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Helicobacter Pylori Infection: The Extragastric Manifestations - A Review

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ABSTRACT

Helicobacter pylori (H. pylori**)** is a gram-negative bacterium colonizing stomach, liver and intestine, is found to cause variety of gastrointestinal impairments. As per latest studies, H.pylori is increasingly being associated with extragastric manifestations like neurological, hematological, cardiovascular, metabolic, hepatobiliary and autoimmune also. Recent studies have found 90 percent ulcers in duodenum and 80 percent ulcers in stomach associated to H.pylori infection.
This review aims to focus upon and summarize extragastric manifestations of H.pylori infection. Such manifestations caused by it are mainly related to alterations in Gut-brain axis and altered gut microbiome too. Thus, potential role of H.pylori in disorders like iron-deficiency anemia, Vitamin B-12 deficiency anemia, stroke, cardiovascular diseases, diabetes mellitus, metabolic syndrome, Alzheimer's disease, anxiety, depression and other autoimmune skin and ophthalmic disorders need to be explored for better understanding and management. The microbiome gut-brain axis needs to be studied further in association with helicobacter pylori infection.

KEYWORDS: iron-deficiency anemia, h.pylori gastritis, neurological manifestations, metabolic syndrome, carcinoma

INTRODUCTION

Helicobacter pylori (H. pylori) is a gram negative bacterium and one of the most successful human pathogens infecting more than half of the population of the world [(1)]. It is a spiral shaped bacterium which measures 2 to 4 micrometers lengthwise and 0.5 to 1 micrometers widthwise [(2)]. Though it is mainly related to duodenal ulcers, many studies [(3 ,4 ,5 ,6 ,7 ,8)] have shown that it may also influence the various extragastric organs. It is a subdivision of Proteobacteria belonging to group of family known as Helicobacteraceae. H pylori is found in human gastric mucosa as it is the only niche known that provides stable conditions for its growth. H.pylori colonization should not be called a disease rather it is a condition which affects the relative risk of developing many clinical conditions of upper gastrointestinal tract and hepatobiliary tract. It was successfully isolated and cultured from the human stomach 20 years

ago by Barry Marshall and Robin Warren. These bacteria have the capacity to grow in the form of colonies in the human stomach, thus leading to inflammation of the gastric mucosa. H.pylori is now known as one of the common causes of chronic active type B gastritis. Its colonization usually persists lifelong unless it is treated. This review aims to collect studies associating H. pylori infection with extragastric conditions and discuss the phenomena that may explain the underlying cause of H. pylori infections.

PATHOPHYSIOLOGY OF GASTRIC MANIFESTATIONS

H. pylori infection is one of the common etiological factors in various gastrointestinal diseases, like chronic active gastritis, peptic ulceration, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue lymphoma. The disease progression is decided by interaction between the host and the bacterium. Factors like gene polymorphisms of the host immune system and gastric acid secretion affect the bacterium's colonizing capabilities. Bacterial factors of virulence like the cytotoxin-associated gene Cag A and the vacuolating cytotoxin Vac A help in the colonization of the gastric mucosa and also seem to influence the immune system of the host [(9)].

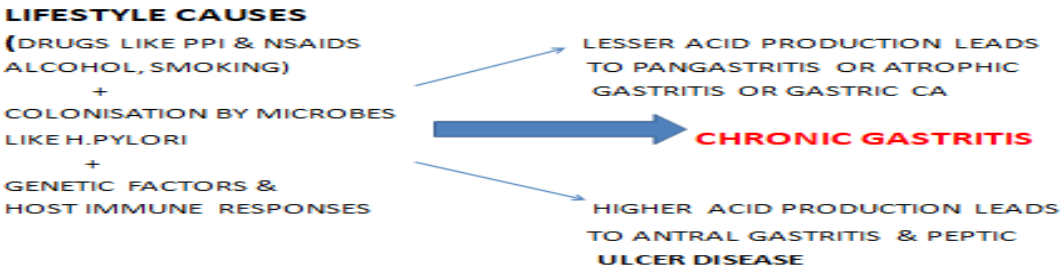

Figure 1- Pathophysiology Of Gastric Manifestations In H. Pylori Infection Including The Site Of Stomach Involved

Bacterial products like ammonia, cytotoxins, phospholipases, lipopolysaccharides, platelet-activating factor damage tissues causing degeneration of surface epithelium. Immune response to bacterial antigens by the mucosa leads to infiltration by chronic inflammatory products and neutrophil polymorphs. Chemotaxins like complement products and interleukin (IL)-8 are also released. Antigen processing by monocytes and later by Helper T cells is followed by B cell responses in mucosa. Production of reactive oxygen species (ROS) and other autodestructive proteases by activation of monocytes and neutrophils lead to atrophy. Injury by various irritants like bile reflux may aggravate intestinal metaplasia also [(10, 11, 12, 13)].

As per one more hypothesis, in such an infection which affects lifelong, virulence factors produced can't let the host lose its life. Therefore, gastroduodenal disease in H.pylori infection is mainly because of impaired immune response by gastric mucosa. One such gene polymorph associated with H. pylori infection is IL-1B-511 which leads to gastric carcinogenesis in the Chinese patients infected by H. pylori [(9)].

Gastro oesophageal reflux disease (GERD) is one of the most common conditions related to H.pylori infection. Antral gastritis associated

with H. pylori cause hyperacidity, thus aggravating GERD. While in corpus gastritis associated with it, there is hypoacidity, thus playing a protective role against GERD. This protective behavior is due to genetic factors like H.pylori Cag A positivity [(14)]. Figure 2 and 3 shows geimsa stain image and endoscopic image of H.pylori

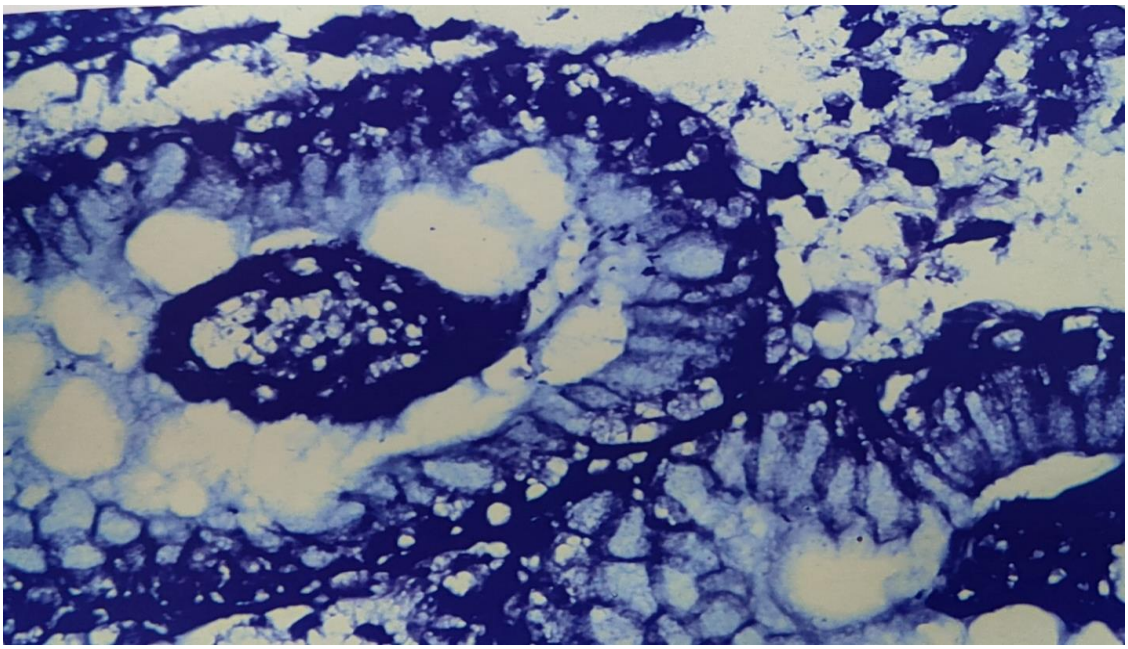

Figure 2 The Above Is A Biopsy Of Gastric Mucosa Using Giemsa Stain Under 1000x Showing Colonization With Spiral Shaped H.Pylori Attached To The Epithelium Of The Gastric pit.

FIGURE 3 the second picture was taken while endoscopy viewing a gastric ulcer, taking biopsy sample for H.pylori

HELICOBACTER PYLORI AND EXTRAGASTRIC MANIFESTATIONS

Helicobacter pylori is a well-known factor in the pathogenesis of various extragastric diseases like iron deficiency anemia [(15)],

Vitamin B12 deficiency anemia [16] & idiopathic thrombocytopenic purpura [17, 18]. H.pylori infected patients also manifest neurodegeneration related to hyperhomocysteinemia [19]. Multiple sclerosis [20], Parkinson's disease [8], Alzheimer's disease [21] and Guillain-Barré syndrome [22] are also associated with this infection as per some new studies. Risk of developing atherosclerosis is also affected by this infection as per some latest studies [4, 23, 24, 25] . Inflammation caused by H.pylori infection may be playing some role in increasing insulin resistance, causing greater risk of developing diabetes mellitus [7,26,27]. Some ophthalmic [28,29] and skin disorders [30,31,32,33,34,35] may also be associated with this infection.

A study [36] highlighted the association of H. pylori infection with ischemic heart disease, idiopathic thrombocytopenic purpura, iron deficiency anemia and other diseases but recommended that the evidence must be produced from larger studies than banking on case reports, pilot studies or *in-vitro* data. They also linked H. pylori infection (HPI) with neurodegenerative, respiratory, and other miscellaneous disorders. They held low-grade inflammatory state and molecular mechanisms triggered by HPI to be responsible for pathogenesis of these conditions. A brief description of some of the extragastric manifestations of HPI are as follows:

Hematological and Nutritional Deficiencies

Chronic gastritis caused by HPI infection is related with gastric hypochlorhydia that is instrumental in impairing the iron absorption and conversion of dietary iron from ferric to ferrous form [37]. It must be understood that iron in hemoglobin is in the reduced ferrous state and hence this impairment of iron absorption and inability to convert the dietary iron from ferric to ferrous form is instrumental in bringing about iron deficiency anemia in HPI patients. Apart from this, a link between HPI and hepcidin (a hormone related with iron metabolism) has also been reported. Hepcidin is reported to show a turbulent increase triggered by HPI, as an acute phase reactant in response to the inflammation in the gastric mucosa simulating the conditions similar to "anemia of inflammation or chronic disease" [38,39]. The association of HPI with iron deficiency anemia is one of the most commonly reported extragastric manifestation of HPI.

A study carried out a case-control study that included 150 adult (18-50 years old) patients infected with H. pylori as cases and 150 age- and sex-matched healthy adults as controls [5]. They found the mean Hb, RBC, WBC and HCt levels to be significantly lower. The authors also observed that mean serum B_{12} and iron levels of cases were significantly lower as compared to that of controls. On follow-up of HPI patients, they found a significant increase in vitamin B12 and serum iron levels and their restoration to close to normal levels as a result of treatment.

Allergic and Respiratory Diseases

A recent meta-analysis also found that HPI shows an inverse relationship with atopy/allergic diseases [9,40,41,42] .

Autoimmune Diseases

Another study also found the HPI infection to be associated with an increase in inflammatory marker (IL-6, TNF-α) levels [43].

Eye Diseases

A systematic review discussed the role of HPI induced oxidative stress in affecting the integrity of trabecular meshwork, conjunctiva and retina and thereby an increased risk of eye diseases [44].

Another systematic review and meta-analysis that included 15 studies with 2664 participants (872 glaucoma patients and 1792 controls) found a significant association between HPI and glaucoma. The authors were of the view that active *H. pylori* infection may be associated with glaucoma [45].

Cardiovascular Disease and Metabolic syndrome

A recent systematic review and meta-analysis that included a total of 22 studies that evaluated 206,911 subjects found the pooled estimate of odds ratio between HPI and metabolic syndrome was 1.19 in case-control and pooled risk ratio was 1.31 in cohort studies [(46)]. They also found a significantly higher pooled odds ratio (OR=1.54) for the association between insulin resistance and HPI in case-control studies.

A meta-analysis found a significant association of positive anti-*H. pylori* IgG with increased risk of coronary heart disease (OR=1.58) [(47)]. They also found a significant association of anti-CagA, *H. pylori* stool antigen and histopathological staining for *H. pylori* with subsequent development of CHD

A systematic review and meta-analysis that included thirteen studies with 2298 individuals (1360 HPI positive and 938 HPI negative) who were assessed for carotid intima media thickness (CIMT) found the CIMT of HPI positive cases to be significantly thicker as compared to HPI negative individuals (Mean difference 0.07 mm) thus showing an association of HPI with CIMT thickening which is considered as a subclinical marker of atherosclerosis and increases the cardiovascular risk [(48)].

Type 2 Diabetes

A study done on diabetic patients found that among T2DM patients those with higher BMI were more likely to have HPI as compared to those with normal BMI [(49)].

Hypertension

A positive association has been seen between H.pylori infection and prevalence of hypertension as per another study [(50)].

Neurological Diseases

The odds of prevalent stroke in relation to HPI to be significantly higher (OR=1.19) as compared to those without HPI, thus linking HPI with stroke [(51)].

Greater neuro-inflammation has been seen in H.pylori infected patients of Alzheimer's disease associated with impairment of cognitive abilities [(52)].

H.Pylori may also affect the brain-gut axis linking it to psychiatric disorders also eg depression [(53)].

EXTRAGASTRIC MANIFESTATION	SUGGESTED PATHOPHYSIOLOGY
Iron deficiency anemia	damaged gastric mucosa affecting functioning of iron transporters
B12 deficiency anemia	increased incidences of gastritis affecting gastric mucosa and thus, hampered release of intrinsic factor in absorption of vitamin b12
bronchial asthma	suppressed th2 mediated [(54)] allergic response
Cholelithiasis [(55)]	h.pylori infection in bile
gastroesophageal reflux disease	Hyperacidity
coronary artery disease	increased levels of homocysteine
diabetes mellitus	increased production of cytokines, phosphorylation of serine residues from insulin receptor
idiopathic thrombocytopenic purpura (ITP)	CagA may stimulate synthesis of anti- Cag A antibodies that cross react with platelet surface antigens
Non - alcoholic fatty liver disease [(56,58,59)]	H.pylori induced insulin resistance, reduced adiponectin [(57)] production, liver inflammation

Summarizing the understood mechanisms for various extra-gastric manifestations of H.pylori in the table 1

CONCLUSION

H.pylori infection is known to be commonly associated with gastric manifestations. But, now recent studies are evidently showing its role in extragastric diseases. There is a paucity of studies and knowledge about the

extragastric manifestations of H.pylori infection. More extensive studies with larger sample sizes and meta analysis need to be conducted in future not only to elucidate and understand the pathophysiology of such extragastric manifestations but also for exploring its therapeutic role in management of h.pylor infection. Thus, there is a need for making health programmes like school level screening for eradication of this infection at early stages.

Declaration by Authors

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