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Co-Relation Between Presence of Helicobacter Pylori in Gall Bladder Wall and Gall Stone Disease in a Tertiary Care Centre in North India

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Helicobacter pylori; Gall stone disease; Gall bladder cancer; Giemsa stain

1. Abstract

1.1. Background: Helicobacter pylori was first described in the gallbladder mucosa in patients with gallstones in 1996, and a relationship between h. pylori and gallstone formation was reported. Gallbladder stone is a common condition in surgical practice. In India, especially North India, the Ganga belt and the eastern region, there is higher incidence of Gall bladder cancer than rest of the country. Chronic inflammation increases the frequency of expression of cancers. A history suggestive of chronic cholecystitis is present in approximately 50 % of the GBC patients.

1.2. Methodology: The aim of the study was to study the presence of helicobacter pylori in gall bladder wall and its histopathological profile in patients with cholelithiasis and to establish a possible co relation with it. A total of 120 patients with diagnosis of gall stone disease were included in the study, with a female to male ratio of 3.6:1 with maximum number of patients in the age group of 44-60 years. We performed routine H&E staining of the sections of gall bladder specimen as per standard lab protocol and additional sections were subjected to Giemsa staining to detect the presence of h. pylori.

1.3. Result: A total of 15 patients out of 120 patients of cholelithiasis who were subjected to cholecystectomy (12.5%) were tested positive for h. pylori. Among all the histopathological features that were found, metaplasia in gall bladder mucosa was found most commonly in our study group. We found a statistically significant co relation between presence of helicobacter pylori and hyperplasia on H&E stain in gall bladder wall, with p value <0.001. All patients with helicobacter pylori showed chronic inflammatory changes in gall bladder wall.

1.4. Conclusion: We conclude that h. pylori is present in the gallbladder mucosa in patients with gall stones, and leads to a statistically significant higher incidence of hyperplasia in the mucosa of the gall bladder. Therefore, there is need to undertake more studies to reach a definitive conclusion regarding the causal relationship between h. pylori infection and gallstone formation and gall bladder cancer.

2. Introduction

Helicobacter pylori infection is one of the commonest infections worldwide, occurring in all regions and infecting at least half of the world's population. [1] Helicobacter pylori is a Gram-negative bacillus thought to infect more than half the global population. However, increasing number of studies have investigated localization of H. pylori outside the stomach and diseases potentially related to such infections [2]. H. pylori was first described in the gallbladder mucosa in patients with gallstones in 1996, and a relationship between h. pylori and gallstone formation was reported [3].

Gallbladder stone is a common condition in surgical practice. In India, it is more common in Northern states than in South India. Incidence of gallstones increases with age [4]. It more commonly presents in females than males with a male to female ratio of 1:4. About 50% of these patients are asymptomatic [4]. In India, especially North India, the Ganga belt and the eastern region, there is higher incidence of GBC than rest of the country. The incidence in north India is 10-12 per 100,000 population [4].

Chronic inflammation increases the frequency of expression of cancers [5]. A history suggestive of chronic cholecystitis is present in approximately 50 % of the GBC patients [6]. 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 cancer of the stomach [7].

The present study was done to assess the presence of H. pylori in gall bladder mucosa in patients with cholelithiasis and the histopathological profile of the gall bladder specimens was studied. With GB cancer having a higher incidence in the indogangetic region any co relation to H. Pylori would prove to be an asset in early diagnosis of the disease.

3. Material and Methods

This was a hospital based prospective type of study, done over a time period from 1st December 2019 to 1st June 2021.The study was conducted in the department of surgery in Shri Guru Ram Rai Institute of Medical and Health Sciences and Shri Mahant Indiresh Hospital Dehradun, Uttarakhand, India.

Patients undergoing cholecystectomy for cholelithiasis in the age group of 18-60 years of both sexes were included in the study. Patients who had previously taken treatment for h. pylori in the past 6 months were excluded from the study. All the selected patients were subjected to a list of questions based on symptomatology in relation to gall stones. Then patients were subjected to surgery (cholecystectomy) after anaesthesia clearance.

Gall bladder specimens were sent for histopathological examination in 10% buffered formaldehyde solution. Gross tissue processing and routine H&E staining of the sections were done as per standard lab protocol. Additional sections were taken and subjected to Giemsa staining.

Based on HPE report, patients were divided into two categories: h. pylori positive and negative group. Further the two groups have been compared based on the histopathological findings as follows:

- Inflammation
- Hyperplasia
- Pyloric and intestinal metaplasia
- Dysplasia
- Features of carcinoma in situ

3.1. Data Analysis

The data obtained from the study were analyzed using SSPS version 21. Independent sample t test and Z score was used for drawing the co relation. All p values less than 0.05 were considered significant.

4. Result

We found the presence of helicobacter pylori in 12.5% of the study group. Out of the 120 patients included in the study, 15 were found to be positive for h.pylori using giemsa stain (Table 1).

Out of 120 patients, 15 patients (12.5%) showed the presence of h. pylori in gall bladder specimen using Giemsa stain, whereas 105 patients (87.5%) did not show the presence of h. pylori (Figure 1 and Table 2).

Out of 120 patients, 94 patients were female which compromised 78.3% of the study group and 26 patients were male.

Among the 94 female patients, 12 (12.8%) were positive for h.pylori and in males 3 (11.5%) showed the presence of h.pylori (Table 3).

In our study, out of the 15 patients who were positive for h. pylori 53.35% (8) were in the age group 44-60 yrs., 33.3% were in 18-30 yrs and 13.3% in between 31-43yrs. The mean age group of h. pylori positive patients in this study was 41.8+/-11.2 (Table 4).

Among all the patients subjected to cholecystectomy, 53 showed metaplasia in gall bladder wall on histopathological examination, 13 showed hyperplasia, 4 showed dysplasia and features of carcinoma in situ or adenocarcinoma were seen in 17 patients.

Out of the 15 patients showing h. pylori, 10 patients had hyperplasia on HPE report, 6 had metaplasia, 2 had features of carcinoma in situ or adenocarcinoma. Whereas, none showed dysplasia on HP report (Figure 2 and Table 5).

Out of 15 patients with h. pylori positive status, 10 patients had hyperplasia in HPE report which amounted to 76.9% and it was a statistically significant co relation (Figure 3 and Table 6).

Out of 15 patients with h. pylori positive status, 06 patients had metaplasia in HPE report which amounted to 11.3%and it was a not statistically significant co relation. Although metaplasia was seen in 53 patients out of 120, which included both intestinal and focal type.

Table 1: Depicting the frequency of presence of h. pylori by Giemsa staining on gall bladder sections after cholecystectomy in this study group.

Presence of h. pylori on HPE by Giemsa stain	Frequency N=120	Percentage
Positive	15	12.50%
Negative	105	87.55%

Table 2: Showing the co-relation of gender distribution with presence of helicobacter pylori on Giemsa stain in this study group.

Gender	H. pylori positive	H. pylori negative
Female	12	82
Male	3	23

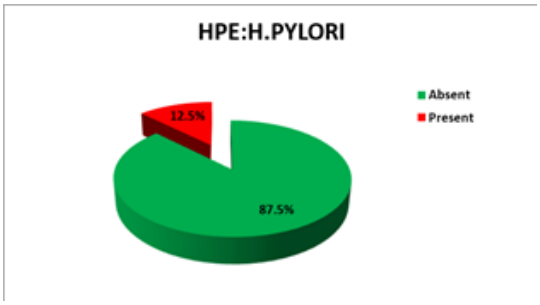

Figure 1:

Table 3: Showing the co-relation of age distribution with presence of helicobacter pylori on Giemsa stain in this study group.

Age group	H. pylori positive N=15	Percentage
18-30 years	5	33.30%
31-43 years	2	13.30%
44-60 years	8	53.35%

Table 4: Showing co-relation of different histopathological findings in gall bladder wall with H&E stain in this study group.

HPE finding	Total number of patients	H. pylori on Giemsa stain	
		Present	Absent
Hyperplasia	13	10	3
Metaplasia	53	6	47
Dysplasia	4	0	4
Features of carcinoma in situ or adenocarcinoma	17	2	15
Total patients	120	15	105

Table 5: Showing the co relation of presence of h. pylori with hyperplasia on HPE in this study group.

Hyperplasia	Total	HPE: H.PYLORI				p value
		Present		Absent		
		Number	%	Number	%	
Present	13	10	76.9	3	23.1	<0.001
Absent	107	5	4.7	102	95.3	
Total	120	15	12.5	105	87.5	

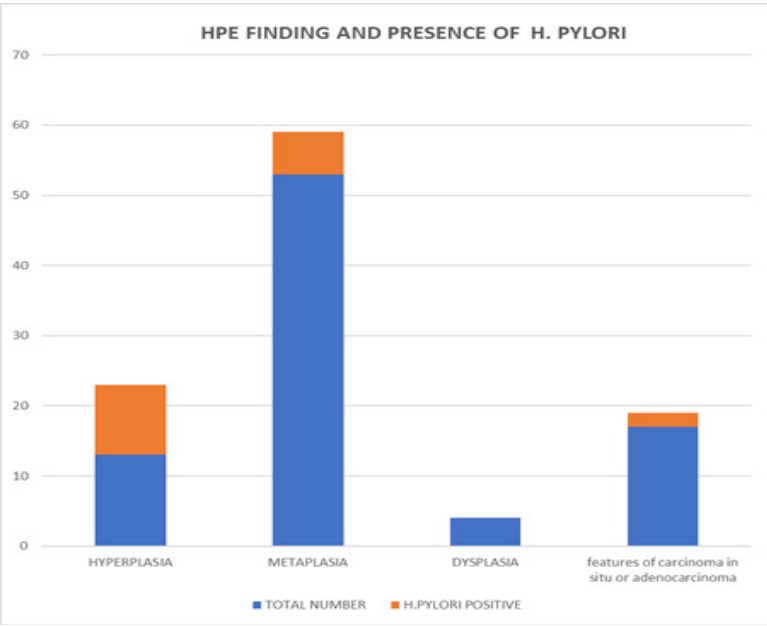

Figure 2:

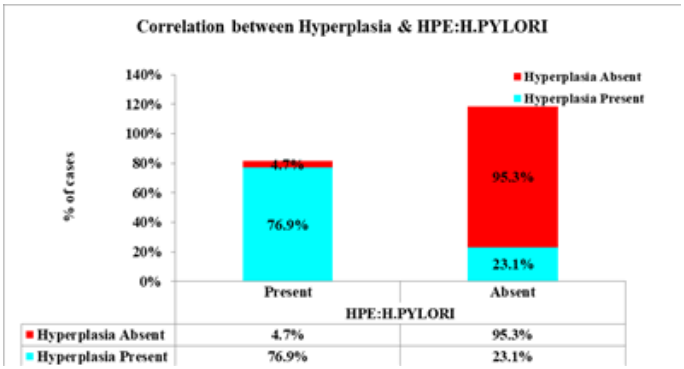

Figure 3:

Table 6: Showing the co relation of presence of h. pylori with metaplasia on HPE in this study group.

Metaplasia	Total	HPE: H. PYLORI				p value
		Present		Absent		
		Number	%	Number	%	
Present	53	6	11.8	47	88.7	0.728
Absent	67	9	13.4	58	86.6	
Total	120	15	12.5	105	88.5	

5. Discussion

The relationship between h. pylori and gallbladder diseases, specifically gallstones (chronicity of inflammation in gall stones and a possible correlation with hyperplasia, metaplasia, dysplasia, carcinoma in situ or invasive cancer,) is still a controversial matter due to conflicting studies and inconclusive reports. There are numerous known causes of chronic cholecystitis. One of them is the presence of bacterial infection in the biliary system. There is currently insufficient evidence data regarding the route whereby h. pylori settles in the gallbladder. It may reach the gallbladder via an ascending route from the duodenum or via the portal circulation system [8,9].

The gallbladder and stomach originated from endoblasts and have similar tissue structures, with the mucosa covered with a slime layer [10-12]. The close anatomical proximity of gall bladder to duodenum could also be on of the possible reason for detection of helicobacter pylori in gall bladder mucosa.

5.1. Histopathological Findings

In our study, chronic inflammation was seen in all the patients. Metaplasia was seen in 53 patients, hyperplasia in 13 patients, dysplasia in 4 patients and cancerous changes was seen in 17 patients.

In our study, 10 patients out of 15 patients with h. pylori showed hyperplasia on HPE and the co relation was found to be statistically significant with p value <0.001. Majority of patients in the study showed metaplasia in the HPE report, but it was not statistically significant.

In the study conducted by Ehsan Hassan et al [13] the most predominant finding was mucosal erosions detected in 38 cases (76 %), hyperplasia was detected in 44 %, varying from mild (18 %), moderate (20 %), and severe (6 %). Metaplasia was detected in only 16 % of the cases and lymphoid follicles in only 8 %.

In the study, conducted by Di Zhou et al [14] metaplasia was identified in 7.67% of the included patients and it was shown to be statistically correlated with h. pylori infection in gallbladder mucosa (p= 0.047).

Chen et al [15] demonstrated that metaplasia may provide suitable conditions for h. pylori colonization in the gallbladder.

5.2. Indo-Gangetic plane and GBC

North India has higher incidence of gall bladder cancer. A large part of the states, along this belt are based along the major rivers of the country namely Sutlej, Ganges, Yamuna and Brahmaputra. These rivers arise from the glaciers and flow from the northern Himalayas towards west and east and have become polluted due to human waste and industrial pollutants [16]. As the Ganges flows towards east, the concentration of pollutants as well as bacterial contamination have been found to steadily rise which may account partially for high incidence in this gangetic region of the country [17]. It is based on these theories, that the varied incidence of gall bladder cancer among all the states is justified.

All studies from India have shown a small but definite risk of H. pylori, in the causation of GBC. However, a study from Japan showed a strong association between H. bilis and GBC (OR 6.5) in comparison to patients with other gallbladder diseases. H. bilis in contrast to H. pylori is resistant to the action of bile and survives in the gallbladder for long duration [18]. In Egypt also H. pylori is found in about 80 % of the population [19].

5.3. Gall stone disease and GBC

In India, the incidence of GBC is out of proportion to the prevalence of gallstones indicating that co-factors may play a significant role in the development of GBC [20,21]. A Combination of multiple repeated insults of varying nature may overwhelm the tissue repair mechanism giving way to chronic inflammation, mutagenesis and carcinogenesis. These may include hyperplasia, metaplasia, dysplasia or invasive cancer [22].

Studies from India have shown that p53 mutations are detected in 70% of cases of GSD [22]. Chronic inflammation results in mutagenesis especially of the p-53 pathway in India. Patients with GS more often have metaplasia and dysplasia compared to those without GS.

6. Conclusion

We conclude that h. pylori is present in the gallbladder mucosa in patients with gall stones, and leads to a statistically significant higher incidence of hyperplasia in the mucosa of the gall bladder. Our study is unable to establish a statistically positive correlation of h. pylori with metaplasia, dysplasia and features of carcinoma in gall stones disease.

However, in setting of developing countries, where patients often

present late, a strategy of recommending prophylactic cholecystectomy in h. pylori positive patients with gall stones, should be advocated.

Gall bladder cancer has high incidence in the Indo-Gangetic plane and therefore studies with lager sample size and with multimodality detection approach, need to be undertaken to reach a definitive conclusion regarding the causal relationship between h. pylori infection and gallstone formation and gall bladder cancer.

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