

Does spontaneous eradication of *Helicobacter pylori* infection lead to functional dyspepsia?

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Research Article

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Abstract

Introduction: The treatment of patients with functional dyspepsia in cases of active helicobacter pylori (H. pylori) infection is not promising. Therefore, the present study was designed to determine in which of the dyspeptic patients with the normal endoscopic examination and negative stool testing for H. pylori antigen (without a history of specific treatment for H. pylori) there is evidence of a previous H. pylori infection in the serum.

Materials and methods: In this cross-sectional study, patients with functional dyspepsia who were negative in terms of the H. pylori stool antigen test and rapid urease test, and had no obvious gross pathologic sign in gastroduodenoscopy were considered suitable candidates for serological study for the detection of H. pylori IgG specific antibodies.

Results: A total of 200 patients were enrolled in this study, including 86 men (43%) and 114 women (57%), with an average age of 38.76 ± 12.35 years. The results showed that 109 (54.5%) were positive subjects were positive by anti-H. pylori IgG ELISA tests. It was found that positive anti-H. pylori IgG ELISA tests were a higher significant difference among rural residents (75.2%) compared with urban residents (24%) ($p < 0.001$).

Conclusion: More than half of patients with functional dyspepsia have a history of previous H.pylori infection. Despite the possibility of spontaneous H. pylori infection, the complication of old infections may be sustained by dyspepsia and early treatment of acute H. pylori infections may prevent this complication.

Introduction

Helicobacter pylori, a gram-negative bacterium, is widely distributed throughout the world and can be found in the stomach of many people. It can play an important role in peptic ulcer disease, gastric carcinoma, and gastric lymphoma.^{1,2} In developing countries such as Iran, the prevalence of H. pylori infection is higher.³ The dyspepsia is a clinical condition that refers to symptoms such as pain or discomfort in the upper abdomen, early satiety, abdominal bloating and distention, fullness, belching, and nausea.⁴ Dyspepsia has been reported to affect more than 40 percent of the world's population in the West and is very common in Asian countries.⁵

Although there is no precise mechanism for dyspepsia, it has suggested several pathophysiological mechanisms, including delayed as well as accelerated gastric emptying, motility disorders, acute and chronic infections, visceral hypersensitivity, genetic susceptibility, acid disorders, impaired gastric accommodation, abnormal fundic phasic contractions, Helicobacter pylori infection, and psychological factors.⁶ Some patients with acute dyspepsia have H. pylori-associated gastritis, and as a result of infection with H. pylori in the gastric mucosa, disturbances in gastric secretion and motor function may occur and the patient expresses it as symptoms of dyspepsia.⁷ In the province of Ardabil, the prevalence

of *H. pylori* infection may be as high as 89.2% among dyspeptic patients who have not received specific treatment for *H. pylori*.⁸ However, it is not clear how many dyspeptic patients who have no evidence of *H. pylori* infection have a history of the previous infection.

In our previous experience, the treatment of patients with dyspepsia in cases of active infection with *Helicobacter pylori* infection is not promising and the eradication of this infection does not help to resolve these symptoms, and there was no significant difference in the mean symptom score of patients in the treated group compared to the placebo group.⁹ It can be hypothesized that only timely treatment in the acute phase of the infection may prevent the onset of symptoms of dyspepsia.

Therefore, the present study was designed to determine in which of the dyspeptic patients with the normal endoscopic examination and negative stool testing for *H. pylori* antigen (without a history of specific treatment for *H. pylori*) there is evidence of a previous *H. pylori* infection in the serum? The results of this study can also help to determine the rate of *H. pylori* infection that has been eradicated without specific treatment.

Methods And Materials

Design and population

This cross-sectional study was approved by the Ethics Committee of the Ardabil University of Medical Sciences. Patients presenting with functional dyspepsia to the referral gastroenterology outpatient clinic of Imam Khomeini Hospital in Ardabil, Iran between Jun 2015 and March 2016 were recruited for the study subjects. Written informed consent was obtained from all participants.

Functional dyspepsia was diagnosed if a patient met all of the following criteria: persistent or recurring dyspepsia for more than 3 months within the past 6 months; the absence of a possible organic cause of the symptoms on endoscopy; and without any sign that the dyspepsia is diminished only by defecation or of a correlation with fecal irregularities.

A total of 200 participants with functional dyspepsia who had a negative stool exam for *Helicobacter pylori* antigen were included in this study. All patients were assessed by a thorough history, physical examination, and routine laboratory investigations. In order to evaluate the cause, the patients were a candidate for endoscopy based on the opinion of the gastroenterologist. The criteria for entering the study were only those who complained of functional dyspepsia with negative stool antigen test, negative rapid urease test, and normal upper gastrointestinal endoscopy.

Patients who met the following criteria were excluded from the study: (1) a positive *H. pylori* infection using a positive stool antigen test; (2) a positive *H. pylori* infection using a rapid urease test and histology; (3) a history of hospitalization for ≤ 1 month before the study; (4) evidence of biliary disease at ultrasonography; (5) receiving antacids, non-steroidal anti-inflammatory drugs, antibiotics, bismuth, or

proton-pump inhibitors within the prior 4 weeks; (6) past medical history of H. pylori-eradication therapy; and (7) Unwillingness to participate in the study.

H. pylori stool antigen test

The H. pylori stool antigen test, using a monoclonal antibody-based sandwich enzyme-linked immunosorbent assay, was used to analyze the stool samples.

Upper gastrointestinal endoscopy

The standard upper gastrointestinal endoscopy was performed with a Pentax EG-2990K Video Gastroscope (Pentax Medical Company, Tokyo, Japan) after overnight fasting by two experienced gastroenterologists. Multiple biopsy specimens were obtained from the antrum of the stomach for rapid urease test (Kimberly-Clark, CLO test, Rapid Urease Test Gel, GA 30076-2199 USA) and histology.

H. pylori serological assessment

Patients who were negative in terms of stool antigen test and rapid urease test, and had no obvious gross pathologic sign in gastroduodenoscopy were considered suitable candidates for serological study. The method used for serum analysis of the samples was based on Enzyme-Linked Immunosorbent Assay techniques (ELISA) and the use of the commercial kits for IgG assay (EIAgen, Clone system S.P.A., Casalecchio Di Reno, Italy). This assay system was based on the qualitative detection of IgG specific antibodies to H. pylori. The cut-off values of more than 15 arbitrary units (AU) per milliliter (ml) were considered as a positive test. The advantage of serological tests is based on the findings of anti-H. pylori antibodies is that are less likely to be confounded by suppression of H. pylori infection by medications.¹⁰

Statistical analysis

The results were expressed as means \pm standard deviations (SD). The statistical analysis of the data was done using SPSS software (version 21, SPSS Inc., Chicago, IL, USA). A value of $P < 0.05$ was considered significant.

Results

A total of 200 patients were enrolled in this study, including 86 men (43%) and 114 women (57%). Their age ranged from 18 to 65 years, with an average age of 38.76 ± 12.35 years. The highest percentage of patients was between the ages of 18 and 35 (44.5%).

Of the 200 patients, 109 (54.5%) were positive and 91 (45.5%) were negative for the anti-H. pylori IgG ELISA tests (**Figure 1**). Of the 109 patients with a positive test, 67 (61.5%) were female and 42 (38.5%) were male, and there was no significant difference between sex and positive anti-H. pylori IgG ELISA test ($p = 0.113$). In addition, the results showed that there was no significant difference in the IgG ELISA test at different ages.

Of the total cases, 139 cases (69.5%) were rural residents and 61 (30.5%) were urban residents, which had a statistically significant association ($p < 0.001$). In addition, it was found that positive anti-*H. pylori* IgG ELISA tests were a higher significant difference among rural residents (75.2%) compared with urban residents (24%) ($p < 0.001$, **Figure 2**).

Discussion

In this study, patients with functional dyspepsia without a history of eradication therapy for *H. pylori* infection, which had a negative stool antigen test, negative rapid urease test, and normal upper gastrointestinal endoscopy, were examined for anti-*H. pylori* IgG test. We found that more than half of these patients (54.5%) have a positive anti-*H. pylori* IgG test. This means that these patients have had a history of infection, and have improved without special treatment. It seems that functional dyspepsia may be a complication of *H. pylori* infection, not caused by the infection itself. Therefore, perhaps the treatment of acute cases of *H. pylori* infection may prevent complications such as dyspepsia.

Spontaneous eradication refers to cases where *Helicobacter pylori* infection has been removed without specific treatment. The results of two separate studies in children with a follow-up of two years have shown that 2.15% to 16.6% of the infection is self-eradicated.^{11,12} Concerning the higher rate of spontaneous eradication of patients in the present study, it can be concluded that the passage of time may cause spontaneous eradication of the *H. pylori* infection. It is also possible that the spontaneous recovery of some patients is due to the excessive consumption of antibiotics for the treatment of other infections. However, it remains a question of whether spontaneous eradication of the *H. pylori* infection may be accompanied by complications such as functional dyspepsia.

Regarding the absence of any obvious pathologic findings in gastroendoscopy and negative test results of Stool antigen test and negative Rapid urease test, it can be concluded that more than half of the patients with functional dyspepsia have a history of *Helicobacter* infection which is eradicated without specific treatment. The results also warn that the decision to eradicate the infection based solely on a positive serologic test, such as *H. Pylori* IgG, as the only evidence of the presence of the disease will lead to overtreatment. On the other hand, the hypothesis is that spontaneous healing of the infection may end with dyspepsia, which reminds us that timely treatment may prevent these complications.

Concerning the higher rate of self-eradication of patients in the present study, it can be concluded that self-eradication may increase with time. It is also possible that the spontaneous healing of some patients was due to excessive consumption of antibiotics for treating other infections. However, whether self-eradication is accompanied by complications such as dyspepsia remains a question.

In Italy, a prospective study, involving 304 children (age range, 4.5 to 18.5 years), conducted to evaluate whether *H. pylori* infection can undergo spontaneous eradication in children.¹² The children were tested for *H. pylori* using the ¹³C-urea breath test. Infected children were followed up every 6 months for as long as 2 years. Parents were instructed to record the consumption of antibiotics. Eighty-five out of 304

(27.9%) children were *H. pylori*-infected. Forty-eight out of 85 infected children (56.4%) participated in the follow-up study. After 2 years, 8 (16.6%) infected children had negative results on 13C-urea breath tests; 2 of them were given antibiotics for concomitant infections. One child was negative at 6 months but became positive again at the next 6-month 13C-urea breath test. Forty children remained persistently positive; of them, 10 were treated with a short course of antibiotics. The results of their study supported the hypothesis that, at least during childhood, *H. pylori* infection may be a fluctuating disease with spontaneous eradication and possible recurrence.¹²

The prevalence of *H. pylori* infection depends on a variety of factors, such as geographical location, educational level, economic conditions, Individual health level, and close contact with *H. pylori* infectious people.¹³ Our previous study showed that 72% of non-treated functional dyspepsia have a positive stool antigen test, and the results showed that functional dyspepsia does not respond well to the treatment of *H. pylori*.⁹ In the present study, the history of *H. pylori* infection in rural residents was significantly higher than that of urban residents, which is consistent with previous studies and may be associated with poor health and lower quality of life.¹⁴

Conclusion

In summary, despite the possibility of spontaneous *H. pylori* infection, the complication of old infections may be sustained by dyspepsia and early treatment of acute *H. pylori* infections may prevent this complication. To prove this hypothesis, we need complementary studies. However, it still remains unclear whether a spontaneous eradication can occur over time.

Declarations

Ethical considerations: Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Conflict of Interest: We declare that there is no conflict of interest in our article.

Competing interests: We declare that there is no competing interests in our article.

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Authors' contributions: SH, MRA, JM, AY& MIA conceived the concept, researched and analyzed the literature, and wrote the manuscript; SH, BC & NM analyzed the literature and edited the manuscript. All read and approved the final manuscript.

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Figures

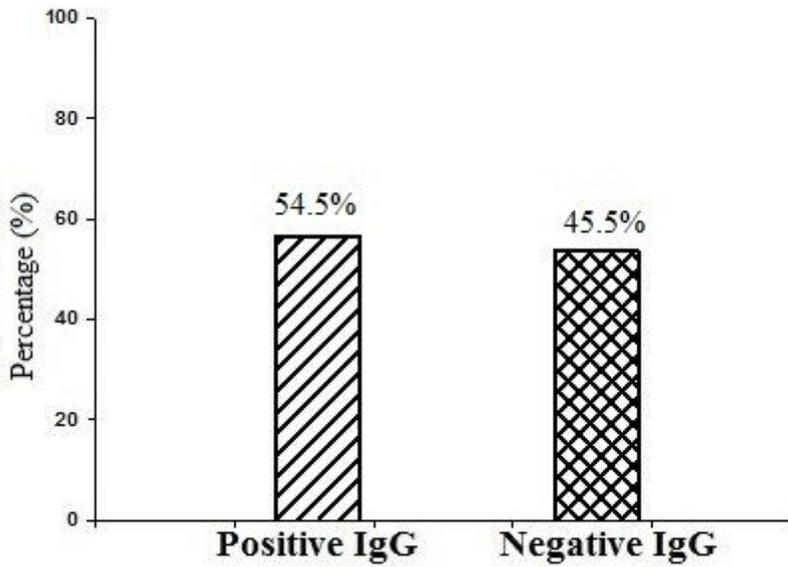


Figure 1

Percentage of anti-H. Pylori IgG ELISA positive or negative tests in the study population.

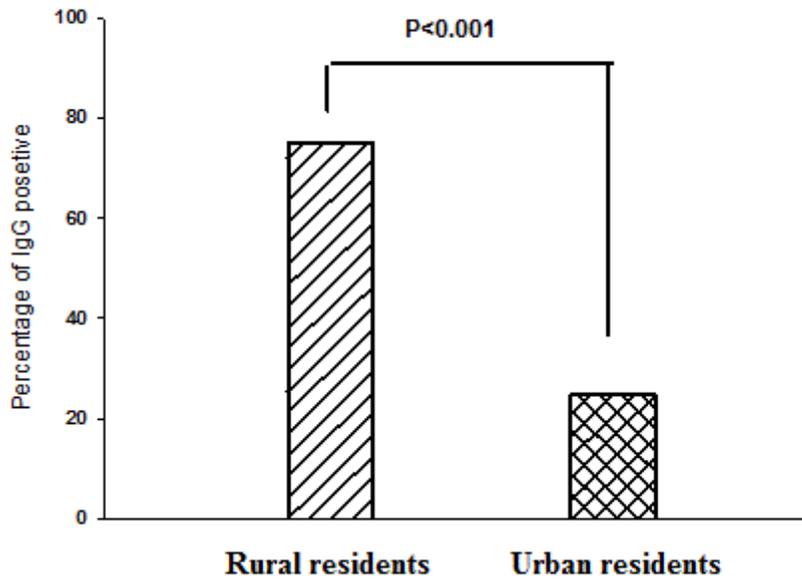


Figure 2

The percentage of anti-H. pylori IgG ELISA positive tests in rural and urban residents.