia, atrophy was found in only 5.5% of cases [24]. In our study, the incidence of atrophy and intestinal metaplasia was approximately 13%. This issue wherein only the HP rate is high in patients with inactive hepatitis B, but not other factors such as inflammation, atrophy, and intestinal metaplasia, when compared to the control group, warrants further investigation and discussion.

In our study, the HP rate was higher in the group with HBV DNA ≥ 2,000 IU/ml than the group with HBV DNA < 2,000 IU/ml, but this was not statistically significant (85.0% vs. 68%, respectively) ($p = 0.062$). In Huang's ^{3}C-urea breath test study, HPV was significantly higher in the HBV-DNA ≥ 10^3 copies/ml group than the HBV-DNA < 10^3 copies/ml group [12]. In some studies, no relation was found between HBV DNA levels and HP rate [25, 26].

In conclusion, in this study, we investigated the frequency of HP in inactive hepatitis B carriers, and the rate of HP was higher than in the control group. Inflammation, activity, atrophy, intestinal metaplasia, and ulcer frequency were not different though. While only HP prevalence was investigated in previous studies with inactive hepatitis B patients, no histopathological evaluation was performed. Large-scale studies are needed for validation.

Conflict of interest

The authors declare no conflict of interest.

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