Typical and atypical symptoms of gastro esophageal reflux disease: Does Helicobacter pylori infection matter?

Laurino Grossi, Antonio Francesco Ciccaglione, Leonardo Marzio

Laurino Grossi, Antonio Francesco Ciccaglione, Leonardo Marzio, c/o Digestive Sciences Unit, School of Gastroenterology, G. d’Annunzio University Chieti-Pescara, Ospedale Spirito Santo, 65124 Pescara, Italy

Author contributions: Grossi L was the author involved in the conception of the study and drafting the manuscript; Grossi L and Ciccaglione AF performed the exams and obtained the clinical history of patients and interpreted the results; Marzio L supervised the report and gave final approval of the version submitted.

Institutional review board statement: It was not necessary to get an Ethics Committee approval as no drugs or therapeutic techniques have been used in this study. However, the work has been done with the permit of the Ethics Committee of Ospedale Spirito Santo, Pescara, which was fully informed about the research.

Informed consent statement: Patients were not required to give a complete informed consent. All patients recruited into the study had been referred to our Unit to perform a pH-monitoring. They were only interviewed about H. pylori status, without assuming any drugs or testing medical techniques. After receiving full information about the study and giving informed, written consent, each patient underwent C13 Urea Breath test. All patients were reassured about the anonymous characteristics of data recruitments.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Correspondence to: Laurino Grossi, MD, Associate Professor, c/o Digestive Sciences Unit, School of Gastroenterology, G. d’Annunzio University Chieti-Pescara, Ospedale Spirito Santo, Via Fonte Romana, 8, 65124 Pescara, Italy. lgrossi@unich.it Telephone: +39-085-4252460

Received: May 26, 2015
Peer-review started: May 28, 2015
First decision: June 18, 2015
Revised: July 15, 2015
Accepted: September 7, 2015
Article in press: September 8, 2015
Published online: November 6, 2015

Abstract

AIM: To analyze whether the presence of Helicobacter pylori (H. pylori) infection could affect the quality of symptoms in gastro-esophageal reflux disease (GERD) patients.

METHODS: one hundred and forty-four consecutive patients referred to our Unit for suspected GERD were recruited for the study. All patients underwent esophageal pH-metric recording. For those with a positive test, C13 urea breath test was then performed to assess the H. pylori status. GERD patients were stratified according to the quality of their symptoms and classified as typical, if affected by heartburn and regurgitation, and atypical if complaining of chest pain, respiratory and ears, nose, and throat features. H. pylori-negative patients were also asked whether they had a previous diagnosis of H. pylori infection. If a positive response was given, on the basis of the time period after successful eradication, patients were considered as “eradicated” (E) if H. pylori eradication occurred more than six months earlier or “recently eradicated” if the therapy had been administered within the last six months. Patients without history of infection were identified as “negative” (N). $\chi^2$ test was performed by combining the clinical aspects with the H. pylori status.
RESULTS: one hundred and twenty-nine of the 144 patients, including 44 H. pylori-positive and 85 H. pylori-negative (41 negative, 21 recently eradicated, 23 eradicated more than 6 mo before), were eligible for the analysis. No difference has been found between H. pylori status and either the number of reflux episodes (138 ± 23 vs 146 ± 36, respectively, P = 0.2, not significant) or the percentage of time with pH values < 4 (6.8 ± 1.2 vs 7.4 ± 2.1, respectively, P = 0.3, not significant). The distribution of symptoms was as follows: 13 typical (30%) and 31 atypical (70%) among the 44 H. pylori-positive cases; 44 typical (52%) and 41 atypical (48%) among the 85 H. pylori-negative cases, \( P = 0.017 \) vs H. pylori+; OR = 2.55, 95%CI: 1.17-5.55). Furthermore, clinical signs in patients with recent H. pylori eradication were similar to those of H. pylori-positive \( (P = 0.49; OR = 1.46, 95\% CI: 0.49-4.37) \); on the other hand, patients with ancient H. pylori eradication showed a clinical behavior similar to that of H. pylori-negative subjects \( (P = 0.13; OR = 0.89, 95\% CI: 0.77-6.51) \) but different as compared to the H. pylori-positive group \( (P < 0.05; OR = 3.71, 95\% CI: 0.83-16.47) \).

CONCLUSION: Atypical symptoms of GERD occur more frequently in H. pylori-positive patients than in H. pylori-negative subjects. In addition, atypical symptoms tend to decrease after H. pylori eradication.

Key words: Eradication; Helicobacter pylori; C13 urea breath test; Symptoms; Gastro-esophageal reflux disease; pH-metry

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: This study aimed to investigate whether the presence of Helicobacter pylori (H. pylori) infection could affect the symptom pattern of patients with gastro-esophageal reflux disease (GERD). GERD patients with H. pylori were predominantly affected by atypical symptoms (chest pain, respiratory pain, nose, throat features) whilst patients without infection mainly referred typical GERD symptoms (heartburn, regurgitation). Therefore, it seems reasonable to assume that H. pylori infection may have a role in GERD pathogenesis or at least in the modulation of symptoms appearance.

Grossi L, Ciccaglione AF, Marzio L. Typical and atypical symptoms of gastro esophageal reflux disease: Does Helicobacter pylori infection matter? World J Gastrointest Pharmacol Ther 2015; 6(4): 238-243 Available from: URL: http://www.wjgnet.com/2150-5349/full/v6/i4/238.htm DOI: http://dx.doi.org/10.4292/wjgpt.v6.i4.238

INTRODUCTION

Gastro-esophageal reflux disease (GERD) and Helicobacter pylori (H. pylori) infection represent two of the most common diseases affecting upper GI tract. GERD is clinically characterized by different patterns, generally identified as typical or atypical. Typical symptoms are heartburn and acid regurgitation\(^1\), while atypical extraesophageal manifestations can include symptoms primarily attributable to other organs, such as chronic cough, non cardiac chest pain, chronic pharyngitis and laryngitis\(^2\). A small amount of patients refer symptoms (epigastric pain, nausea, belching, vomiting) that may overlap with other gastrointestinal conditions, such as dyspepsia, severe gastritis, peptic ulcer disease or hiatal hernia. Despite a huge amount of evidence on diagnosis and therapy of such different patients, limited information is available to explain why one can experience typical or atypical symptoms and whether the presence of H. pylori infection could affect the quality of symptoms in GERD patients. Whilst the role of H. pylori has been widely recognized in the pathogenesis of gastritis\(^3,4\), peptic ulcer\(^5,6\) and even gastric malignancies\(^7,8\), there is conflicting evidence in the literature about a possible link between infection and natural history of GERD. Many authors proposed a “protective” role of H. pylori against acid refluxes, probably due to the reduced acid production in infected patients, but the exact mechanism is not well known\(^9\). On the contrary, other studies have demonstrated the lack of any influences between the two diseases\(^10\). Therefore, the question has been mainly limited to demonstrate whether H. pylori could protect from or facilitate the onset of pathological gastro-esophageal refluxes. In the present study we investigated whether H. pylori infection has a role in the clinical appearance of GERD.

MATERIALS AND METHODS

Selection of patients

We enrolled 144 consecutive patients undergoing esophageal 24-h pH-metric recording for suspected GERD on the basis of typical or atypical extraesophageal symptoms. To rule out overlapping with other upper GI diseases, we did not consider patients with epigastric pain, nausea, vomiting as predominant symptoms and scheduled for pH monitoring. The procedure was performed using a probe with a single glass electrode on the tip (Jubileum, Microbioprobe and Telemedecine srl, Marigliano-NA, Italy) connected to a portable data logger (pH-day, Menfis Biomedical, Bologna Italy). The main inclusion criteria was the confirmation of GERD by the pH monitoring, according to De Meester criteria\(^11\). All patients had a previous upper GI endoscopy within the last six months in order to exclude the presence of malignancies, Los Angeles grade C or D esophagitis, peptic ulcer, erosive gastritis, and hiatal hernia. In addition, recent full examinations by cardiologist, pneumologist and otolaryngologist were required to rule out specific diseases of their competence. All patients were required to complete a minimum four-week wash-out period of antisecretory drugs (PPI, H-
H. pylori infection

A C13 Urea Breath Test was performed on all patients on the same day of pH-meter recording. Patients were classified as H. pylori-positive (H. pylori+) or H. pylori-negative (H. pylori-). H. pylori-negative patients were also asked whether they had a previous diagnosis of H. pylori infection. If a positive response was given, on the basis of the time period after successful eradication, patients were considered as “eradicated” (E) if the therapy had been administered six months earlier (E). Group RE: 13 patients (70%) showed typical pattern (Figure 1). Group N: 16 of the 41 patients (39%) without H. pylori infection were affected by atypical manifestations, whereas 27 of them (65%) referred typical clinical signs. Group RE: 13 of 21 patients (62%) with recent H. pylori eradication had typical symptoms and 8 of 21 (38%) presenting typical GERD manifestations (Figure 2). Group E: 12 of the 23 patients (52%) with H. pylori eradication performed more than 6 mo earlier had atypical GERD symptoms. Typical signs occurring in 9 patients (48%) (Figure 2).

Statistical analysis

After collecting the data, χ2 test was performed to identify significant correlations between clinical aspects (i.e., typical or atypical) and H. pylori status (i.e., positive or negative; if negative: eradicated or recently eradicated). A P-value less than 0.05 (P < 0.05) was inferred significant. Odd ratio (OR) and 95%CI were also calculated. The primary endpoint was to find a correlation between symptoms pattern and H. pylori presence; then, we wanted to evaluate whether this correlation could change in relation of period of time after bacterial eradication.

RESULTS

pH profile and H. pylori status

Of the 144 initially enrolled subjects, 129 patients (73 male, 56 female, age: 19-65) resulted affected by GERD at 24-h pH monitoring. In this case series, 44 were H. pylori-positive and 85 were H. pylori-negative. No difference has been found between H. pylori status and either the number of reflux episodes (138 ± 23 vs 146 ± 36, respectively, P = 0.2, not significant) or the percentage of time with pH values < 4 (6.8 ± 1.2 vs 7.4 ± 2.1, respectively, P = 0.3, not significant). Among the negative group, 41 patients had no history of previous H. pylori infection (N), 21 patients had been recently H. pylori-eradicated (RE) and 23 patients had been successfully treated for H. pylori eradication more than six months earlier (E).

GERD symptoms

Typical symptoms of GERD were present in 57 patients (34 male, 23 female), whereas 72 patients (38 male, 34 female) resulted affected by atypical manifestations.

BMI and smoking habits

Among 129 patients with GERD, 12 subjects (7/72 patients of atypical group and 5/57 patients of typical group) had a BMI indicative of slight overweight, i.e., between 25 and 30 (9.7% vs 8.3%, respectively, P = 0.1, not significant). Furthermore, there were 41 active smokers with 22 patients among atypical group and 19 patients among typical group (30.5% vs 33.3%, respectively, P = 0.2, not significant).

H. pylori infection and quality of symptoms

Group H. pylori+: 31 of the 44 patients (70%) with H. pylori infection were affected by atypical symptoms, whereas 13 of them (30%) referred typical clinical signs. Group H. pylori-: 41 of the 85 patients (48%) without infection had atypical manifestations and 44 of them (52%) showed typical pattern (Figure 1). Group N: 16 of the 41 patients (39%) without H. pylori infection were affected by atypical symptoms, whereas 27 of them (65%) referred typical clinical signs. Group RE: 13 of 21 patients (62%) with recent H. pylori eradication had atypical symptoms and 8 of 21 (38%) presenting typical GERD manifestations (Figure 2). Group E: 12 of the 23 patients (52%) with H. pylori eradication performed more than 6 mo earlier had atypical GERD symptoms. Typical signs occurring in 9 patients (48%) (Figure 2).

Statistical significance

Atypical GERD symptoms were significantly more frequent in H. pylori-positive than in H. pylori-negative patients (P = 0.017; OR = 2.55, 95%CI: 1.17-5.55). Also, patients with recent eradication of H. pylori infection had a predominance of atypical signs that resulted not significantly different from H. pylori-positive (P = 0.49; OR = 1.46, 95%CI: 0.49-4.37), but
were different in comparison with H. pylori-negative patients ($P < 0.05; \text{OR} = 2.36, 95\%\text{CI}: 1.12-1.06$). In patients with H. pylori eradication obtained more than 6 mo earlier, the clinical pattern was similar to the H. pylori-negative group ($P = 0.13; \text{OR} = 0.89, 95\%\text{CI}: 0.77-6.51$) and their symptoms were mainly typical with a distribution significantly different as compared to the H. pylori-positive group ($P < 0.05; \text{OR} = 3.71, 95\%\text{CI}: 0.83-16.47$) (Figure 3).

**DISCUSSION**

The results of our study indicate that the presence of H. pylori infection in patients affected by GERD is associated with a greater frequency of atypical extraesophageal manifestations. In addition, GERD patients without H. pylori infection are preferentially affected by typical heartburn and regurgitation.

The relationship between GERD and H. pylori infection has been widely analyzed over the years but the question is still controversial. There are data supporting a protective role of H. pylori\cite{12,13} as a consequence of gastric atrophy and hypochlorhydria from parietal cells destruction due to chronic H. pylori infection\cite{14}. In the meanwhile, mild antral gastritis could be associated with hyperchlorhydria and more severe GERD by reduction in the number of somatostatin-secreting D-cells with loss of negative feedback on gastric acid secretion\cite{15}. Discordant results are also referred to the need of H. pylori eradication in GERD patients. In fact, some evidence suggests that eradication of the infection may be a risk factor for de-novo endoscopic esophagitis\cite{16}, whereas other studies report a low risk of gastric atrophy in patients with successful H. pylori eradication and undergoing long-term acid suppression with PPI\cite{17}.

Our study tried to look at this relationship from another perspective. We analyzed data of patients with GERD to determine whether the status of H. pylori infection affects the clinical pattern of reflux disease, without considering whether H. pylori could determine or prevent GERD. We found that the presence of gastric infection seems to facilitate the insurgence of atypical extraesophageal manifestations of reflux. It is unlikely that this association arose by chance as clinical pattern in GERD patients shows a clear trend towards atypical manifestations, directly correlated to H. pylori status. In fact, the symptoms of H. pylori-positive patients were predominantly atypical, a condition confirmed in the cases with very recent eradication. On the other hand, clinical aspects of patients successfully treated for H. pylori infection long time earlier resulted similar to those of H. pylori-negative patients. This suggests that the presence of bacterial infection has an action on GERD clinical pattern which is progressively reduced by the time the infection is eradicated. The major criticism of our results is that other factors, e.g., smoking, obesity and alimentary habits, could potentially affect the course of reflux disease and its clinical patterns\cite{18}. However, these factors were unlikely to play a role in our population since we ruled out severe obese patients and recruited only slightly overweight patients, whose distribution was similar between subjects with typical and atypical symptoms. Furthermore, no correlation was found between smoking and clinical characteristics. Therefore, albeit considering the potential limit of a retrospective analysis, our data seem to indicate that lifestyle probably affect the characteristics of GERD less than H. pylori status.

In the present study, we did not identify the mechanisms through which H. pylori acts on the quality of reflux disease. Therefore, we can only make some speculations on the underlying conditions affecting different symptom patterns. First, the more severe degrees of esophagitis seem to be less correlated to H. pylori presence\cite{19}; this could be one explanation for a major heartburn in our patients without infection. However, we can only partially confirm this assumption because in order to properly reduce the chance of confounding bias in our analysis, we excluded patients with Los Angeles grade C-D, known to have fewer reflux symptoms\cite{20}. Second, the onset of symptoms (chronic cough, laryngitis or chest pain) seems strictly related to reflux episodes that extend proximally\cite{21}. It could be that H. pylori-associated antral

---

**Figure 2** Distribution of symptoms in patients who eradicated Helicobacter pylori less than 6 mo before pH monitoring (on the left) and in patients who eradicated Helicobacter pylori more than 6 mo earlier (on the right). The data represent the percentage distribution of typical symptoms (in dark grey) and atypical extraesophageal symptoms (in light grey). H. pylori: Helicobacter pylori.

**Figure 3** Percentage distribution of typical (dark grey) and atypical (light grey) symptoms in our four different groups of patients. From left to right, the bars indicate the group of patients Helicobacter pylori (H. pylori)-positive (P), eradicated less than 6 mo before pH monitoring (RE), eradicated more than 6 mo earlier (E), and H. pylori-negative (N). As shown, there is a progressive change in the percentage of symptoms related to the pattern of H. pylori infection. $P < 0.01$ between N and P; $P < 0.01$ between N and RE; $P < 0.05$ between E and P.
gastritis increases the release of gastrin concomitantly with higher acidity and increased volume of refluxate that more easily reaches the proximal site of the esophagus. Our study did not directly analyze the extension of refluxate as a single-channel pH-metric probe was used; however, there is some evidence on a greater frequency of proximal reflux episodes in pediatric patients with H. pylori infection[22] in good accordance with our results. Another possible explanation of the relationship between H. pylori and clinical appearance of GERD may be found in the modulation of afferent neural signals by H. pylori[23] an effect that seems related to ghrelin, a peptide with intense prokinetic activity on LES region[24]. It is well known that H. pylori-positive patients show low levels of circulating ghrelin, which tend to increase after bacterial eradication[25]. It is also demonstrated that patients with H. pylori infection have a lower LES tone and a reduced esophageal body motility[26]; therefore, it seems likely that a low plasma ghrelin concentration limits the clearance of acid inside the esophagus, thus facilitating proximal extension of reflux episodes.

A final consideration is that our present findings were made on the Caucasian population so it is reasonably difficult to extrapolate data from our study to predict what might happen to patients from other countries. In fact, the literature shows that the relationship between GERD and H. pylori seems completely different in East Asia compared to Western countries[27,28]. It is also well known that genetic predisposition can alter acid secretion[29] as well as visceral sensitivity of esophageal wall to acid[30]. Therefore, the interaction between host genetic factors and other agents, such H. pylori itself, could lead to different expression of GERD, but this aspect needs to be further clarified.

In conclusion, our findings suggest a role for H. pylori infection in the clinical pattern of GERD. Further analyses are required to evaluate if our results represent a potentially new strategy to modulate symptoms occurrence or indicate a simple association with no roles in the pathogenesis of GERD. Since it is already known that H. pylori does not affect the pH profile of patients with GERD[31], it seems appropriate to say that the relationship between H. pylori and pH appears more complex than previously thought. In fact, H. pylori is likely to interact with GERD, but when these two entities coexist, H. pylori seems to change the way of GERD symptoms appear rather than promoting or facilitating it.

ACKNOWLEDGMENTS

The Authors thank Dr. Sonia Torracchio for reviewing the English style of the manuscript.

REFERENCES

1 Petroff OA, Burlina AP, Black J, Prichard JW. Metabolism of [1-13C]glucose in a synaptosomally enriched fraction of rat cerebrum studied by 1H/13C magnetic resonance spectroscopy. Neurochem Res 1991; 16: 1245-1251 [PMID: 1667675 DOI: 10.1007/BF00263347]
2 Hom C, Vaezi MF. Extra-esophageal manifestations of gastroesophageal reflux disease: diagnosis and treatment. Drugs 2013; 73: 1281-1295 [PMID: 23881666 DOI: 10.1007/s40265-013-0101-8]
3 Beji A, Vincent P, Darchis I, Husson MO, Cortot A, Leclere H. Evidence of gastritis with several Helicobacter pylori strains. Lancet 1989; 2: 1402-1403 [PMID: 2574351 DOI: 10.1016/S0140-6736(89)92020-5]
4 Dooley CP, Cohen H, Fitzgibbons PL, Bauer M, Appleman MD, Perez-Perez GI, Blaser MJ. Prevalence of Helicobacter pylori infection and histologic gastritis in asymptomatic persons. N Engl J Med 1989; 321: 1562-1566 [PMID: 2586553 DOI: 10.1056/NEJM198907133212302]
5 Glise H. Epidemiology in peptic ulcer disease. Current status and future aspects. Scand J Gastroenterol Suppl 1990; 175: 13-18 [PMID: 2232775 DOI: 10.3109/00365529009093122]
6 Sidebotham RL, Baron JH. Hypothesis: Helicobacter pylori, urease, mucus, and gastric ulcer. Lancet 1990; 335: 193-195 [PMID: 1967668 DOI: 10.1016/0140-6736(90)90279-E]
7 Loffeld RJ, Willems JF, Fendrig A, Arends JW. Helicobacter pylori pylori and gastric carcinoma. Histopathology 1990; 17: 537-541 [PMID: 2076886 DOI: 10.1111/j.1365-2559.1990.tb00793.x]
8 Helicobacter and cancer Collaborative Group. Gastric cancer and Helicobacter pylori: a combined analysis of 12 case control studies nested within prospective cohorts. Gut 2001; 49: 347-353 [PMID:
null
