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Main Article

Helicobacter pylori infection and chronic, persistent cough: is there an association?

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Abstract

Introduction: Chronic, persistent cough is a common clinical problem, the cause of which sometimes remains unidentifiable.

Aims: To study a potential association between *Helicobacter pylori* infection and chronic, persistent cough.

Materials and methods: A clinical observational study with symptom analysis, including 162 patients whose main presenting complaint was chronic, persistent cough of unidentifiable cause (study group) and 42 patients with chronic, non-specific laryngopharyngeal manifestations not including chronic cough (control group).

Results: Active *H pylori* infection was present in 86.4 per cent (140/162) of patients in the chronic cough group, as opposed to 45.2 per cent (19/42) of the control group, as confirmed by detection of *H pylori* antigen in stool specimens. This difference was statistically significant ($p < 0.001$). There was a significant improvement of the chronic cough of 75.4 per cent (98/130) of patients after successful *H pylori* eradication using appropriate medical therapy ($p < 0.001$).

Conclusions: *Helicobacter pylori* infection may lead to laryngopharyngeal irritation, with several clinical manifestations including chronic, persistent cough. However, the exact mechanism of this requires further research.

Key words: Helicobacter Pylori; Cough; Pharynx; Larynx

Introduction

Persistent cough is a common clinical problem which can disrupt patients' sleep as well as their academic, professional and social activities. The prevalence of chronic cough among the non-smoking adult population is reported to range from 14 to 23 per cent.[1] By definition, chronic, persistent cough is a cough lasting for more than eight weeks in a non-smoking, immunocompetent patient who has a normal chest radiograph, is not receiving therapy with an angiotensin-converting enzyme inhibitor and has not been exposed to an environmental irritant. In this setting, the three most common causes of chronic cough are: postnasal drip (41 to 58 per cent), cough variant asthma (24 to 59 per cent) and gastroesophageal reflux (21 to 41 per cent). Eosinophilic bronchitis is another, relatively recently recognised condition which may account for up to 10–15 per cent of patients attending cough clinics. Frequently, patients have more than one of these conditions.[2,3]

Historically, a number of approaches have been proposed for the diagnosis and management of patients with chronic, persistent cough, including: an anatomical diagnostic protocol; full investigation for common causes in all patients; and empirical trials of therapy without initial investigations.[3–8] The most cost-effective, widely accepted approach is a systemic evaluation that initially assesses the likelihood of the most common causes, via trials of empirical therapy and avoidance of irritants and relevant drugs. This is accompanied by focused laboratory testing (e.g. chest radiography or methacholine challenge), followed by additional testing and consultation with a specialist if necessary.[9,10]

After excluding asthma, postnasal drip syndrome and eosinophilic bronchitis, gastroesophageal reflux related cough should be considered. Ours *et al.*[11] concluded that the 'best diagnostic and therapeutic approach' was empirical treatment for two weeks with a high dose proton pump inhibitor. This empirical diagnostic trial was much more cost-effective than pH testing followed by treatment. These authors reported that none of the patients with a negative pH test responded to high dose proton pump inhibitor, and only 35 per cent of patients with an abnormal pH test improved. This suggests that an abnormal pH test alone is not a reliable predictor of acid-related

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cough. Treatment failures may be due to inadequate acid suppression (which would be detected by oesophageal pH testing), resistance to acid suppression, non-acid reflux, and/or failure to recognise and treat other conditions that could cause chronic cough.[12–14]

Helicobacter pylori has been recently identified in the tracheobronchial aspirates of mechanically ventilated patients, and the possibility that it might cause ventilator-associated pneumonia has been raised.[15]

These findings led us to investigate the role of *H pylori* infection in the aetiology of chronic, persistent cough and the effect of *H pylori* eradication on the symptomatology of such patients. The prevalence of various laryngopharyngeal manifestations in *H pylori* infected patients was also assessed.

Materials and methods

Patients and inclusion criteria

We enrolled in the study 162 adult patients referred to our otolaryngology out-patient clinics complaining of chronic, persistent cough, over a two-year period between October 2003 and September 2005. The inclusion criteria were: (1) normal or near-normal chest radiograph; (2) non-smokers and no exposure to other environmental irritants; (3) no treatment with angiotensin-converting enzyme inhibitors; (4) no improvement following appropriate, specific treatment for postnasal drip syndrome; (5) exclusion of asthma and eosinophilic bronchitis via pulmonary function testing, histamine challenge testing and induced sputum analysis; and (6) no improvement (partial or complete) following treatment with histamine antagonists or proton pump inhibitors.

Forty-two age- and sex-matched subjects with no history of chronic cough were included as a control group. They presented to us with benign, chronic laryngopharyngeal symptoms that did not respond to medical treatment, including empirical treatment for gastroesophageal reflux disease. None had received prior *H pylori* eradication therapy.

Methods

The patients included in this study underwent thorough history-taking, including meticulous assessment of symptoms. A self-administered symptom questionnaire was used to evaluate each symptom on a ranking scale, with zero indicating no complaints and one to four indicating mild, moderate, severe and intolerable complaints, respectively. The questions concerned the following symptom subcategories: chronic, persistent cough and its effect on quality of life; symptoms related to the upper gastrointestinal tract (dyspepsia, heartburn and food regurgitation); and laryngopharyngeal symptoms (hoarseness of voice or dysphonia, globus pharyngeus, frequent throat-clearing and excessive throat mucus, halitosis, chronic sore throat, choking, and laryngospasm, especially at night).

A thorough clinical examination was performed, including general, cardiac, thoracic, abdominal and neurological examinations. Patients with thyroid enlargement and lymphadenopathy of the neck were excluded.

A thorough ear, nose and throat examination was performed, including examination with a magnifying 90° rigid laryngoscope.

General, routine laboratory investigations were performed.

As a screening test, *H pylori* immunoglobulin (Ig) G antibody titres were assayed using a serum enzyme-linked immunosorbent assay. An IgG value of 15 IU/ml was determined as the cut-off value, above which the patient was accepted as positive for *H pylori*. In seropositive patients, the active status of *H pylori* infection was confirmed through the detection of *H pylori* antigen in stool specimens.[16]

At the time of diagnosis, all *H pylori* infected subjects received triple therapy consisting of amoxicillin (1 g twice daily), clarithromycin (500 mg twice daily) and omeprazole (20 mg twice daily) for 14 days. Omeprazole was then continued at a dose of 40 mg/day for four weeks.

Helicobacter pylori status was followed up six weeks after the completion of treatment, either by detection of *H pylori* antigen in stools[17] or by the urea breath test.[18,19] This approach was chosen to confirm cure, as *H pylori* seropositivity may persist long after eradication of the organism.[20] Symptomatology was reassessed following therapy, and improvement was defined as a reduction in the ranking score of the evaluated symptom of at least two.

Ethical considerations

The study protocol was approved by the ethics committee of the Faculty of Medicine of Alexandria University. Informed consent was obtained from all participating subjects prior to their inclusion.

Statistical analysis

Statistical analysis was carried out by using the Statistical Package for the Social Sciences computer software for Windows (SPSS Inc, Chicago, Illinois, USA). Comparisons of mean age in patient groups were performed using the unpaired *t*-test. The chi-square test was used to compare the prevalence of *H pylori* infection between the chronic cough group and the control group. Comparisons of the male to female ratios and the prevalence of various upper gastrointestinal and laryngopharyngeal symptoms between *H pylori* positive and negative subjects were also performed using the chi-square test. Following treatment, the exact binomial test was used to test the significance of changes in the prevalence of chronic cough, upper gastrointestinal symptoms and laryngopharyngeal symptoms, for patients with successful *H pylori* eradication and those with unaltered *H pylori* status. We considered $p < 0.05$ to be statistically significant.

Results and analysis

Demographic data

This study was conducted on a total of 204 subjects, divided into two groups. The study group included

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162 patients with chronic, persistent cough, of whom 92 were women and 70 men (female:male ratio = 1.3:1), with a mean age of 44 ± 10.5 years. The control group included 42 age- and sex-matched subjects with no history of chronic cough, of whom 23 were women and 19 men (female:male ratio = 1.2:1), with a mean age of 40.6 ± 10.9 years.

Helicobacter pylori positivity

The rate of seropositivity to *H pylori* was 147/162 (90.7 per cent) in the chronic cough group and 24/42 (57.1 per cent) in the control group. The difference was found to be statistically significant ($p < 0.001$). Detection of *H pylori* antigen in stools confirmed active infection in 86.4 per cent (140/162) of patients in the chronic cough group and in 45.2 per cent (19/42) of the control group; this difference was also statistically significant ($p < 0.001$). Thus, at presentation, a total of 159 subjects were actively infected with *H pylori* (i.e. positive) and 45 subjects were not infected with *H pylori* (i.e. negative). The mean age was significantly higher in the *H pylori* infected patients (46 ± 10 *vs* 33.8 ± 7 years; $p < 0.001$). In both groups studied, no significant difference was found between women and men regarding *H pylori* positivity.

Patients' symptoms and laryngoscopic findings

A total of 127 patients (62.3 per cent) had at least one symptom related to the upper gastrointestinal tract. This was reported in 66 per cent of *H pylori* positive patients and in 48.9 per cent of *H pylori* negative patients. The prevalence of dyspepsia and heartburn was significantly greater in *H pylori* positive subjects. As for laryngopharyngeal symptoms, at enrolment, the prevalence of dysphonia, globus sensation, frequent throat-clearing, chronic sore throat and choking was significantly greater in the *H pylori* positive patients compared with the *H pylori* negative ones. The prevalence of upper gastrointestinal and laryngopharyngeal symptoms among the 204 subjects studied is shown in Table I. The associated laryngoscopic findings at presentation are shown in Table II and Figure 1. Oedema and erythema of the posterior larynx and interarytenoid mucosal heaping were more frequently reported in *H pylori* positive subjects. However, no statistically significant differences were observed.

Rate and effect of H pylori eradication

The bacterium was eradicated in 137 out of 159 (86.2 per cent) *H pylori* infected patients (130/140 of the chronic cough group and 7/19 of the control group) after six weeks of therapy, as assessed by either *H pylori* antigen stool test or urea breath test. All patients were compliant with their therapy, with only mild adverse effects that did not result in discontinuation of treatment in any patient. Dyspepsia and heartburn were significantly reduced following treatment. Comparison of *H pylori* positive patients' chronic cough and other laryngopharyngeal symptoms before and after *H pylori* treatment revealed a significant reduction in the prevalence of the majority of these symptoms, including chronic cough (Table III). Conversely, the prevalence of evaluated symptoms did not significantly change following treatment in the group of patients with unchanged *H pylori* infection status (22 patients).

Discussion

Since Warren and Marshall reported in 1983 the culture of spiral organisms from the stomach, subsequently named *Helicobacter pylori*, the role of this organism as a potential cause of serious upper gastrointestinal disease has been increasingly appreciated.[21] *Helicobacter pylori* is a microaerophilic, gram-negative bacterium which is causally related to chronic active gastritis, peptic ulcer disease, primary low-grade B-cell gastric lymphoma and gastric carcinoma.[15] Approximately half the world's population is infected with *H pylori*, with higher isolation rates in developing countries.[22,23]

Recently, several studies have assessed the association between *H pylori* infection and a miscellany of extra-digestive diseases, such as cardiovascular, immunological and various other pathologies. This prompted us to investigate the possible relationship between *H pylori* infection and chronic, non-specific laryngopharyngeal manifestations, with special emphasis on chronic, persistent cough of

TABLE I

PREVALENCE OF UPPER GASTROINTESTINAL AND LARYNGOPHARYNGEAL SYMPTOMS*

Symptom	*H pylori* positive† [*n* (%)]	*H pylori* negative‡ [*n* (%)]	*p*
Upper gastrointestinal			
Dyspepsia	77 (48.4)	11 (24.4)	0.004**
Heartburn	78 (49)	11 (24.4)	0.003**
Food regurgitation	26 (16.4)	4 (8.9)	0.212
Laryngopharyngeal			
Dysphonia	64 (40.3)	10 (22.2)	0.026**
Globus sensation	97 (61)	10 (22.2)	<0.0001**
Frequent throat-clearing	101 (63.5)	12 (26.7)	<0.0001**
Halitosis	14 (8.8)	7 (15.6)	0.188
Chronic sore throat	60 (37.7)	6 (13.3)	0.002**
Choking	124 (78)	9 (20)	<0.0001**

*In 204 subjects. †$n = 159$; ‡$n = 45$; ** = statistically significant

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TABLE II

PREVALENCE OF LARYNGOSCOPIC FINDINGS*

Laryngoscopic finding	*H pylori* positive† [*n* (%)]	*H pylori* negative‡ [*n* (%)]	*p*
Oedema & erythema of posterior larynx	85 (53.5)	18 (40)	0.111
Interarytenoid mucosal heaping	50 (31.4)	13 (28.9)	0.743
Contact ulcer	3 (1.9)	1(2.2)	0.886
Granuloma	8 (5)	2 (4.4)	0.872
Reinke's oedema	9 (5.7)	3 (6.7)	0.800
Polyp/nodule	11 (7)	4 (8.9)	0.655
Leukoplakia	10 (6.3)	3 (6.7)	0.927

*In 204 studied subjects. †$n = 159$; ‡$n = 45$

unidentifiable cause. Our results clearly show that a high percentage (up to 86.4 per cent) of patients with chronic, persistent cough appeared to suffer from active *H pylori* infection. This was significantly higher than the percentage of active infection among age- and sex-matched controls without cough.

No definitive data are available on the role of *H pylori* in the pathogenesis of airway disorders.

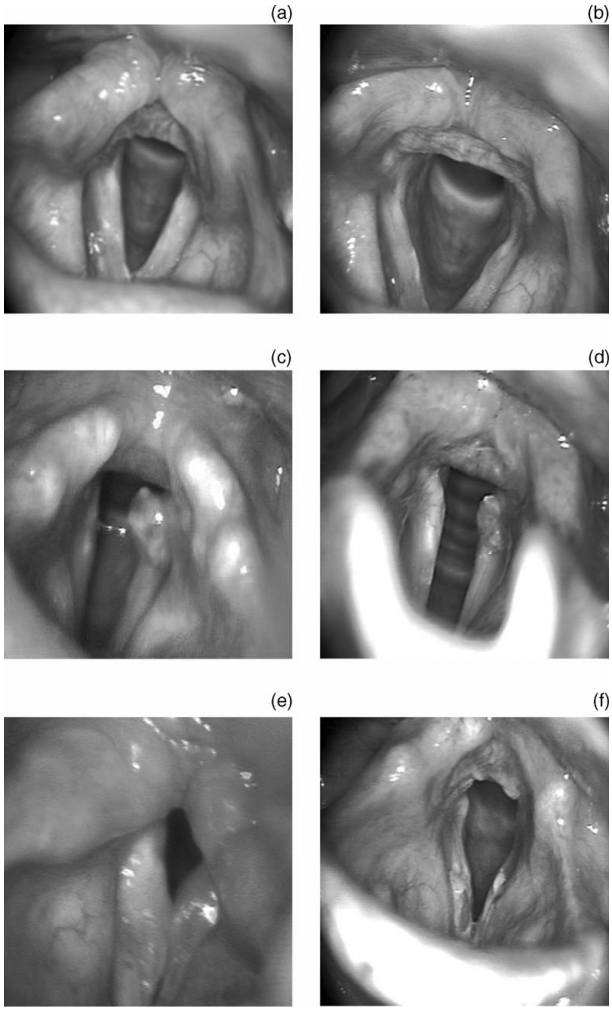

FIG. 1

Laryngoscopic findings in *Helicobacter pylori* positive patients: (a) erythema of the medial surface of both arytenoids; (b) interarytenoid mucosal heaping; (c) left vocal process granuloma; (d) left contact ulcer; (e) Reinke's oedema; (f) leukoplakia of both vocal folds.

However, the pro-inflammatory nature of *H pylori* infection could be a key triggering factor. *Helicobacter pylori* is capable of adhering to epithelial cell lines originally derived from different organs, particularly the respiratory tract. The organism is characterised by the release of large amounts of various pro-inflammatory and vasoactive substances, such as cytokines (interleukin 8 and tumour necrosis factor α), eicosanoids and acute phase proteins.[24,25] It is possible that spilling or inhalation of *H pylori* or its exotoxins into the respiratory tract may induce chronic airway inflammation, resulting in a chronic, dry cough in these patients. This mechanism is supported by a previous study which found a high concentration of interleukin 8 and tumour necrosis factor α in samples of induced sputum from non-asthmatic patients with chronic, dry cough, including those with idiopathic cough.[26]

Another possible explanation focuses on the relationship between *H pylori* and gastroesophageal reflux disease, still a complex and poorly understood association. Manes *et al.*[27] suggested that continuous release of inflammatory mediators in the proximal stomach could result in *H pylori* colonisation, which could exert direct or indirect effects on the oesophageal mucosa, increasing oesophageal sensitivity to acid. Moreover, *H pylori* infection may also affect lower oesophageal sphincter motility directly through inflammation at the gastroesophageal junction.[28] As a result, exposure of the lower oesophagus to comparably short term reflux episodes, through vagally mediated reflexes, could result in coughing and chronic throat-clearing, which eventually could lead to the evolution of laryngeal mucosal signs and symptoms.

In the present study, meticulous history-taking revealed a significantly higher prevalence of a wide range of laryngopharyngeal symptoms in *H pylori* positive subjects, compared with *H pylori* negative ones. The associated laryngoscopic findings, particularly oedema and erythema of the posterior larynx and interarytenoid mucosal heaping, were also more prevalent in the infected group, but the difference did not reach statistical significance when compared with *H pylori* negative subjects.

Clinically, these findings are usually attributed to gastroesophageal reflux related laryngitis. However, several studies showed that these signs are not specific and were significantly associated with the presence of other laryngeal irritants such as

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TABLE III

IMPROVEMENT OF SYMPTOMS FOLLOWING SUCCESSFUL *H PYLORI* ERADICATION*

Symptom	Prevalence before treatment (*n*)	Improved after treatment		*p*
		n (%)	95% CI	
Chronic cough	130	98 (75.4)	67.1, 82.5	<0.0001†
Gastrointestinal				
Dyspepsia	70	48 (68.6)	56.4, 79.1	0.001†
Heartburn	66	47 (71.2)	58.7, 81.7	<0.001†
Food regurgitation	21	10 (47.6)	25.7, 70.2	0.668
Laryngopharyngeal				
Dysphonia	60	41 (68.3)	55.0, 79.7	0.003†
Globus sensation	88	64 (72.7)	62.2, 81.7	<0.0001†
Frequent throat-clearing	95	60 (63.2)	52.6, 72.8	0.007†
Halitosis	12	5 (41.7)	15.2, 72.3	0.806
Chronic sore throat	49	33 (67.3)	52.5, 80.1	0.011†
Choking	109	67 (61.5)	51.7, 70.6	0.011†

*In 137 *H pylori* positive patients. †Statistically significant. CI = confidence interval

smoking, allergies, asthma and postnasal drip.[29] Moreover, findings similar to those seen in laryngopharyngeal reflux patients were revealed in asymptomatic participants.[30,31] Therefore, there is a strong possibility that these findings may not be related to gastroesophageal reflux. Therefore, lack of response to empirical proton pump inhibitor therapy should not be followed by escalating treatment for gastroesophageal reflux but, rather, by searching for another contributing factor.[32] The presence of inflammatory mediators in the upper airway could enhance the sensitivity of afferent nerves, and this might explain the wide range of laryngopharyngeal manifestations in *H pylori* positive patients. Recently, *H pylori* was positively identified in 31 per cent of vocal fold specimens, which might suggest a possible link between *H pylori* infection and organic vocal fold lesions.[33]

- **Chronic, persistent cough is a common, annoying clinical problem with numerous aetiologies**
- **This study investigated the possible role of *Helicobacter pylori* infection in the aetiology of chronic, persistent cough of an unidentifiable cause**
- ***Helicobacter pylori* active infection was statistically more prevalent in patients with chronic cough compared with controls**
- **Eradication of *H pylori* appeared to result in a significant improvement in patient symptomatology**
- **The results of this clinical study support the concept of a potential association between *H pylori* infection and the development of chronic, persistent cough; the exact mechanism of this association is unknown, however, and further research is needed**

The results of our study suggest that chronic, persistent cough and a variety of other chronic laryngopharyngeal manifestations that are unresponsive to diagnostic empirical treatment with high dose proton pump inhibitor could be considered as extra-digestive manifestations of *H pylori* infection. This is further supported by the significant improvement in patients' symptoms following successful eradication of the bacterium. However, further research is required to confirm the aetiological role of *H pylori* infection. Until then, we recommend (1) investigations to detect *H pylori* infection in all patients with non-specific laryngeal and pharyngeal symptoms which do not respond to conventional medical therapy, and (2) bacterial eradication in those found to be infected. This management strategy could be sufficient to reduce the impact of these symptoms on patients' quality of life.

Conclusions

The results of this study support the theory of a potential relationship between *Helicobacter pylori* infection and various chronic, non-specific laryngopharyngeal manifestations, including chronic, persistent cough. Although the exact pathogenesis of such a relationship is still not well defined, it is possible that the pro-inflammatory nature of *H pylori* infection could be the key triggering factor. Our results are further supported by the significant improvement in patients' symptoms following successful eradication of the bacterium.

These findings prompt us to recommend (1) investigations to detect *H pylori* infection in patients with manifestations of persistent, non-specific laryngopharyngeal irritation, and (2) *H pylori* eradication treatment for patients with active infection, as a simple and inexpensive curative tool for such cases.

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