ORIGINAL ARTICLE

Outcome of H. Pylori Infection of Gallbladder Mucosa in Patients of Chronic Cholecystitis

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Abstract

Background: The association between H. pylori and biliary tract disease has been investigated but not clearly demonstrated. Presence of H. pylori in the biliary tree of few individuals has led to the conjecture that it is a cause of gallbladder disease. ***Objectives:*** To study association between chronic cholecystitis and H pylori infection in gallbladder mucosa and compare clinical and histopathological features between H pylori positive and negative chronic cholecystitis patients. ***Material and Methods:*** The study entailed comprised of 50 patients admitted for cholecystectomy. The study was carried out in Postgraduate Department of Surgery, G.M.C. & Hospital, Jammu over a period of one year (1st Nov. 2018 - 31st Oct. 2019). Detailed history and clinical examination were performed with assessment of biochemical, hematological and radiological parameters after obtaining written informed consent. All patients were subjected to urea breath test and H. pylori stool antigen test to detect H. pylori in their gastrointestinal tract pre-operatively. After cholecystectomy and gross examination of specimen, two biopsies each were taken from fundus, body and neck of gallbladder for histopathology and microbiological studies. ***Results:*** Patients undergoing cholecystectomy with colonization of gallbladder mucosa with H. pylori are likely to have a higher frequency of heartburn with higher incidence of thickened gallbladder containing multiple stones and contracted gallbladder on USG and intraoperatively a difficult gallbladder with evidence of features of chronic cholecystitis on histopathology. ***Conclusion:*** The observations noted in this study highlight the need to take appropriate preventive and eradicative measures for H. pylori in the gallbladder.

Key Words

Calcular Cholecystitis, Cholecystectomy, H. pylori

Introduction

Cholecystitis is defined as inflammation of gallbladder. Ninety percent of cases represent calculous cholecystitis and ten percent acalculous cholecystitis (1). About two thirds of patients with gallstone disease present with chronic cholecystitis. Histologically, chronic cholecystitis presents a large range of inflammatory epithelial changes including mononuclear infiltrate, fibrosis, thickening of muscular layer, hyperplasia, dysplasia and metaplasia.

Findings of microbiological studies suggest that bacterial infection in biliary system might play a role. The blocking of the cystic duct leads to thickening of bile, bile stasis, and secondary infection by gut organisms predominantly E. coli and Bacteroides species (2). The association between H. pylori and biliary tract disease has been investigated but not clearly demonstrated. H. pylori, a gram negative and microaerophilic organism, persists in the healthy host in equilibrium, which is disturbed at times,

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leading to acute and chronic gastritis, peptic ulcer disease and two forms of gastric cancer. It could reach the gallbladder directly from the stomach or through the portal circulation. Microorganism resembling H. pylori has been detected in resected gallbladder mucosa of patient with gallstones (3). The organism causes chronic infection by breaking down the mucosal barrier; its urease enzyme converts urea to ammonia which causes injury and potentiates effects of cytotoxins and neutralizes H+ ions of gastric acid (4-6).

Helicobacter pylori can be diagnosed by rapid urease test, demonstration of the bacterium on histology, and positive urea breath test. Molecular tests identify the genes of Helicobacter pylori in the tissue. Immunological evidence of H. pylori infection is provided by presence of H. pylori-specific IgG and IgM antibodies in the blood. Demonstration of H pylori in gallbladder tissue histology varies from 0 % to 28% (7-9). The presence of H. pylori DNA in gallstones was established by polymerase chain reaction (PCR) in several reports (10,11). The positive rate of H. pylori in gallbladder with chronic cholecystitis is reported to be 10% to 20% by culture (12-14). Various researchers have demonstrated the presence of Helicobacter in gallbladder of patients with gallstones and cholecystitis (15-18). However, few studies so far have specifically assessed the characteristics of H. pylori positive cholecystitis.

Material and Methods

The study entailed comprised of 50 patients admitted for cholecystectomy for comparison of clinicopathological features between H. pylori positive and negative patients in gallbladder mucosa admitted in Postgraduate Department of Surgery, G.M.C. & Hospital, Jammu over a period of one year (1st Nov. 2018 - 31st Oct. 2019). The due clearance for the study was obtained as per protocols from Institutional Ethics Committee. Detailed history and clinical examination were performed with assessment of biochemical, hematological and radiological parameters. Written informed consent was obtained from the patients for inclusion in study.

Inclusion Criteria: All patients requiring cholecystectomy for gallstone disease.

Exclusion Criteria: History of hepatobiliary or pancreatic or gastric surgery; already received (<6 weeks) or on standard therapy for H. pylori eradication; immunocompromised patients.

All the patients in pre-operative period were subjected to urea breath test and H. pylori stool antigen test to detect H. pylori in their gastrointestinal tract. In most of the patients (n=48), laparoscopic cholecystectomy was performed. Two patients needed conversion to open cholecystectomy. After gross examination of specimen, two biopsy specimens each were taken from fundus, body and neck of gallbladder before sending specimen for histopathology. Part of specimen was subjected to Urease test and impression smears of mucosa with staining for detection of H. pylori in gall bladder mucosa. A scoring system proposed by Bracia *et al.* (19) was used to assess the histological changes of chronic cholecystitis.

The results were tabulated and statistical analysis done using Student's *t*-test for comparing age and BMI, and Chi-square test and Fischer's exact test to examine the rest of clinicopathological parameters. Significance levels were set at p value <0.05.

Results

The mean age of patients was 42.88 years, ranging from 19 years to 78 years. 37 (74%) patients were female and 13 (26%) were male. Out of the total 50 patients, 11 tested positive for H. pylori in GB mucosa and 39 were negative.

History of heart burn was present in 6 out of 11 (54.5%) H. pylori positive patients and 4 out of 39 (10.3%) H. pylori negative patients. It was statistically significant (p=0.001). There was no statistically significant difference observed between the two groups in terms of history of abdominal pain, biliary colic and anorexia (*Table 1*).

Statistically significant differences in ultrasonography were detected between the two groups, in terms of frequency of presence of multiple stones (81.8%), thickened GB (81.8%) and contracted GB (72.7%) in H. pylori positive patients. These differences have been summarized in *Table 2*.

Special intraoperative findings were seen in all of the 11 (100%) H. pylori positive patients out of which 2 patients had cholecystoduodenal and 1 patient had cholecysto-colonic fistula whereas 20 (51.3%) out of 39 H. pylori negative patients showed special intraoperative findings. It was statistically significant (p=0.003). Most of the H. pylori positive patients had a difficult gallbladder, with dense adhesions.

Stool antigen for H. pylori was positive in 6 out of 11 (54.5%) H. pylori positive patients. It was negative in all H. pylori negative patients (n=39). It was statistically significant (p=0.000).

Urea Breath Test was positive in 2 out of 11 (18.2%) H. pylori positive patients. It was negative in all H. pylori

Table 1: Differences in Clinical Characteristics of Both Groups

Clinical Characteristics	H. Pylori +ve in GB Mucosa	H. Pylori -ve in GB Mucosa	*p* value
1. Number (n)	11 (22%)	39 (78%)	-
2. Age (mean)	44.45	42.44	0.686
3. BMI {kg/m^2} (mean)	24.41	22.95	0.230
4. Gender: Male; Female (% Male)	3;8 (27.3%)	10;29 (25.6%)	0.913
5. History:			
A. Mild Abdominal Pain	9 (81.8%)	26 (66.7%)	0.333
B. Biliary Colic	6 (54.5%)	19 (48.7%)	0.733
C. Loss of Appetite	2 (18.2%)	4 (10.3%)	0.475
D. Heart Burn	6 (54.5%)	4 (10.3%)	0.001

Table 2: Differences in USG Findings of Both Groups

USG Findings	H. Pylori +ve in GB Mucosa	H. Pylori -ve in GB Mucosa	*p* value
1. Gall Stones: Single; Multiple (% Multiple)	2;9 (81.8%)	20;19 (48.7%)	0.05
2. Polypoid Lesion: Single; Multiple (% Single)	2;2 (50%) {n=4}	4:2 (66.7%) {n=6}	0.253
3. GB Wall Thickening	9 (81.8%)	10 (25.6%)	0.001
4. Contracted GB	8 (72.7%)	10 (25.6%)	0.004

Table 3: Histopathological Characteristics of H. Pylori Positive vs Negative Cholecystitis

Characteristics	H. Pylori +ve in GB Mucosa	H. Pylori -ve in GB Mucosa	*p* value
A. Inflammatory Mononuclear Infiltrate	Mild 2 (18.2%) Moderate 6 (54.5%) Severe 3 (27.3%)	Mild 14 (35.9%) Moderate 8 (20.5%) Severe 1 (2.6%)	0.001
B. Degree of Fibrosis	Mild 6 (54.5%) Moderate 3 (27.3%) Severe 2 (18.2%)	Mild 35 (89.7%) Moderate 3 (7.7%) Severe 1 (2.6%)	0.023
C. Thickness of Muscular Layer	Mild 3 (27.3%) Moderate 5 (45.5%) Severe 3 (27.3%)	Mild 34 (87.2%) Moderate 4 (10.3%) Severe 1 (2.6%)	0.000
D. Adipose Tissue Deposition	Mild 7 (63.6%) Moderate 3 (27.3%) Severe 1 (9.1%)	Mild 33 (84.6%) Moderate 5 (12.8%) Severe 1 (2.6%)	0.286
E. Degree of Hyperplasia	Diffuse 8 (72.7%) Focal 3 (27.3%)	Diffuse 4 (10.3%) Focal 35 (89.7%)	0.000
F. Dysplasia	Low Grade 2 (18.2%) High Grade 0	Low Grade 1 (2.6%) High Grade 0	0.054
G. Metaplasia	Pyloric 2 (18.2%) Intestinal 0 Gastric 0	Pyloric 1 (2.6%) Intestinal 0 Gastric 0	0.054

negative patients (n=39). It was statistically significant (p=0.007).

In terms of histopathological changes in GB wall, we found a higher frequency of moderate and severe grade changes in terms of inflammatory infiltrate, fibrosis and muscle layer thickening in H. pylori positive cases, along with a higher frequency of diffuse hyperplasia, which was statistically significant, and has been summarized in *Table 3*. Differences in low-grade dysplasia and metaplasia between the two groups were not statistically significant.

Discussion

In this study, we included 50 patients who underwent laparoscopic or open cholecystectomy for calcular cholecystitis with age ranging from 19 to 78 years. The mean age of study population was 42.88 years. The mean age of H. pylori positive patients was 44.45 years where as those who were H. pylori negative had mean age of 42.44 years, a finding that goes well with those of other authors (20-22). 37 patients (74%) were female and 13 (26%) were male. Thus, females outnumbered males in our study which goes well with other studies (20,23).

History of heart burn was present in 6 out of 11 (54.5%) H. pylori positive patients and 4 out of 39 (10.3%) H. pylori negative patients (p=0.001), whereas no statistically significant difference was seen in history of biliary colic/ abdominal pain and anorexia, which goes well with studies by other authors (17,20,24,25).

Our study showed an increased likelihood of multiple stones (81.8%), thickened gall bladder (81.8%), and contracted gall bladder (72.7%) on pre-operative ultrasonography of patients who were H. pylori positive as compared to H. pylori negative (48.7%, 25.6% and 25.6% respectively) which correlates well with the studies by other authors (20).

In our study, we found that moderate to severe histopathological changes in gall bladder mucosa were present more frequently in H. pylori positive patients as compared to H. pylori negative patients. Similar changes have been noted in histopathology in studies by other authors (20,26,27).

Stool antigen for H. pylori was positive in 6 out of 11 (54.5%) H. pylori positive patients. Urea Breath Test was positive in 2 out of 11 (18.2%) H. pylori positive patients. This goes well with findings in studies of other authors (18,22).

In our study, urease test on gallbladder mucosa was positive in 11 (22%) cases and we designated them as H. pylori positive cases. Impression smear and staining microscopy (gram staining) of gall bladder mucosa was positive for H. pylori in 6 (12%) cases. This correlates well with studies by other authors (14,20,25,28,29).

Conclusion

We concluded that there exists a positive correlation between H. pylori in gallbladder and presence of chronic cholecystitis on histopathological examination, higher incidence of heartburn, multiple stones, contracted gallbladder, thickened gallbladder wall on ultrasonography and difficult gallbladder intra-operatively. These observations highlight the need to take appropriate preventive and eradicative measures for H. pylori in gallbladder. More studies with larger sample size are required to clarify the role of H. Pylori as causative agent or a cofactor for chronic cholecystitis.

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Conflicts of Interest

There are no conflicts of interest.

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