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Are Histopathological Changes of *H. pylori* Infection in Young Dyspeptic Patients Necessitate Endoscopy?

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Abstract

BACKGROUND: *Helicobacter pylori* is an important gastrointestinal infective bacteria with many serious complications including gastric erosions and ulceration, duodenal ulcer, gastric carcinoma and MALT gastric lymphoma. The gastric biopsy is commonly performed in *H. pylori*-positive dyspeptic individuals, and many previous researchers studied the histopathological features of infected gastric biopsies however little previous studies focused on the histopathological findings in young population in comparison to the older one.

AIM: To make a focus on the histopathological effects of *H. pylori* infection in young patients compared with the older one and predicts the need for endoscopy in this population, also to estimates the prevalence of infection in Iraqi patients.

MATERIAL AND METHODS: the sample for this study is 180 patients in total, they attended Marjan medical city in Iraq for dyspepsia of more than 3 months and prepared for OGD. Patients asked for their permission to do immunological tests for *H. pylori*. Both serology for H. pylori antibodies and stool for antigen tests are used, and the case is included in the study only if both tests were positive, after OGD, the gastric biopsies are processed and examined histopathologically.

RESULTS: Normal gastric biopsy is the most common histopathological finding in young (< 25 years) patients (75%) while chronic atrophic gastritis is the most common one in patients > 25 years age (57%). The prevalence of *Helicobacter pylori* infection in dyspeptic patients was 73.3%, the correlation between infection and sex was insignificant (p-value 0.06), and no significant correlation between infection and age (p-value 0.07) was concluded.

CONCLUSION: *H. pylori*-related histopathological changes of gastric mucosa in young (< 25 years) are commonly mild and does not necessitate endoscopy at this age unless there are alarming signs.

Introduction

Dyspepsia is the most common gastrointestinal problem all over the world. Its meaning refers to a variety of unpleasant symptoms such as nausea, vomiting, epigastric pain or discomfort, heartburn, feeling of gastric fullness and early satiety [1]. In the recent Asian consensus, most of the members agreed to define dyspepsia as symptoms that related to the gastroduodenal region and that continues for three months or more [2].

Helicobacter pylori infection is one of the important treatable causes of dyspepsia. Its prevalence varies among different countries and regions in the same country, including Asian countries as a result of different social habits, geographical conditions, races and ethnicity [3], [4]. The prevalence of infection with this microorganism is 25-50 per cent in the developed countries and 70-90 percent in the developing countries in 2001 [5]. It had been found that individuals who lived in low social classes are more likely to harbour the organism as the chance for getting contaminated food and water is more. Overcrowding and bad hygiene are important predisposing factors for bacterial transmission [6]. The general prevalence of infection all over the world is about 50% [7]. *H. pylori* is a gram-negative actively motile bacteria. It is urease producing bacteria and its pathogenicity is mainly attributed to its production of urease enzyme, active motility and toxins production

[8]. The histopathological effect of *H*. *pylori* varies from just dyspepsia with normal endoscopic findings to chronic superficial gastritis in which inflammation is limited to the faveola, chronic atrophic gastritis with varying degree of glandular atrophy, peptic ulcer, gastric carcinoma, and even lymphoma. So, it is a risky organism that if it is given suitable attention and treated properly, this will prevent a problematic squally [8], [9]. Many previous studies had been made on the prevalence of *H*. *pylori* and found that there is no significant sex predilection [10], [11]. Age predilection for infection varies among studies with multiple studies refer to increased prevalence with age [10], [11]. However, it is common for this bacterial infection to be acquired during childhood and continue to adulthood [12], [13].

The common route for infection transmission is through oral-oral route, also feco-oral and less commonly incidentally through an endoscopy procedure. The infection with this microorganism is most common in developing Asian countries than in developed countries. This may be belonging to less hygienic water use, insufficient diet and overcrowding in these regions [14], [15]. The pathogenesis of *Helicobacter pylori* includes multiple steps. After entering the gastrointestinal tract, the organism utilises its ability to produce urease to neutralise gastric acidity and survive in the macrophages [16], then it uses its flagella to move toward the epithelial cell surface and attach to surface epithelial cells by adhesins- receptor interaction [17]. Finally, *H*. *pylori* has the capacity to produce cytotoxins: cytotoxin associated gene A (Cag A) and vacuolating cytotoxin A (VacA), these toxins together with the cytokines produced by the inflammatory cells that recruited by immunological response result in tissue damage and ulceration and it had been found that some types of these toxins may have a role in carcinogenesis [18], [19].

Many methodologies for the diagnosis of *Helicobacter pylori* are existing. Invasive and non-invasive methods may differ in their sensitivity and accuracy. Invasive antral biopsy with the histopathological examination, Giemsa stain and rapid urease test (RUT) prove its efficacy as gold standards method, however not all patients prefer this invasive procedure unless they are severely suffering [20]. The RUT also required a bacterial load of about 10^5 bacteria to be adequately sensitive, so it is not advisable for follow up after treatment [21], [22]. Non-invasive procedures including serology with IgG and IgM detection against microorganism in the sera of the patients and stool examination for bacterial antigen are rapid tests, of low cost and more acceptable to the patients. Blood examination with serological detection of anti-bacterial antibodies was less specific as it continues to give positive results for several months after eradication of microorganism [23].

On the other hand, detection of bacterial antigen in the stool proved to be more specific in the diagnosis as well as in patients follow up after treatment and eradication. A study of Mohammad Khalifehgholi et al., found that the sensitivity and specificity of stool antigen test is 74% and 78 % respectively [24]. The same study also found that the sensitivity and specificity of serology is 91.3% and 55.6% respectively [24]. The histopathological changes of gastric mucosa, which are the most important axis in this paper, are variable among most studies. In a study of Mohamed Hasan et al., gastritis had been identified histologically in 100% of H. pylori-positive population [25]. Non-atrophic (superficial) gastritis was detected in the majority of H. pylori-infected individual with no risk of transformation to peptic ulcer or adenocarcinoma [26] while chronic atrophic gastritis is often associated with metaplasia with increased risk of adenocarcinoma [27]. Multiple previous papers and articles talked about histopathological changes of H. pylori in the gastric biopsy of infected patients but little previous studies focused on the histological changes in dyspeptic young people harbouring the organism and if these changes are serious enough to recommend endoscopy in this age group. Our study will target this age group and comparing them with the older population to show if there is an urgent need for endoscopy or not.

Patients and Methods

In total, 180 dyspeptic patients were investigated for *H*. *pylori* infection over ten months. The cases were collected from Marjan medical teaching city for internal medicine/ laboratory unit and endoscopy unit between March 2018 and December 2018.

Exclusion criteria are 1. Patients with a known history of the previous infection with *Helicobacter pylori* and those who took a course of antibiotics for eradication recently (in the last month); 2. Those with dyspepsia for less than three months were excluded from the study because the histopathological changes might not be evident yet, and 3. patients with positive stool antigen but negative serology also excluded because of the possibility of recent infection and inadequate histological findings.

Ethical issues: the agreement of the hospital where the samples are collected had been taken. The permission for serum and stool antigen test had been provided by our patients. Gastric biopsies had been already planned for our patients as part of their management, and we only utilised the slides and paraffin blocks.

The complaints of the sample individuals vary, including nausea, epigastric pain, heartburn, flatulence, and bloating sensation. Patients with these

symptoms for three months or more were included in the study. Methods that used for diagnosis were both serology for IgG and IgM, stool for H. pylori antigen detection and histopathological examination of Giemsa stained sections of gastric biopsy. Patients who prepared for OGD attended the lab for routine investigations, and at that time, they asked for their permission for both blood and stool sample test of *Helicobacter pylori*. For the serological test, 5 ml of blood was drawn from the patients; the sera were separated and examined immediately for both IgG and IgM against organism using commercial *H*. *pylori* ELISA kit (Genedia). A stool sample was examined for *H*. *pylori* antigen using antibody of commercial ELISA kit (ARG80556). The case was regarded as positive if both serology and stool test were positive. Of 180 patients who prepared for the endoscopic examination, 5 patients did not attend the hospital at the time of endoscope (the remaining 175 samples). Of the 175 cases of endoscopic samples, 48 cases were excluded from histopathological assessment because they were negative for H. pylori by both serology and stool for antigen tests. After routine processing of the gastric endoscopic biopsies, histopathological examination was performed using formalin-fixed paraffin-embedded sections and hematoxylin & eosin-stained slides. The remaining 127 biopsies are reviewed by examination of H&E stained sections by two pathologists and independently from previous reports and sections of paraffin blocks are stained with Giemsa for H. pylori clarification in cases that were negative by H&E stained slides.

Statistical analysis

Chi-square test is used for data analysis and p-value of ≤ 0.05 is regarded as significant. The data were analysed with SPSS software version 20.

The descriptive analysis also used and percentages are calculated.

Results

Of the total 180 cases, 132 (73.3%) cases were positive for infection, 60 (33.33%) were male, and 42 (70%) of them was positive, while 120 (66.66%) were female with 90 (75%) cases were positive. Of the total 132 positive cases, 31.8% were males and 68.18% were females (Table 1). There is no significant correlation between the sex and *H*. *pylori* infection with p-value 0.06; however, about two-thirds of *H*. *pylori*-positive cases were female. The mean age for total positive cases was 33.4 year. Regardless of the infection with *H*. *pylori*, the number of females who are suffering from dyspepsia were more than males. The age distribution of infected individuals showed that the number (and percentage) of positive cases was more in the age group > 25 years (54.54% vs 45.45%).

There is a mild increase in the prevalence of infection in patients with age > 25 years. The histopathological examination showed that of 60 cases whom < 25 years old, 45 cases were normal gastric biopsy (75%) apart from a few scattered inflammatory cells infiltrate.

Table 1: prevalence of Helicobacter pylori infection and pattern of distribution among gender and ages

Variable	Patients	H.pylori positive No.(%)
Gender		
Male	60 (33.33 %)	42 (31.8%)
Female	120 (66.66 %)	90 (68.18%)
Total	180	132 (73.3%)
Age (year)		
≤ 25	72 (40%)	60 (45.45%)
> 25	108 (59.99%)	72 (54.54%)

While 12 biopsy (20%) showed mild superficial gastritis with chronic inflammatory cells restriction to the faveolar region and no atrophy, and only 3 cases (5%) showed moderate chronic superficial gastritis. So that the chance of serious histopathological findings (more than mild superficial gastritis) in young, infection positive people is low significantly (with p-value 0.035). In patients over 25 years age, mild superficial gastritis was found in 3 cases (4%), moderate superficial gastritis in 17 cases (23%), mild to moderate chronic atrophic gastritis in 20 cases (27%), severe atrophic gastritis in 22 cases (30%), chronic gastric ulcer in 8 cases (11%) and 2 cases (2.7%) of gastric adenocarcinoma (both of them were over 60 years age). In age group > 25 years, there was a predominance of chronic atrophic gastritis histologically over other pathological findings but there was no significant difference (p-value > 0.05), Table 2.

Examination of Giemsa stained sections and H&E stained sections showed positivity for H. pylori organism in gastric mucosa in 102 cases with only 30 cases where negative (23 negative cases were in young patients with near-normal biopsy). This might be attributed to the patchy colonisation of the mucosa or low-density bacteria. Giemsa stain was required only in 50 cases with 52 cases were positive by H&E stained sections. So that only 77% of H. pylori-positive patients by immunology proved to be positive by histopathological examination.

Table 2: distribution of histopathological findings among two population of H. pylori-positive patients (< 25 years age and > 25 years age group)

Histopathological findings	No. of patients < 25 yr. (%)	No. of patients > 25 yr. (%)
Normal gastric biopsy	45 (75)	0 (0)
Mild superficial gastritis	12 (20)	3 (4)
Moderate superficial gastritis	3 (5)	17 (23)
Mild to Moderate chronic atrophic gastritis	0 (0)	20 (27)
Sever chronic atrophic gastrits	0 (0)	22 (30)
Chronic gastric ulcer	0 (0)	8 (11)
Gastric adenocarcinoma	0 (0)	2 (2.7)
total	60 (100)	72 (100)

Discussion

The American Gastroenterological Association (AGA) recommended endoscopy in patients older than 55 years and those with alarming signs (weight loss, bleeding, persistent vomiting and family history of gastric carcinoma) [28]. In the current work, the histopathological finding matched the AGA recommendation about the importance of age as a limiting factor in endoscopy but with 25 years age rather than 55. In a study of Uemura, only atrophic gastritis can progress to metaplasia and adenocarcinoma [27]. So it is not horrible to find superficial gastritis which is the most serious finding that is revealed in this study, in young. Hong Koh et al., the study revealed mild atrophy in 55.2% and moderate atrophy in 3.4% [29]. While Kamada T et al., found that atrophy is present in 27.7% in the antrum and 28.6% in the corpus of Japanese young [30]. Both previously mentioned results were away from the findings of the current study, putting in mind the differences in the populations of the studies and their health and diet habit. The histopathological findings of Carvalho MA et al., research was very close to this study regarding the absence of gastric atrophy in young age group [31].

Histopathological examination proved the presence of H. pylori in gastric mucosa of only 77% of infection positive patients, somewhat similar to Mohamed Hasan et al., a study which discovered it histologically in 83.8% of stool antigen-positive [25]. This may be attributed to patchy colonisation of the microorganism.

The study showed that the prevalence of *Helicobacter pylori* infection in Iraq is 73.3%; the value is similar to that conducted by other studies from developing countries in Asia and the middle eastern [32]. Two studies performed in India showed that about 80% of the population was infected with Helicobacter pylori [33], [34]. Several studies that performed in other Asian countries such as Kuwait and Iran reported a decrease in the prevalence of infection in these regions with a prevalence of 49.7% and 47.9% respectively [35], [36]. In Iran, another two old studies reported a prevalence of 85% and 89.2%, so there is a decreased prevalence in this area as later study showed a prevalence of only 31% [35]. In this study, the prevalence is higher than other values that reported in nearby countries and this may reflect a low health care services in Iraqi community after a series of wars that follow in Iraq and the resultant low socioeconomic status. As in other similar studies, the correlation between the sex and the infection with *Helicobacter pylori* was insignificant. However, some of these researches, as in this study, showed a frank predominance of infection in dyspeptic females patients [3], [10], [35].

It had been found that there is a slight predominance of *Helicobacter pylori* infection in the age group of more than 25 years (54.54% in > 25 years vs 45.45% in ≤ 25 years). However, there was no significant correlation of infection with age. Studies of Ramin Niknam et al. and other researchers showed a significant correlation and increased prevalence with age [1], [3], [10].

In conclusion, the *H. pylori*-related histopathological changes of the gastric mucosa are less significant in young individual (< 25 years). The prevalence of *Helicobacter pylori* infection is still high in Iraq, in contrast, to declining prevalence in many Asian countries.

Recommendations: 1. there is no urgent need to do gastric endoscopy in H. pylori-positive people whom less than 25 years age (unless there are alarming signs) and its complications can be avoided; 2. studies about the causes of the high prevalence of helicobacter pylori are recommended to achieve a good preventive measure.

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