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Prevalence of oesophagitis in patients with persistent upper respiratory symptoms

F. Catalano, M.D., C. Terminella, M.D., Ph.D., C. Grillo, M.D.*, S. Biondi, M.D.*, M. Zappalà, M.D.*, C. Bentivegna, M.D., Ph.D.

Abstract

A growing body of evidence suggests that a variety of upper respiratory symptoms (URS) are associated with gastro-oesophageal reflux (GORD). The aim of this study was to determine the prevalence of endoscopic erosive, and non-erosive, oesophagitis among patients complaining of persistent URS, in the absence of typical GORD symptoms, and to compare them with a comparison group of similar age. A group of 110 patients aged 18–75, presenting with persistent URS with no suspicion of GORD symptoms, underwent upper flexible endoscopy, with biopsy sampling for histology, and was compared with a group of 117 patients of similar age undergoing endoscopy for reasons other than GORD. Patients affected with upper airway disorders, such as posterior laryngitis, chronic sinusitis and vocal fold nodules, had a significantly higher prevalence of oesophagitis of varying degrees (31 per cent) compared to the comparison population (15.4 per cent) ($p < 0.01$). These data suggest that in many patients with chronic URS occult gastro-oesophageal diseases are present.

Key words: Respiratory Tract Infections; Oesophagitis; Gastroesophageal Reflux

Introduction

Gastro-oesophageal reflux disease (GORD) is a common disorder caused by the abnormal exposure of the oesophageal mucosa to refluxed gastric content. It is a widespread condition affecting up to 40 per cent of the Western population.[1,2] The most common referred symptoms of GORD are heartburn and regurgitation. Over the last two decades, much evidence has implicated refluxed gastric acid as a contributory factor in the development of chronic laryngeal and pharyngeal disorders.[3–7] The prevalence of these atypical symptoms is still debated.[8] In addition, GORD has a wide spectrum of disease severity, ranging from the mild to the incapacitating,[9] therefore, the measurement of its frequency and its impact on the patient's quality of life is very important in assessing treatment outcome.

The presence or the frequency of these extra-oesophageal symptoms is not predictive of endoscopic findings to the distal oesophagus. Only 50–60 per cent of patients with typical GORD symptoms who seek medical attention are diagnosed with oesophagitis of varying degrees on endoscopy.[10] Moreover, severe disease, including Barrett's oesophagus or peptic stricture can occur in the absence of specific GORD symptoms, just as many patients with daily heartburn symptoms will have no endoscopic findings.[11] Therefore, the absence of heartburn and regurgitation should not preclude the diagnosis of GORD in patients with atypical symptoms. The aim of the present study was to determine the prevalence of endoscopic oesophagitis in a group of patients, who presented to the department of otorhinolaryngology complaining of persistent upper respiratory symptoms in the absence of GORD symptoms, and to compare these patients with patients of a similar age undergoing endoscopy for reasons other than GORD.

Materials and methods

The study population was drawn from 1360 consecutive out-patient visits referred to the Garibaldi Hospital, Otorhinolaryngology unit, and to our endoscopy unit for the chronic complaint of upper airway symptoms over a 12-month period. The study protocol was approved by the institutional Review Boards of both Institutions (University). Exclusion criteria included the use of H_2-receptor antagonists and promotility agents within 30 days before endoscopy, Barrett's oesophagus patients who were taking proton pump inhibitors, previous

From the Gastroenterology and Digestive Endoscopy Service, University of Catania, Garibaldi Hospital, Catania, and the Otorhinolaryngology Unit*, University of Catania, Italy.
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major upper gastrointestinal surgery, known or suspected Zollinger Ellison syndrome, or hypochlorhydria due to autoimmune atrophic gastritis. Patients in whom *Helicobacter pylori* status was already known were also excluded. Inclusion criteria were absence of current or previous typical symptoms of GORD and chronic complaints of at least one or more URS, such as: sensation of globus pharyngeus, hoarseness, sore throat, cough, voice fatigue or laryngospasm that the authors assumed might possibly be attributable to asymptomatic GORD.

Seven hundred and sixty-five patients were excluded by the study criteria and patients declining to enter the study and to undergo endoscopy were 485. Therefore, the final study population consisted of 110 patients. Informed written consent was obtained from all participants. Each patient was subjected to a complete examination of the head and the neck. Inflammatory disorders of the nose and paranasal sinuses was evaluated by nasal endoscopy and computed tomography (CT) scan respectively. Laryngoscopy was performed in all patients. Before undergoing upper flexible endoscopy, background data were collected on age, sex, race, diagnosis and reflux symptoms. Each patient was questioned about past medical history, frequency and duration of the presenting symptoms and medications.

The comparison group included 117 consecutive patients who had undergone upper flexible endoscopy for disorders such as familial adenomatous polyposis, chronic diarrhoea (requiring small bowel biopsy), abdominal pain referred as discomfort centred to the upper abdomen, haemoccult-positive stools, unexplained nausea and vomiting, and achalasia. The exclusion criteria included patients with persistent upper respiratory symptoms such as asthma, chronic cough, laryngitis, but also other rhinopharyngeal and laryngeal disorders, (e.g. sore throat, globus sensation, hoarseness). Patients taking H_2-receptor antagonists and promotility agents within 30 days before endoscopy, Barrett's oesophagus patients who were taking proton pump inhibitors, previous major upper gastrointestinal surgery, known or suspected Zollinger Ellison syndrome, or hypochlorhydria due to autoimmune atrophic gastritis were excluded. Patients in whom the *Helicobacter pylori* status were already known were also excluded as were potential control patients who were taking proton pump inhibitors.

Endoscopy and biopsies

Endoscopy was performed with the Olympus type GIF 100 HI videoendoscope. Presence and grade of oesophagitis, diaphragmal herniation, Barrett's oesophagus, or any other abnormality was recorded. All biopsy specimens were obtained with standard biopsy forceps. A total of five oesophageal biopsies were taken from all patients between 2 and 4 cm above the squamocolumnar junction regardless of its location in the tubular oesophagus. Endoscopic grading of oesophageal mucosa was performed using the following criteria of Hetzel *et al.*:[12] grade 0, normal mucosa or no abnormalities; grade 1, erythema or hyperaemia of the oesophageal mucosa with no macroscopic erosions; grade 2, superficial ulcerations or erosions involving < 10 per cent or the last 5 cm of the oesophageal squamous mucosal surface; grade 3, superficial ulcerations or erosions involving >10–50 per cent of the last 5 cm of the oesophageal squamous mucosal surface; and grade 4, deep ulcerations anywhere in the oesophagus or confluent erosions involving >50 per cent of the last 5 cm of the oesophageal squamous surface. Patients with an oesophagitis grade < 2 were considered to have non-erosive oesophagitis, whereas patients with an oesophagitis grade > 2 were considered to have erosive oesophagitis.

Histological analysis

All biopsy specimens were fixed in 10 per cent formalin. After both haematoxylin and eosin and modified Giemsa staining, biopsies were graded by one pathologist. Microscopic oesophagitis was defined as papillae extending upwards for two-thirds or more of the thickness of the squamous epithelium, with, or without, infiltration of the oesophageal epithelium by inflammatory cells.[11]

Statistical analysis

Statistical analysis was performed using the unpaired *t* test to compare mean ages of the groups. Differences in gender, oesophagitis prevalence (95 per cent confidence intervals (CIs) were also calculated) and erosive oesophagitis between groups were compared using Chi-squared tests. The Fisher's exact test was used when applicable. All statistical tests were two-tailed and $p < 0.05$ was considered significant.

Results

As shown in Table I, a total of 227 patients were evaluated; 110 were referred from the Otorhinolaryngology Department to our Endoscopy Unit for gastrointestinal evaluation. This group of patients presented with chronic complaints of at least one of the upper airway symptoms listed in Table II, during a minimum period of three months. The main otolaryngological findings are also shown in Table II. The control population ($n = 117$) included patients with familial adenomatous polyposis (five), chronic diarrhoea requiring small bowel biopsy (nine), lower abdominal pain (38), haemoccult-positive stools (18), nausea and vomiting (15), dysphagia (17) and achalasia (15). A demographic description of the patients included in the study is shown in Table I. Of the entire study population 93 (41 per cent) were men and 134 (59 per cent) were women; the male/female percentage for each group is also shown in Table I. Significant differences were found between the URS group and comparison patients with respect to mean age (SD) (59.1 ± 14.4 *vs* 51.9 ± 15.1 yr, respectively; $p = 0.042$, Student's *t*-test).

The most frequent endoscopic finding in the URS group was hiatal hernia (45 per cent) that appeared

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TABLE I

DEMOGRAPHIC OF THE STUDY POPULATION

Patients	Control (n = 117)	URS (n = 110)	p value
Female %	59.8	58.2	0.888
Mean Age ± SD (yr)	59.1 ± 14.4	50.6 ± 15.1	< 0.05
European	110	107	
African	3	1	
Caucasian	4	2	
Oesophagitis prevalence	18 (15.4%)	34 (31%)	0.008*

URS = upper respiratory symptoms; *Fisher's Exact Test

TABLE II

PATIENT ATYPICAL SYMPTOMS AND EXTRA-OESOPHAGEAL FINDINGS

Atypical symptoms	(n)	Extra-oesophageal disorders		%
Globus pharyngeus	37	PL	n = 22	20
Hoarseness	28	PL-SIN	n = 17	15.4
Laryngospasm	18	PL-VCN	n = 15	14
Post-nasal drip	10	SIN	n = 21	19
Asthma	9	NURD	n = 35	32
Sore throat	33			
Cough	40			
Voice fatigue	16			
Throat clearing	15			

PL = posterior laryngitis; PL-SIN = posterior laryngitis and chronic sinusitis; PL-VCN = posterior laryngitis and vocal fold nodules; SIN = chronic sinusitis; NURD = no upper respiratory disorders.

solely or in combination with various degrees of oesophagitis (data not shown). The prevalence of oesophagitis among patients with the chronic complaint of URS symptoms was higher (31 per cent; 95 per cent CI, 22.4–39.6 per cent) than the comparison group (15.4 per cent; 95 per cent CI, 8.8–21.9 per cent), and differed significantly (p = 0.008, Fisher's Exact Test) (Table I). As shown in Table III, among the 34 patients with oesophagitis 17 (50 per cent) of them did not have erosive oesophagitis proven by histology, 17 (50 per cent) had erosive oesophagitis: 12 = grade 2 and 5 = grade 3. In the comparison population of a total of 18 patients diagnosed with oesophagitis, 15 (83 per cent) did not have erosive oesophagitis while three (17 per cent) had grade 2 erosive oesophagitis. The prevalence of erosive oesophagitis in the whole groups differed significantly (p = 0.001). The most frequent otolaryngological disorders observed in the patient population (Table II) were posterior pharyngitis (PL) (20 per cent), chronic sinusitis (SIN) (19 per cent), posterior laryngitis and sinusitis (PL-SIN) (15.4 per cent) and posterior laryngitis and vocal fold nodules (PL-VCN) (14 per cent). The prevalence of oesophagitis among the five groups of patients with upper airway disorders, are shown in Table IV and did not differ significantly.

Discussion

In this study, the authors showed that the prevalence of endoscopic findings to the distal oesophagus (erosive and non-erosive oesophagitis) in patients complaining of persistent URS symptoms and asymptomatic for GORD symptoms was significantly higher than a comparison group of similar age. These findings agree with some earlier observations.[13–14] Many reports have implicated GORD as a cause of a wide spectrum of otolaryngological disorders and extra-oesophageal complications of the upper airway tract but, unfortunately, a direct relationship between refluxed gastric content and the majority of these suspected supra-oesophageal complications has been difficult to establish to date.

The prevalence of these atypical symptoms and their frequency of occurrence in the general population is still an object of study.[15] In a large survey[8] carried out in order to assess the prevalence of GORD in the general population, it was found

TABLE III

HISTOLOGY RESULTS

Oesophagitis	URS (n = 110)	Control (n = 117)
Grade 0	7	10
Grade 1	10	5
Grade 2	12	3
Grade 3	5	0
Total	34	18
EE prevalence (%)	17/110 (15.4%)*	3/117 (2.6%)*

URS = upper respiratory symptoms; EE = prevalence of erosive oesophagitis in the whole group; *p = 0.001

TABLE IV

PREVALENCE OF OESOPHAGITIS

PL	13/22 (59%)
PL-SIN	8/17 (47%)
PL-VCN	8/15 (53%)
SIN	3/21 (14%)
NURD	2/35 (5.7%)

PL = posterior laryngitis; PL-SIN = posterior laryngitis and chronic sinusitis; PL-VCN = posterior laryngitis and vocal fold nodules; SIN = chronic sinusitis; NURD = no upper respiratory disorders.

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that among patients with symptoms of heartburn and regurgitation about 23 per cent experienced unexplained chest pain without evidence of coronary artery disease, nine per cent reported asthma, 20 per cent bronchitis and 15 per cent chronic hoarseness. In comparison, only six per cent of the general population is affected by asthma and bronchitis.[16] On the other hand, other investigations reported that approximately 40 per cent of patients with extra-oesophageal symptoms did not experience heartburn or regurgitation.[17–21] Therefore, heartburn and regurgitation were not predictive of otolaryngological symptoms.

- **There is evidence that a variety of upper respiratory symptoms (URS) are associated with gastro-oesophageal reflux (GORD)**
- **The aim of this study was to determine the prevalence of endoscopic erosive and non-erosive oesophagitis among patients with URS in the absence of typical GORD symptoms and to compare them with a group of similar age**
- **Thirty-one per cent compared with the comparison group (15.4 per cent) had a higher prevalence of oesophagitis**
- **This suggests that in a significant number of patients with chronic URS there is co-existing occult gastro-oesophageal disease**

These findings are further complicated by the fact that patients with atypical symptoms frequently also lack the characteristic features of oesophageal peptic injury.[10] The authors supported the hypothesis of a causal relationship between oesophagitis and persistent upper airway disorders. Although resistance to acid exposure may differ from patient to patient, the authors postulate that subjects with chronic airway conditions would correlate with significant oesophageal mucosal injury from reflux disease. Based on this evidence, the subjects of the present study were selected on the basis of their chronic upper airway disorders and not GORD symptoms. The diagnosis of oesophagitis in these subjects was confirmed by upper flexible endoscopy.

The present study demonstrated that subjects with asymptomatic GORD and chronic upper respiratory disorder have a significantly higher percentage (31 per cent) of oesophagitis of varying degrees than comparison subjects of similar age in the absence of URS. Moreover, among the patient population with upper airway disorders, the prevalence of oesophagitis was higher in the group of patients diagnosed with PL, followed by PL-VCN, PL-SIN and SIN, confirming the recent observations of Kuhn and Ulualp.[22–23] Although in the present study the results were not significant because of differences in sample size, by including a larger number of patients with persistent upper respiratory disorders, the authors' results extend the earlier observations.[22–23]

These findings suggest that in many patients suffering from chronic upper airway disturbances, resistant to treatment and asymptomatic GORD, occult gastroesophageal diseases are frequently present. This higher oesophagitis prevalence supports an association of upper airway symptoms with GORD, although the mechanisms underlying the occurrence of these disorders remain to be elucidated. The cause of laryngeal symptoms in many individuals may be multifactorial,[24–27] and to identify at which point GORD might play a key role still remains a challenge. Therefore, well-designed controlled clinical studies and the development of better diagnostic techniques are required in order to determine reliably which markers can predict the definitive cause and effect relationship between acid reflux and pharyngo-laryngeal disorders.

Conclusion

These data suggest that the approach to the patient should be individualized. In patients with atypical symptoms or warning symptoms of dysphagia, odynophagia, or weight loss, early diagnostic evaluation is suggested. Diagnostic evaluation should begin with endoscopy followed by ambulatory pH monitoring, especially in patients with negative findings or persistent URS recalcitrant to therapy. Every patient should be treated with the goal of achieving complete long-term relief in order to avoid the development of chronic aerodigestive disorders.

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Address for correspondence:
Prof. Filippo Catalano,
Via Sgroppillo 21 (Pal. A). S.
Gregorio di Catania,
95027 Italy.

Fax +39/0957594086
E-mail: f.catalano@mbox.unict.it

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