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Pathology

# A Study of Gall Stone Disease with Special Reference to *H. Pylori* Infections in a Tertiary Care Centre in India

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**Original Research Article**

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**Abstract:** To find out the various clinicopathological presentations of gall stone disease with special relation to H,pylori infections of Gall Bladder. Institution based prospective observational study in a tertiary care centre. Study was conducted on patients who attended the department of General Surgery of Medical College Kolkata. A total of 50 patients were taken up for the study. Rapid urease test of the gall bladder mucosa was positive in 5 out of 10 male patients (50%) who were admitted with chronic calculus cholecystitis. Rapid urease test was positive in 17 out of 40 female patients (42.5%) who were admitted with chronic calculus cholecystitis. So total 22 patients out of 50 (44%) were affected with H. Pylori infections. IgG antibody kit test were positive in 3 out of 10 male patients (30%) who were admitted with chronic calculus cholecystitis. IgG kit test were positive in 7 out of 40 female patients (17.5%). Total 10 out of 50 patients (20%) with chronic calculus cholecystitis were IgG positive i.e. chronic H.Pylori infections. The identification of H Pylori antibody IgG in serum and H Pylori infection in gallbladder and pathological changes in gallbladder among the patients with gallstones provides a strong evidence of association of the organism with chronic calculus cholecystitis or gallstone diseases and H Pylori may be an etiological agent in gallstone formation. Further studies required to determine its role in gall bladder cancer formation

**Keywords**: H Pylori, gallstone, cholecystitis.

## INTRODUCTION

*H. pylori* infection is one of the commonest infections worldwide, occurring in all regions and infecting at least half of the world's population [1]. The prevalence of *H. pylori* infection worldwide is approximately 50%[2], as high as 80%–90% in developing countries, and ≈35%–40% in the United States. While within countries, the prevalence is higher among groups with lower socioeconomic status [3, 4]. *H. pylori* prevalence is generally found to increase with age, reaching 20-50% in adult populations in Europe and North America [5]. The annual incidence of *H. pylori* infection is ≈4%–15% in developing countries, compared with approximately 0.5% in industrialized countries [2].

*H. pylori*-positivity in adults is more closely associated with living conditions and with the parents' socioeconomic status in childhood than with current living conditions and socioeconomic status [6,7].

Three likely routes of transmission have been put forward:

- Fecal-oral transmission is the most important route in developing countries
- Person to person transmission via aspiration of *H. pylori* from vomit is also a possibility, but has not been welldocumented (1 and 2 have been reviewed by Brown [27].
- *H. pylori* infection appears to be preferentially intra familial in industrialized countries [28, 29].

Chronic cholecystitis is one of the most prevalent diseases requiring surgical intervention. The causes of chronic cholecystitis still remain unclear. Recently, many findings obtained from microbiological studies suggest that bacterial infection in biliary system might play a role. The presence of H. pylori in gallbladder mucosa was first confirmed by Kawaguchi *et al*. in 1996[8] H. pylori have been found 3.5 times more frequently in presence of chronic cholecystitis [9].

It is demonstrated that *Helicobacter pylori* (*H. pylori*) in human biliary system was correlated with chronic cholecystitis, especially in the regions with higher prevalence of this infectious agent such as South Asia, East Asia and Latin America [10]. Evidences supporting the association between *H. pylori* infection and chronic cholecystitis could be found by using direct culture or staining of *H. pylori* in gallbladder tissues as well as indirect techniques such as PCR, ELISA and serology for detecting *H. pylori*-specific genes or antibodies [11-13]. The positive rate of *H. pylori* in gallbladder is reported to be 10%–20% by culture [14]. *H. pylori* can induce oxidative stress through producing reactive oxygen species (ROS) and reactive nitrogen species (RNS), which are considered to be the important causes of chronic inflammation, ulcer and canceration of the stomach [15]. In *H. pylori*-infected stomach, possible sources of ROS/RNS include neutrophils, vascular endothelial cells, gastric mucosal cells, and *H. pylori* itself. One of the most important pathways of *H. pylori*-induced RNS is mediated by overproduction of endogenous synthesis nitric oxide (NO) through inducible NO synthase (I NOS) expression [16]. In benign inflammatory and malignant gallbladder diseases, ROS and I NOS also play an important role [17].

However, in biliary system, the correlation between *H. pylori* and ROS/RNS production still needs further investigation. Two-thirds of the world population is infected with *H. pylori* [18]. The findings of *H. pylori* in biliary tract implicated that the stomach might not be the only arena of activity of this agent.

However, few studies by far have specifically assessed the characteristics of "*Helicobacter pylori* positive cholecystitis". Therefore, this study aims to find out the clinic pathological correlation of Helicobacter *pylori* infection with gallstone diseases.

**Aims and Objectives**

- To find out the incidence of H. pylori infection in patient with gall stone disease.
- To find out any variations in findings of the patient with gall stone & H. pylori infection in relation to investigations pre operative and per operative findings
- To find out any specific symptoms related to gall stone disease in patient with H pylori positive.
- To find out any abnormality and any specific changes in radiological and biochemical investigations.
- To find out histopathological changes in gall bladder mucosa in patient with H. pylori infection.
- To find out any associations of other microorganism in bile with H. pylori infections.

**SUBJECTS AND METHODS**

- STUDY AREA: Medical College, Kolkata in the Dept. of General Surgery and Dept of Microbiology.
- STUDY POPULATION: Patient with gall stone diseases admitted in Dept. of General Surgery.
- STUDY PERIOD: 2016-2017 (2 years)
- SAMPLE SIZE: Approximately 50 patients.
- SAMPLE DESIGN:All the patients with gall stone disease who give consent to be included in this study and purposive sampling will be done.
- INCLUSION CRITERIA: Patients with chronic gall stone disease with negative hepatitis viral profile that will undergo cholecystectomy.

**Exclusion criteria**

- Haemolytic disorder
- Patient operated for Acute Cholecystitis
- Obstructive biliopathy
- Viral Hepatitis
- Gall bladder Malignancy.
- Patients with repeated attacks of acute cholecystitis

**Study design**

Institutional based prospective study

**Study tools**

- History of illness
- Clinical examination
- Investigations: Hb% TLC, DLC, Platelet count, Prothrombin time, Sugar(R), Urea, Creatinine, LFT, ECG, Chest X Ray, USG and Elisa for IgG antibody and rapid urease test from Gall Bladder mucosa. Special emphasis to LFT & USG finding
- Intra operative finding

**Study techniques**

- All the patients included in these studies with gall stones will be studied.
- Base line investigations of the patient will be done which will include Hb% TLC, DLC, Platelet count, Prothrombin time, Sugar(R), Urea, Creatinine, LFT, ECG, Chest X Ray, USG. Special emphasis will be given to LFT & USG findings.
- Patient will be tested for blood by ELISA pre operatively for IgG antibody
- Histopathological examination of the gall bladder will be done post operatively.
- Urease test from gall bladder mucosa will be done immediately after removal of gall bladder.
- Bile culture.

**Plan of analysis of data**

The data will be analyzed with respect to association of H pylori infection in GB with any specific correlation pre-operative (clinical, radiological and biochemical), per operative findings &

postoperative histopathology. The data collected from all the patients in my study will be tabulated and analyzed in details. The result will be directed to establish the specific objectives of this study. A total of about 50 patients being operated for gallstone diseases which matches with our criteria will be included in this study.

**Specimens**

- 3-4 ml of venous blood will be collected from each patient a day before operation. The serum will be separated and sera will be stored at -20 degree centigrade in sterile vials till further testing.
- A small piece of gall bladder sample will be collected from the operation theatre with sterile precaution in a vial containing 5 ml of normal saline and rest of the gall bladder tissue put in 10% formalin and sent for histopathological examination.
- 2-3 ml bile will be collected from gall bladder after cholecystectomy for culture of microorganisms.

**Specimen processing**

Gall bladder sample will be crushed in a sterile mortar and pestle in 1 ml of saline and tissue homogenate used for rapid urease test. Quantitative ELISA for IgG antibodies will be per-formed in duplicate by using the specific ELISA kit as per manufacturer instruction.

## RESULTS AND ANALYSIS

**Rapid Urease Test**

Rapid urease test was positive in 5 out of 10 male patients (50%) who were admitted with chronic calculus cholecystitis. Rapid urease test was positive in 17 out of 40 female patients (42.5%) who were admitted with chronic calculus cholecystitis. So total 22 patients out of 50 (44%) were affected with H. Pylori infections (Table :1).

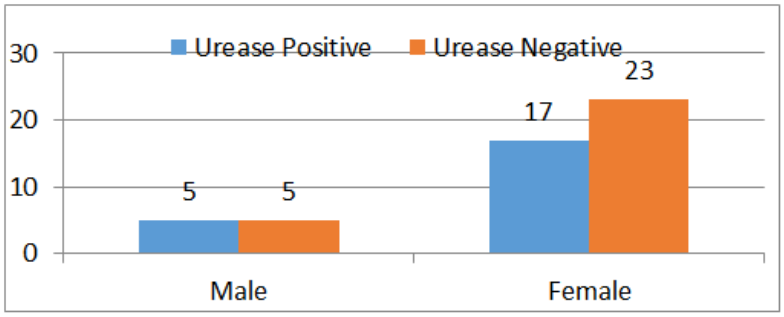


**Fig-1: Showing the number of male and female patients who were reactive/nonreactive to urease test**

**IgG antibody test**

IgG antibody kit test were positive in 3 out of 10 male patients (30%) who were admitted with chronic calculus cholecystitis. IgG kit test were positive in 7 out of 40 female patients (17.5%). Total 10 out of 50 patients (20%) with chronic calculus cholecystitis were IgG positive i.e. H.Pylori infections.

**Age groups**

8 out of 22 patients (36.36%) with H. Pylori infection belonged to 21-30 years of age; 10 belonged to 31-40 years of age (45.45%); 2 belonged to 41-50 years of age (9.09%) and the remaining 2 belonged to 51-60 years of age (9.09%).

**Liver function tests**

SGOT was high in 7 out of 22 patients (31.81%) who were associated with H. Pylori infection. SGOT was found high in 4 out of 28 patients (18.18%) who were not associated with H. Pylori infection.

**Leucocyte count**

WBC count was high in 5 out of 22 patients who had H Pylori infections (22.7%). On the other hand, 3 out of 28 patients (10.71%) who were not associated with H Pylori infections showed elevated WBC count.

**Presence of anemia**

8 patients out of 22 who were affected with H. Pylori infection were anaemic (36.36%). Also 6 out of 28 patients who were not affected with H. Pylori were anaemic (21.42%).

**Ultrasonography findings**

On Ultrasonography of the abdomen, GB was found contracted in 11 out of 22 patients (50%) with H. Pylori infection and oedematous in 2 out of 22 patients (9.09%) with H Pylori infection. GB was found fibrosis and thickened in 3 out of 22 patients (13.63%) with H. Pylori infection (Table-2).

**Table-2: Showing various ultra-sonographic features of Gall Bladder wall**

| Gall Bladder Wall | H. pylori -ve | H.pylori+ve | Total |
|---|---|---|---|
| Contracted | 11 | 15 | 26 |
| Oedematous | 2 | 3 | 5 |
| Fibrosed /thickened | 3 | 5 | 8 |
| Normal | 6 | 5 | 11 |
| Total | 22 | 28 | 50 |

**Bile culture**

Growth of H Pylori in bile culture has not been found in any patient

**Histopathological Examination**

On HPE, Mucosal erosion was found in 16/22 patients (72.72%), Mucosal atrophy in 07/22 patients (31.81%), mucosal hyperplasia in 12/22 patients (54.54%), mucosal hypertrophy in 07/22 patients (31.81%), mucosal dysplasia in 01/22 patients (4.54%), lymphoid infiltration in 12/22 (54.54%) and fibrosis in 07/22 patients (31.81%) (Table-3).

**Table-3: Showing different pathological changes in Gall Bladder with H. pylori and without H. pylori infections**

| Histology | Degree | H.pylori +ve | | H.pylori -ve | |
|---|---|---|---|---|---|
| | | No | % | No | % |
| Mucosal Erosions | No | 6 | 22.27 | 10 | 35.71 |
| | Mild | 12 | 54.54 | 12 | 42.85 |
| | Moderate | 4 | 18.18 | 4 | 14.28 |
| | Severe | 0 | 0 | 2 | 7.42 |
| Mucosal Atrophy | No | 15 | 68.18 | 13 | 46.42 |
| | Mild | 5 | 22.72 | 5 | 17.85 |
| | Moderate | 2 | 9.09 | 4 | 14.28 |
| | Severe | 0 | 0 | 6 | 21.42 |
| Mucosal Hyperplasia | No | 10 | 45.45 | 20 | 71.42 |
| | Mild | 8 | 36.36 | 4 | 14.28 |
| | Moderate | 3 | 13.63 | 3 | 10.71 |
| | Severe | 1 | 4.54 | 1 | 3.57 |
| Mucosal Metaplasia | No | 21 | 95.45 | 27 | 96.42 |
| | Yes | 1 | 4.54 | 1 | 3.57 |
| Lymphoid infiltration | No | 10 | 45.45 | 22 | 78.57 |
| | Yes | 12 | 54.54 | 6 | 21.42 |
| Musculae Hypertrophy | No | 15 | 68.18 | 21 | 75 |
| | Yes | 7 | 31.81 | 7 | 28 |
| Fibrosis | No | 14 | 63.63 | 20 | 71.42 |
| | Yes | 7 | 31.81 | 7 | 28 |

**DISCUSSION**

In this study it was found that 22(44%) patient with gallstone disease are associated with H Pylori infection out of 50 patients who had gallstone diseases. It was also found that in the age group 31-40yrs female with chronic calculus Cholecystitis H Pylori infections were high and the male patients in the same group were more affected with this infection.

SGOT level were found high in seven patients associated with H Pylori infection and high in 4 patients not associated with H Pylori infection. In some study it was found that higher SGOT levels in cagA positive H Pylori infection [19].

The WBC count was high in 5 out of 22 patients with H Pylori infection and in 3 out of 28 patients without H Pylori infection. There were some study it was found that H Pylori infection were associated high WBC count[19].

Estimation of haemoglobin was done in all patients who were undergone cholecystectomy. It was found that anaemia was more in patients with H Pylori infection .The mechanisms through which *H. Pylori* infection can cause iron deficiency and further lead to anemia have not been fully elucidated. It has been suggested that *H. pylori* infection may increase the iron demand as *H. pylori* itself uses iron for its growth and may capture ingested iron and iron from human lactoferrin[20-22].

Ultrasonography can detect the condition of GB wall like oedematous fibrosed or thickened and contracted. In this study it was found that gallbladder wall contracted in 11 patients, oedematous in 2 patients,

fibrosed and thickened in two patients who were associated with H Pylori infection whereas gall bladder wall contracted found in15 patients, oedematous in 3 patients and thickened in 5 patients who were not associated with H Pylori infection.

Despite prolonged incubation, it was not possible to isolate *H. pylori* from any of the patients. This could be due to the fact that all the patients have taken broad spectrum antibiotics with metronidazole and which constitute a part of eradication therapy for *H. pylori*. It is possible that the number of bacteria remains very low and they may have been partially inhibited by adverse conditions in the biliary milieu. Other possibility is that there is patchy colonization of the biliary epithelium, thus culturing a small piece may not give positive results. Most other workers were also not successful in getting positive cultures, but could demonstrate DNA by PCR. Culturing is technically demanding, time-consuming, and its sensitivity varies among laboratories [23].

Chronic cholecystitis also associated similar atypical histopathological changes like hyperplasia; metaplasia and lymphoid infiltration, mucosal hyperplasia and lymphoid infiltration were more in chronic calculus cholecystitis with H Pylori infection. The Helicobacteria produce several toxins and metabolites of known carcinogenic potential [24]. Murata *et al*. showed that H. bilis specific sequences could be amplified in three of 11 (27.2%) gallbladder cancer cases and in one of three (33.3%) cases with biliary duct cancer. A recent study has shown that H. pylori can damage human gallbladder epithelial cells in vitro, and could be the key factor that leads to clinical Cholecystitis [25]. Histological changes, considered pre-neoplastic, were demonstrated in the mucosa of gallbladder, limited to mice infected with Helicobacter spp such as, intestinal metaplasia, hyperplasia, dysplasia in addition to eosinophilic inflammation and hyalinosis [26]. In our study comparison between the histological findings of the H. pylori infected gallbladders with the non-infected ones, the gallbladders with mucosal hyperplasia and lymphoid infiltration were more in the H. pylori infected group which suggest the role of H. pylori infection in aggravating these pathological changes.

Although human biliary system is thought to be sterile, this can be broken through an ascending infection via duodenal papillary sphincter and descending through portal system [30]. Although the exact mechanismis not known, bacterial biofilm composed of glycocalyx is suggested to play a role as a nucleation factor. Changes of bile juice composition by beta-glucuronidase and phospholipase produced by bacteria, excessive mucin production of gall bladder epithelial cells triggered by lipopolysaccharides produced by bacteria and promotion of nucleation process through activation of immune system by bacterial itself [31]. It has been proposed that the presence of *H. pylori* in bile may represent an increased risk of gall stone formation [19]. A possible consequence of colonization by *H. pylori* in chronic inflammation of gall bladder mucosa which may impair gall bladder acid secretion and acidification of content, reducing the solubility of calcium salts in the bile and increasing the risk of their precipitation in gall bladder lumen [32]. Together with the discovery of *H. pylori* in bile juice [33].

In this present study the identification of H Pylori antibody IgG in serum and H Pylori infection in gallbladder and pathological changes in gallbladder among the patients with gallstones provides a strong evidence of association of the organism with chronic calculus cholecystitis or gallstone diseases and H Pylori may be an etiological agent in gall stone formation.

**SUMMARY**

In this study, a total of 50 patients diagnosed with symptomatic gall stones have been admitted for cholecystectomy where blood sample and gall bladder mucosa tested for IgG antibody and rapid urease test respectively. There were 40 female (80%) and 10 (20%) males with age ranging from 21-60 years. Rapid urease test positive in 22 patients and IgG positive for five patients. One of the two tests positive should be considered positive. In female seventeen are positive out of forty females and in male five are positive out of ten. In age wise distribution it is found that the females in the age group 31 to 40 years are more affected with H pylori infections. In this study it is also found that the young age group 21 to 30 yrs are also next commonly affected with H pylori infection.

Majority of the subjects were female with cholelithiasis, the female population was also predominant in relation to H pylori infection in patient with calculus cholecystitis.

In this study all the patient with pain in upper abdomen and other main symptoms were dyspepsia heart burn and epigastric discomfort. SGOT level was found high in patients (31.81%) with H Pylori infection .In comparison to the pt (14.28%) not associated with this infection.

Anaemia and WBC count were found in more no. of patient with H Pylori infection than the patient without H Pylori infection. Multiple calculi in gallbladder found in 46 patients. All the 50 pts had undergone cholecystectomy only in two cases out of 50 found adhesions of omentum to the gallbladder. But these two cases were not associated with H pylori infections. Bile culture of all the patients (50) has been done. Five patients out of fifty growths of E Coli were found and growth of enterococcus found in one pt. Growth of H Pylori in bile culture has not been found in any patient. It has also been found that E. coli and

enterococcus found in bile culture of that patient who was not associated with H Pylori infection.

Histopathological examination of gallbladder was done in all patients. In the histopathological examination of gallbladder chronic inflammation was found in 49 cases, mucosal erosion found in 34 patients. Mucosal atrophy and mucosal hyperplasia was found in 22 (44%) and 20(40%)pts respectively .Metaplasia and lymphoid infiltration were found in 2 pts and 18(36%) pts respectively and muscularis muosae hypertrophy and fibrosis found in 14(28%) and 16(32%) pts. Mucosal erosion, mucosal atrophy and mucosal hyperplasia divided the severity into mild moderate and severe. Histopathological variation specific for H Pylori infection was that mucosal hyperplasia was found in 12 out of 22 patients who were associated with H Pylori infection and 8 patients out of 28 without H Pylori infection. Lymphoid infiltration were found in 12 pts with associated with this infection and metaplasia was found in 1 patient with and without infection .Mucosal hyperplasia and lymphoid infiltration were more in chronic calculus cholecystitis with H Pylori infection. In this study the identification of H Pylori antibody IgG in serum and H Pylori infection in gallbladder and pathological changes in gallbladder among the patients with gallstones provides a strong evidence of association of the organism with chronic calculous cholecystitis or gall stone diseases and H Pylori may be an etiological agent in gall stone formation.

## CONCLUSION

- H Pylori infection is one of the commonest infections worldwide, occurring in all regions and infecting at least half of the world's population
- Its role in Gastric Cancer is well proved however its role in gall bladder carcinoma and other organs is still under study.
- Long term presence of H pylori infections in stomach may lead to gall stone and metaplasia leading to carcinoma gall bladder.
- Changes associated with H. pylori infection of gall bladder has been anemia, increased WBC Count and SGOT, USG and histopathological changes.
- Patients with H Pylori infection should be treated and preventive measure should be taken against the transmission of H Pylori infection

### Ethical Clearance

Taken from institutional ethical committee and patient's written permission taken for study.

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