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ORIGINAL ARTICLE

INCIDENCE OF HELICOBACTER PYLORI IN PATIENTS WITH LARYNGOPHARYNGEAL REFLUX DISEASE, AND ITS CORRELATION WITH SYMPTOM SEVERITY

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Abstract

Aim: The purpose of this study was to determine the Incidence of Helicobacter Pylori infection in patients with laryngopharyngeal reflux disease and whether the severity of symptoms in positive H. pylori patients is different than negative H. pylori patients.
Laryngopharyngeal Reflux Disease (LPRD) implies a backward of part of the stomach contents up the throat. The literature has reported a relationship between reflux esophagitis with Helicobacter pylori infection but not yet with reflux laryngitis.

Methods: 483 patients with atypical symptoms of LFRD were subjected to laryngoscopic evaluation, ambulatory 24 hours pH monitoring and HpSA test.

Results: an incidence of HpSA positive test was 64% among the study population.
There is no significant difference between hoarseness of voice, chronic unexplained cough, feeling of a lump in throat, frequent throat clearing, bad/bitter taste in mouth with HpSA test results. Also there was no significant difference between the mean intensity, frequency and indices of the symptoms with the HpSA test results

Conclusion: The incidence of the H. pylori infection in patients with LFRD in our study was 64%, statistical analysis did not reveal significant difference in symptom severity among patients, the questionable role of H pylori infection is discussed.

Keywords: H pylori, larynx, inflammation, symptoms.

INTRODUCTION

Gastro esophageal Reflux Disease (GERD) defined as a backward flow of gastric contents into the esophagus,[1] GERD is a very common condition affecting 25-40% of the population[2] Beaver et al 2003 suggested that Laryngopharyngeal Reflux Disease (LPRD) means a backward of the stomach contents up to throat.[3]

With retrograde reflux into the larynx, pharynx, trachea and bronchus[4] The clinical symptoms usually occurred

secondary to a refluxate of hydrochloric acid and pepsin.[5]

The clinical manifestation and symptoms of LPRD distinctly differ from the pattern of typical gastroesophageal reflux disease (GERD) followed with esophagitis.[6]

LPRD represents itself as atypical form of GERD and often manifests with atypical symptoms (AS) such as hoarseness, globus pharyngeus, throat itching, throat clearing, cough, asthma, dysphagia or/and odynophagia.[4,6]

The gastric refluxate in the larynx might be the causative factor in posterior laryngeal inflammation, laryngeal contact ulcers, and laryngeal granuloma formation.[5,7]

It is associated with many otolaryngologic complications such as reflux laryngitis, cervical dysphagia, globus pharyngeus, chronic cough, laryngeal / tracheal stenosis,and laryngeal carcinoma.[7]

The incidence of laryngopharyngeal symptoms is greater than expected.[8]

There is a complex multi-factorial pathophysiology of LPRD than simple acid reflux.[9]

Various questionnaires and scales for the evaluation of the intensity of the symptoms filled in by the patient have been used in several studies.[4,10,11]

Helicobacter pylori (H. pylori) is a Gram –negative, microaerophilic bacterium can cause infection of the stomach also strongly linked to the development of duodenal and gastric ulcer.[12,13]

H. pylori infection is quite common, affecting approximately 30% of the population.[14]

It has been linked to gastritis, gastric cancer, and gastric lymphomas.[15]

Risk factors for acquiring H. pylori infection include residence in developing countries, poor socioeconomic conditions, family overcrowding, and possibly an ethnic or genetic predisposition.[16]

It is now generally agreed that H. pylori infections are acquired in developing as well as developed countries.[17]

Relationship has been reported between the rates and degree of reflux esophagitis with Helicobacter pylori infection but not yet with reflux laryngitis.[18,19]

Two categories of diagnostic methods used for detection of H.pylori: invasive tests such as histology, rapid urease test and culture, and noninvasive tests such as 13C-urea breath test (UBT) and serology.[20]

Serological tests and UBT have certain disadvantages as lack in sufficient reliability; UBT is expensive, causes administrative difficulties and is not available in all countries although it is as reliable as invasive methods.[21]

H.pylori has been detected in the stool; interest has focused on the diagnostic detection of H.pylori antigens in stool samples.[15]

The H.pylori stool antigen test (HpSA) is new noninvasive diagnostic method based on a sandwich enzyme immunoassay with antigen detection which has a high sensitivity and specificity.[15,22]

This test was approved in the United States in 1998 for both diagnosis and monitoring the response to treatment of H.pylori infection in adult patients.[21]

The purpose of this study was to determine the Incidence of Helicobacter Pylori infection in patients with laryngopharyngeal reflux disease and whether the severity of symptoms in positive H. pylori patients is different than negative H. pylori patients.

PATIENTS AND METHODS

A prospective study was carried out in Suez Canal university hospital (Ismailia-Egypt) during the period from January 2007 to January 2009.

483 patients with atypical symptoms of LFRD such as:-

- Hoarseness.
- Chronic unexplained cough.
- Frequent throat clearing.
- Feeling of lump in throat (globus pharyngeus).
- Bad/bitter taste in mouth (5) were included in this study.

Patients with history of, smoking, alcohol intake, rhinosinusitis with infections of the upper respiratory tract, mass lesions of the vocal cords (nodules, polyps, and cysts), mechanical or chemical injures of the larynx and previous used of anti reflux medical therapy were not included into the study.

All patients were subjected to the following:-

A. A special questionnaire was designed to evaluate the intensity of the symptom using the visual analog scale (VAS).[4]

The patients were asked to rate their symptoms on the scale, ranging from the absence of the symptom to the most severe intensity of the symptom, by marking a slash mark where they felt it was appropriate.

A score of 0 indicated absence of the symptom; a score of 10 indicated the most severe intensity of the symptom. Frequency of these symptoms was evaluated from 0 to 2 points: 0 – absence, 1 – recurrent, 2 – permanent. A hoarseness index (HoI), throat clearing index (TCI), globus pharyngeus index (GPI), Chronic unexplained cough (CCI) and Bad/bitter taste in mouth (BTI) were calculated by multiplication of the intensity and frequency the each symptom.

Intensity of throat clearing (TCI), Bad/bitter taste in mouth (BTI) and globus pharyngeus (GPI) were evaluated according to the VAS scale from 0 to 10 points. However, frequency of these symptoms was evaluated only as "recurrent" (1 point). Therefore, the possible values of TCI, BTI and GPI ranged from 0 to 10 points.

The values of HoI and Chronic unexplained cough (CCI) ranged from 0 to 20 points in relation to recurrent (1 point) or permanent (2 points).

B. Laryngoscopic examination to demonstrate the laryngeal physician signs such as:-

- Red, irritated arytenoids.
- Small laryngeal ulcers.
- Swelling of the vocal cords.
- Granulomas in the larynx.[5]

C. Nasopharyngeal examination (to exclude sinusitis and post nasal discharge).

D. Barium swallows (to exclude any associated disorder such as hiatus hernia).

E. 24 h pH-monitoring with calculation of mean percentage of the time (pH <4).[8,23]

F. HpSA test (This test was approved in USA in 1998 for both diagnosis and monitoring the response to treatment of H.pylori infection by the following technique):-

A fresh stool sample with approximately the size of a peanut was collected at home by patients and stored frozen at -20° C and sent to the coordinating centre for analysis .The test is based on a sandwich EIA with antigen detection. This is a qualitative test with a polyclonal rabbit anti-H.pylori antibody adsorbed to microwells as capture antibody. First, 100 µl of a diluted stool sample (10 µl stool in 0.5 ml sample diluent) and thereafter, peroxidase-conjugated polyclonal antibody solution were added to the wells and incubated for 1 hour at room temperature. Unbound material was removed by washing. After addition of a substrate solution, H.pylori antigen could be detected by a color change. A stop solution was added and the absorbance was read at 450 nm by a spectrophotometer. (Yellow microwell=positive OD450>0.160, white microwell= negative OD 450<0.140).[15]

Statistical analysis: Statistical analysis was performed using SPSS 10.0 (Statistical Package for Social Sciences) for Windows. The confidence interval was 0.95.

Correlation of severity and frequency of symptoms with H.Pylori infection were calculated. According to the multinomial logistic regression analysis, The power of tests was not less than 0.95. Student's t test was used to correlate severity, frequency of the symptoms with Helicobacter pylori infection.

Spearman's correlation coefficient r was used for the detection of correlation (weak correlation r<0.3, middle correlation 0.3<r>0.8, strong correlation 0.8<r>1).[24]

RESULTS

483 patients (361 males and 122 females) with atypical symptoms of LFRD and positive 24 hours pH metry were included to our study The Mean age was 37.4 years.

Cough was the main LFRD symptoms represented in 328 patients (68%) followed by Feeling of lump in throat in 252 patients (52%) the Frequent throat clearing noted in 223 patients (46%) , Bad/bitter taste in mouth in 194 patients (40%) while Hoarseness of voice in 116 (24%) Table 1.

Table 1. Shows the LPRD symptoms.

LFRD symptom	Number of patients (n = 483)	%
Hoarseness	**116**	**24%**
Chronic cough	**328**	**68%**
Frequent throat clearing	**223**	**46%**
Feeling of lump in throat	**252**	**52%**
Bad / bitter taste in mouth	**194**	**40%**

Laryngoscopic examination revealed that Red, irritated arytenoids was the main laryngoscopic findings in 271 patients (56%) followed by Swelling of the vocal cords in 136 patients (28%), Small laryngeal ulcers in 58 patients (12%) while Granulomas in the larynx was the lowest represented findings occurred in 19 patients (4%) Table 2.

Table 2. Shows the laryngoscopic findings.

Laryngoscopic findings	Number of patients (n = 483)	%
Red, irritated arytenoids	271	56%
Small laryngeal ulcers	58	12%
Swelling of the vocal cords	136	28%
Granulomas in the larynx	19	4%

The incidence of H pylori infection among our LPRD patients was 64% (312) patients.

No significant difference was found between hoarseness of voice, chronic unexplained cough, Feeling of lump in throat, frequent throat clearing, Bad / bitter taste in mouth with HpSA test results. Table 3.

Table 3, Shows relationship between LFRD symptoms and HpSA results.

LFRD symptom	HpSA		P
	Positive (n=312)	Negative (n=171)	
Hoarseness	74 (23%)	42 (24%)	NS
Chronic unexplained cough	211 (67%)	117 (68%)	NS
Frequent throat clearing	142(45%)	81 (47%)	NS
Feeling of lump in throat	156 (50%)	96 (56%)	NS
Bad / bitter taste in mouth	126 (40%)	68 (39%)	NS

Also there was no significant difference between Red irritated arytenoids, small laryngeal ulcers, swelling of the vocal folds, Granulomas in the larynx with HpSA test results. Table 4.

Table 4. Shows the relationship between laryngoscopic findings and HpSA results.

Laryngoscopic findings	HpSA		P
	Positive (n=312)	Negative (n=171)	
Red, irritated arytenoids	174 (55%)	97 (56%)	NS
Small laryngeal ulcers	39 (12%)	19 (11%)	NS
Swelling of the vocal folds	85 (27%)	51 (29%)	NS
Granulomas in the larynx	14 (4%)	5 (3%)	NS

There was no significant difference between the mean intensity, frequency and indices of the hoarseness of voice, chronic unexplained cough, Feeling of lump in throat, frequent throat clearing, Bad / bitter taste in mouth symptoms with the HpSA test results as seen in Table 5.

Table 5. Mean intensity and Indexes of the symptoms in both H Pylori groups.

LFRD symptom	HpSA				P value
	Positive (n=312)		Negative (n=171)		
	Mean (points)	+/-CI	Mean (points)	+/-CI	
Hoarseness					
Intensity	6.11	0.73	5.93	0.96	NS
HoI	8.01	1.84	7.93	1.67	NS
Chronic cough					
Intensity	4.86	0.64	5.03	0.83	NS
CCI	6.89	1.91	7.11	0.73	NS
Throat clearing					
Intensity	7.59	0.51	7.29	1.02	NS
TCI	8.03	0.38	8.66	1.15	NS
Feeling of lump					
Intensity	3.96	1.56	4.26	0.23	NS
GPI	4.09	0.09	4.86	0.61	NS
Bad/bitter taste					
Intensity	4.09	0.72	3.89	1.19	NS
BTI	6.67	0.29	5.98	0.46	NS

HoI= hoarseness index. **CCI** = Chronic unexplained cough. **TCI** = throat clearing index.
GPI= globus pharyngeus index. **BTI** = Bad / bitter taste in mouth. **CI** = 95% confidence interval.
NS = No significant difference.

DISCUSSION

483 patients with symptoms of LFRD and positive 24 h pH-metry were evaluated, the most common symptoms were cough (68%) followed by feeling of lump in throat (52%) and this was in agreement with the study that was done by Issing et al 2004 who found that Patients with atypical reflux symptoms presented with globus sensation or throat-clearing.[30]

Also Ahmad et al 2004 who examined 303 patients with reflux, he found that Globus, voice change, sore throat, dysphagia and cough were the predominant symptoms.[25]

Also Pinar et al 2003 who found in his study the most common symptom was dysphagia (56%) followed by hoarseness (46%).[26]

Yorulmaz et al 2003 examine 139 patients; 97 patients presented with laryngopharyngeal symptoms of GERD, including unexplained hoarseness, throat clearing, chronic cough, laryngospasm, globus, throat pain, The incidence of laryngopharyngeal reflux was significantly higher in the laryngopharyngeal symptom group than in the other (52% versus 38%).[27]

On the other hand we found that the most common laryngoscopic finding was red, irritated arytenoids (56%) followed by swelling of the vocal folds (28%). These findings were compatible with Ahmad et al 2004 who mentioned that the endoscopic findings were abnormal in 98 per cent of patients. Apart from the finding of non-specific hyperaemia, usually of the posterior larynx (13 per cent), lesions of the larynx and vocal folds were surprisingly uncommon.[25] Also Pinar et al 2003 found that Posterior laryngitis was the most common laryngeal finding (18 patients,

56%).%), 14 of whom (67%) had posterior laryngitis.[26] HpSA was positive in 64% in our study it was higher to Haruma et al 2000 Who mentioned that there is A relationship has been reported between H.Pylori infection and LFRD in Japan ranged from 31% to 41%.[28] this is may be due to several factors such as low economic state for patients , ignorance of treatment, unexpected H Pylori infection for most of the patients and higher cost of investigations for H Pylori or sometimes invasive techniques make patients refuse do continue on.

Also we use the H.pylori stool antigen test (HpSA) in our study as it is new noninvasive diagnostic method based on a sandwich enzyme immunoassay with antigen detection. Easy to perform independent of age.[16]

H. pylori stool antigen test as is Noninvasive technique with sensitivity up to 98% and specificity up to 99% while Serology for immunoglobulin G sensitivity up to 85% and specificity 79% finally Endoscopy with biopsy for Histology and Culture sensitivity up to 80% and specificity 100% but it is Invasive technique.[16]

Mahir et al 2005 found that HpSA has very reliable results showing a high sensitivity and specificity also in monitoring the response to treatment.[15]

Tezer et al 2006 mentioned that there is expression of Helicobacter pylori (HP) positivity and degree of gastroesophageal reflux disease (GERD).[19]

Oridate et al 2006 determined the relationships between H. pylori antibody positivity he found that the incidence of H. pylori antibody positivity in the GERD patients was 59.5%.[18]

In our study no statistical difference was found between most symptoms such as red, irritated arytenoids patients, small laryngeal ulcers, swelling of the vocal folds and granulomas in the larynx with HpSA test results. Rouve et al 2005 investigated 46 patients with LFRD and found Posterior laryngitis in 33 patients and H pylori-positive gastritis in 11 patients.[29]

Laryngopharyngeal reflux is known to contribute to posterior acid laryngitis and laryngeal contact ulceration or granuloma formation, laryngeal cancer, chronic hoarseness, pharyngitis, asthma, pneumonia, nocturnal choking, and dental diseases.[30]

Tauber et al 2002 investigated 30 patients with LFRD he found that Posterior laryngitis was present in 26 patients and in 19 of them was accompanied by erythema and edema of the interarytenoid region in addition to H pylori-positive antrum gastritis (23%).[31]

Ercan et al 2006 demonstrated that there is no relationship between gastric H pylori infection and LPRD.[32]

Finally there is was no significance difference between the mean intensity, frequency and indexes of the hoarseness of voice, chronic unexplained cough, Feeling of lump in throat, frequent throat clearing, Bad / bitter taste in mouth symptoms with the HpSA test results so validated symptom scores including symptoms index failed to demonstrate any difference between the two groups.

The current results confirm that H pylori is a significant finding in patients with LPR, but there is lack of evidence to support its relation to the clinical symptoms, this will add to the current debate of the use of triple therapy in patients with LPR

It is recommended that a double blind controlled trial be found soon in the literature in the hope of developing treatment guidelines for the disease.

In Conclusion the incidence of the H. pylori infection in patients with LFRD in our study was 64%, statistical analysis did not reveal significant difference in symptom severity among patients.

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