Original Research Article

A study on association of Helicobacter pylori in gastric disorders

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Abstract

Introduction: Helicobacter pylori are a ubiquitous organism that can be seen in 50% of general population. Its association with various gastric disorders are well established in numerous studies after its discovery in 1983. Peptic ulcer disease is the most studied disease related to H Pylori infection. H. pylori are seen in 90% of duodenal ulcer and 75% of gastric ulcer Patients. This bacterium is also involved in the pathogenesis of several extra gastric diseases, such as mucosa-associated lymphoid tissue lymphomas (Maltomas) gastroesophageal reflux disease (GERD) and gastric carcinomas. In some population Pylori can be seen associated in 80% of gastric cancers.

Aim of the study: To study the association of H pylori in benign and malignant disorders of stomach and to study presence of H pylori in association with different histological types of carcinoma stomach and benign gastric diseases (such as gastritis, gastric ulcers, erosions and polyps).

Materials and methods: A detailed clinical history was elucidated, followed by careful clinical examination, which were recorded as per the proforma. All the patients included in the study underwent upper gastrointestinal endoscopy and the findings were noted Results: In the study males have a preponderance to have both benign and malignant disorders. In benign group 66% were males and 34% were females. In the malignancy group 78% were males and 22% were females. Of the benign group gastritis is most common. In malignant group poorly differentiated carcinomas are more common.

Conclusion: The incidence and mortality from gastric cancer and the morbidity from benign gastric disease are progressively decreasing worldwide, but gastric cancer remains a major public health problem in several developed and developing countries, especially in Asia. Gastric cancer has an extremely poor prognosis since a 5-year survival rate using currently available treatments, surgery and radio-chemotherapy, is less than 20%.

Key words

Duodenal ulcer, Helicobacter pylori, Gastritis.

Introduction

Helicobacter pylori (H. pylori) are a gram-negative spiral organism that infects more than 50% of the people in the current world [1]. The prevalence of Pylori infection is strongly correlated with socioeconomic conditions. In a number of developing countries, more than 80% of middle-aged adults are infected by the bacterium. Infection rates are lower in industrialised countries [2]. Epidemiological data indicate that the prevalence of infection in the United States has been declining since the second half of the 19th century; decreases corresponding to improved sanitation. H. pylori are 3 micrometres long with a diameter of about 0.5 micrometres. It contains a hydrogenase which can be used to obtain energy by oxidizing molecular hydrogen (H2) that is produced by intestinal bacteria [3]. It produces oxidase, catalase, and urease. It is capable of forming biofilms and can convert from spiral to a possibly viable but non-culturable coccoid form, both likely to favor its survival and be factors in the epidemiology of the bacterium. H. pylori possesses five major outer membrane protein (OMP) families [4]. The largest family includes known and putative adhesins. The other four families include porins, iron transporters, flagellum-associated proteins and proteins of unknown function. Human beings are the only reservoir for Helicobacter pylori. Infection occurs by oral ingestion of the bacterium [5]. Direct transmission from person to person occurs via salvia and feces, and infection also occurs through contact with contaminated water. In developing countries, most individuals are infected during childhood. Family members are at increased risk of infection [6]. A number of occupations show increased rates of H. Pylori infestation, mainly health care workers. Infection with H. Pylori is a chronic disease which will not resolve spontaneously without specific treatment. The gastric contents are normally nearly sterile as a consequence of the acidic luminal environment and the effects of gastric emptying [5]. H. Pylori has adapted to this hostile ecological environment and displays a number of features that permits its entry into the surface mucus layer, attachment to gastric epithelial cells, evasion of immune responses, and persistent colonization. Because of its important role in disease pathogenesis, the organism has been intensively studied. The H. Pylori genome encodes approximately 1500 proteins and contains 1.65million base pairs. H. Pylori expressses a number of novel proteins including urease. Urease hydrolyzes urea to carbon dioxide and ammonia [7]. Ammonia acts as a neutralizing agent for hydrochloric acid and permits the bacterium to survive in an acidic microenvironment. Motility is also central for colonization, and the organism contains a flagellum, which permits the organism to move through mucus and approach the epithelial surface [8]. The H. Pylori genome also encodes a number of bacterial surface adhesins. These outer membrane proteins bind to the Lewis B blood group antigen. Mucosal adhesion is essential to bacterial pathogenesis and persistent infestation. H. Pylori strains expresses a 95-kd exotoxin, vacuolating cytotoxin. This toxin gets inserted into the epithelial cell outer membrane and forms an anion selective, voltage-dependent channel. HCO3- and organic ions are released through this channel, potentially providing the bacterium with nutrient substrate. The exotoxin is also incorporated into the host mitochondrial membrane. The VacA exotoxin causes the release of cyt c from mitochondria and induces apoptosis. This exotoxin is not essential for human colonization, and there is extensive variability in bacterial expression of VacA. A number of observations show that some VacA gene variants are associated with more severe disease [3]. The bacterium also producers a non-toxigenic HMW protein encoded by the *cag* A gene. The *cag*A protein is translocated into the host epithelial cell. Within the epithelial cell,

*cag*A is phosphorylated and binds to a tyrosine phosphatase. This binding is associated with inflammatory phenomena including production of interliukin-8. The *cag*A gene product serves as a pathogenicity phenotype marker [9]. H. pylori has 4-6 flagella; all gastric and enterohepatic Helicobacter species are highly motile due to flagella. The prevalence of H. Pylori among adults is ~30% in the United States and other developed countries as opposed to >80% in most developing countries. H. Pylori infection is usually acquired during childhood, where transmission occurs predominantly within families. Pylori infection is on a steep decline in most of the western countries mainly due to the success of combination therapies and improves personal hygiene and community sanitation to prevent re-infection. The situation is not improving in many of the developing countries due to failure of treatment regimens and emergence of drug resistance. The infection in some cases leads to chronic superficial gastritis, chronic active gastritis, peptic ulcer disease and gastric adenocarcinoma. Humans are the only important reservoir of H. Pylori [10]. Children may acquire the organism from their parents (more often from the mother) or from other children. H. pylori is easily cultured from vomitus and gastroesophageal refluxate and is less easily cultured from stool. One of the most distinctive features of H. pylori is the genetic diversity between clinical isolates obtained from different patient populations. Most H. polyri isolates can be discriminated from others by DNA profiling or sequencing of corresponding genes due to mainly a high degree of sequence divergence between orthologs (3-5%). H. Pylori infestation is followed by continuous gastric inflammation in virtually all individuals. Worldwide, H. pylori-induced gastritis is the most common form, comprising 80-90% of all types of gastritis. Complete healing of infected mucosa is very rare, with rates of 0.4% per year in the absence of active treatment. For most individuals, this persistence means that Pylori infestation causes gastritis which is lifelong. The initial inflammatory response is characterized by recruitment of neutrophils, followed sequentially by T and B lymphocytes, plasma cells, and macrophages. H. pylori infection is not invasive of the gastric mucosa, and the host immune response is triggered by the attachment of bacteria to surface epithelial cells. The resultant chronic gastric inflammation in affected individuals is characterized by enhanced expression of interleukin-1, interleukin-2, interleukin-6, interleukin-8, and tumour necrosis factor [11]. These interleukins serve as potent chemoattractants and as activators of neutrophils. A sustained systemic and mucosal immune response is also noted. The resulting antibody response does not lead to eradication of H. Pylori, but does cause sustained tissue damage. Some individuals infected with H. Pylori develop autoantibodies directed against gastric parietal cells. This autoimmunity correlates with subsequent atrophy of gastric mucosa. H. Pylori infestation is accompanied by an abnormal T-cell response. Immature T-helper cells can differentiate into two functional subtypes. Th1 cells are characterized by the secretion of interliukin-2. Th2 cells secrete interleukin-4,-5, and – 10. In response to extracellular pathogens, Th2 cells stimulate T cells. Intracellular pathogens cause induction of Th1 cells. H. pylori infection is non-invasive and a Th2-cell response would be expected. However, H. pylori gastric infection induces mainly a Th1 phenotype. The Th1 response is associated with the production of cytokines that promote gastric inflammation, whereas Th2 cytokines would be expected to be cytoprotective. This abnormal response may be partially responsible for the long-term persistence of H. pylori infestation [12].

Materials and methods

A prospective clinical study was undertaken at Tirunelveli Medical College Hospital, Tirunelveli to know the various upper gastro-intestinal endoscopic findings in patients presenting with dyspepsia. The study was conducted from December 2013 to August 2014. The patient selection was by convenience sampling. A detailed clinical history was elucidated, followed by careful clinical

examination, which were recorded as per the proforma. All the patients included in the study underwent upper gastrointestinal endoscopy and the findings were noted.

Inclusion criteria

Patients above 13 years of age. Patients showing symptoms of gastric disorders (abdominal pain, vomiting, hematemesis, malena, dyspepsia, loss of appetite, loss of weight etc.

Exclusion criteria

Patients below 12 years of age. Pregnant and lactating women.Patients who had taken Anti H. pylori drugs in the past 6 months. Patients on NSAID for more than one month duration. Unwilling or unfit patients for endoscopy.

Procedure

All the patients in this study group, on inpatient basis underwent upper gastro-intestinal endoscopy under topical anesthesia. The patients were asked to fast for 12 hours prior to the procedure. Only a few patients were given 5-10 mg diazepam intravenously for sedation.

Lignocaine viscous or oral lignocaine sprays were given to the patient 5-10 minutes before the procedure for the local anaesthetic effect. The upper gastro-intestinal endoscopy was conducted with Olympus, flexible, fiberoptic endoscope with patients in left lateral positions. The instrument is advanced under direct vision, with the tip of the endoscope in central lumen. Using the optimal insufflations to keep the lumen of the esophagus well distended. Oesophagus was observed for any inflammatory changes, growth. The gastro-oesophageal mucosal junction was identified at 38-40 cm from the incisors. (This junction is usually serrated and readily identified by the colour difference between the oesophageal and gastric mucosa, called as Z line). The position of the oesophageal hiatus in the diaphragm is identified by asking the patient to inhale deeply, the diaphragmatic hiatus during inspiration creates an imprint on the oesophageal and gastric wall. The position of both the hiatus and the mucosal junction are recorded in order to document the possibility of a hernia or of a columnar lined oesophagus. Gastro-oesophageal junction should be observed for being closed or widely patulous. On entering the stomach, endoscope is progressed slightly down and towards the left, a view of greater curvature and of the posterior wall is obtained. Aspiration of all retained liquid is done to reduce the risk of aspiration and to allow proper examination of the stomach. A rotation movement of the tip of the instrument allows examination of the anterior and posterior walls of the body of the stomach. The lesser curvature down to the angulus and the greater curvature are viewed by the same position motion. The most proximal part of both the curvatures is better examined when using the J manoeuvre. Stomach was looked for inflammatory changes, ulcer, growth, erosions, and polyps. By rotating and angulating the tip, endoscope is advanced to assess the antrum. Prepyloric and pyloric ring observed directly, the passage through the pylorus being done under direct vision. When the pylorus yields, complete assessment of the duodenum is done up to second part. Endoscopic biopsies were taken from the antrum, growth and the edge of the ulcer crater depending on the findings. Antral biopsy is used for rapid urease test (RUT) in which the RUT card is used. Here the biopsied tissue is placed over the card which contains a yellow coloured medium. Then a drop of distilled water is placed over it and the results are studied after 15 mines, 30 mins and at 24 hrs. If the tissue contains urease enzyme which is produced exclusively by H. pylori, the yellow coloured medium changes to pink or end colour then the test is considered positive. If colour change doesn't occur then the test is considered negative and the results are noted. Biopsy specimens taken were also sent for histopathology. Each of the biopsy specimens were fixed in 10% buffered formalin, routinely processed to paraffin and 3µ m sections cut [12].

Results

Tests commonly Used to Detect Helicobacter pylori were as per **Table - 1**. Recommended

Treatment Regimens for Helicobacter pylori were as per **Table – 2**. Frequencies of Gastric Tumors were as per **Table – 3**.

Table – 1: Tests commonly Used to Detect Helicobacter pylori.

Test	Advantages	Disadvantages
Invasive (Based on Endoscopic Biopsy)	Quick, simple	Cost effective
Biopsy urease test	Quick, simple	Some commercial tests not fully sensitive before 24h.
Histology	May give additional histologic information	Sensitivity dependent of experience and use of special stains
Culture	Permits determination of antibiotic susceptibility	Sensitivity dependent on experience
Non Invasive		
Serology	Inexpensive and convenient	Cannot be used for early follow-up; some commercial kits inaccurate
13C or 14C urea breath test	Inexpensive and simpler than endoscopy; useful for follow-up after treatment	Low-dose irradiation in 14C test (although 14C is rarely used)
Stool antigen test	Inexpensive and convenient; useful for follow-up after treatment; may be useful in children	New test; role not fully established; appears less accurate than urea breath test, particularly when used to assess treatment success

Table – 2: Recommended Treatment Regimens for Helicobacter pylori.

Regimen, Duration	Drug 1	Drug 2	Drug 3	Drug 4
First-Line Treatment				
Regimen 1: OCA (7-14 days)a	Omeprazole& (20 mg bid)	Clarithromycin (500 mg bid)	Amoxicillin (1 g bid)	
Regimen 2: OCM (7-14 days)	Omeprazole& (20 mg bid)	Clarithromycin (500 mg bid)	Metronidazole (500 mg bid)	
Second-Line Treatment				
Regimen 3: OBTM (14 days)	Omeprazole& (20 mg bid)	Bismuth subsalicylate (2 tabs qid)	Tetracycline HCI (500 mg qid)	Metronidazole (500 mg bid)

Discussion

A prospective study entitled "A study on Association of Helicobacter pylori in gastric disorders" was undertaken in Tirunelveli Medical College Hospital to study the presence of H. Pylori in various gastric disorders. Slick GD et al did meta-analysis of observational epidemiological studies [13]. A total of 42 studies met the selection criteria and were categorized by the type of study design: eight cohort and 34 case-control studies. They concluded H. Pylori infection is associated with a 2-fold increased risk of developing gastric adenocarcinoma. Xue FB, et al. also did a meta-

analysis observational epidemiological studies. Twenty-one papers of case-control studies were selected, including 11 on gastric cancer, 7 on precancerous lesion of stomach and 3 on lymphoma of stomach and the results of Meta-analysis present a strong evidence to support the conclusion that H.pylori infection is a risk factor for gastric carcinoma [14]. Kang JK, et al. studied the association of helicobacter pylori in gastritis and people ulcer disease. Pylori were present in 96.6% of patients with active gastritis, 100% of patients with duodenal ulcer and 76.9% of patients with gastric ulcer, while present in only 6.3% of individuals with histologically normal gastric mucosa. The bacteria colonized the antral mucosa more frequently than the body or than the duodenal cup mucosa. Sung Hani Kuok and Ann-Lie Cheng studied association of H. pylori in MALTomas. Low grade mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach, gastric MALT lymphoma, is associated with Helicobacter pylori infection. The eradication of H pylori using antibiotics is successful in 60% to 80% of affected patients [15]. The association between H. Pylori and gastric cancer was proven by numerous case control studies nested in large cohorts which could prospectively examine the H.Pylori status of gastric cancer patients. This association was considered sufficient by the Working Group of the International Agency for Research on Cancer/World Health Organization to recognize H. Pylori as a Group I carcinogen for humans in 1994.After informed consent 62 cases of various gastric disorders were included in the study and were studied clinically as per the proforma from December 2013 to August 2014.In the study males have a preponderance to have both benign and malignant disorders. In benign group 66% were males and 34% were females. In the malignancy group 78% were males and 22% were females. Of the benign group gastritis is most common [16]. In malignant group poorly differentiated carcinomas are more common. Mean age for benign diseases is 42 years and for malignancy mean age is 60 years. It is common in 5th and 6th decade of life which is comparable with other literature. In most of the patients, common complaint was abdominal pain (94.44%) Loss of appetite (61.11%) and weight were more common in malignancy group.

Table – 3: Frequencies of Gastric Tumors.

Tumor Type	No. of Cases	%
Malignant tumors	4199	93.0
Carcinoma	3970	7.9
Lymphoma	136	3.0
Leiomyosarcoma	77	1.7
Carcinoid	11	0.3
Others	5	0.1
Benign tumors	315	7.0
Polyp	140	3.1
Leiomyoma	92	2.0
Inflammatory lesions	30	0.7
Heterotopic pancreas	20	0.4
Others	33	0.8

Conclusion

Rapid urease test is positive in 20% of patients with malignancy and 25.71% of patients with benign gastric disorders [17]. This shows that H. Pylori are one of the causes for benign diseases (gastritis) and also a risk factor for malignant transformation of gastric mucosa. Histopathology showed well differentiated carcinoma (27.7%), moderately differentiated carcinoma (5.5%) and poorly differentiated carcinoma (66.6%). 80% of duodenal ulcer patients had positivity for H. Pylori which is significant [18]. Thus we conclude that there is association between H. Pylori infection and gastric disorders (both benign and malignant) but it is less (<30%), which is in contrast to the literature which show high association (>50%) and this may be due to improved hygiene, empirical antibiotic usage for H.Pylori, other common causes like smoking, alcohol, genetic factors. So, in cases of benign gastric disorders endoscope biopsy with rapid urease test followed by anti-H. Pylori therapy will decrease the future development of carcinoma [19].

Summary

The incidence and mortality from gastric cancer and the morbidity from benign gastric disease are progressively decreasing worldwide, but gastric cancer remains a major public health problem in several developed and developing countries, especially in Asia. Gastric cancer has an extremely poor prognosis since a 5-year survival rate using currently available treatments, surgery and radio-chemotherapy, is less than 20%.This study was done from Dec 2013 till Aug 2014, 62 patients were included. All patients were admitted and routinely investigated. The following parameters were observed, age of presentation, risk factors associated, clinical features, investigations like blood routine, ultrasound, upper gastrointestinal endoscope, rapid urease test, histopathology [18]. Rapid urease test is the endoscopic investigation of choice as it is simple, easy to read, has high sensitivity and specificity for detection of H. Pylori than any other tests and hence it is used in this study After analysing all the data using SPSS, Syntax software version 16.0, Chi square analysis the following are observed. Age incidence for malignancy is more in 5th and 6th decade, 78% were males and 22% were females [19]. The mean age group was 60 years.

Histopathology showed well differentiated adenocarcinoma (27.7%) moderately differentiated adenocarcinoma (5.5%) poorly differentiated adenocarcinoma (66.67%) Rapid urease test was positive in 20% of patients in malignancy group. Age incidence for benign gastric diseases is in 4th decade [20]. Gastritis is the most common than gastric ulcers and in others HPE finding of chronic gastritis is the most common. Rapid urease test was positive in 25.71% of the patients in the benign group [21]. We conclude that there is association between H. Pylori infection and carcinoma stomach and benign gastric disorders but it is less (<30%) which is in contrast to the literature which show high association (>50%) and this may be due to improved hygiene, empirical antibiotic usage for H. Pylori, other common causes like smoking, alcohol, genetic factors and also may be due population studied [22].

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