

## ORIGINAL CONTRIBUTIONS

# Limited Diagnostic Value of Laryngopharyngeal Lesions in Patients With Gastroesophageal Reflux During Routine Upper Gastrointestinal Endoscopy

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**BACKGROUND AND AIMS:** There is growing evidence that gastroesophageal reflux disease (GERD) may cause typical laryngeal/pharyngeal lesions secondary to tissue irritation. The prevalence of those lesions in GERD patients is not well established. The aim of this study was to evaluate the prevalence of GERD signs in the laryngopharyngeal area during routine upper gastrointestinal endoscopy.

**METHODS:** Between July 2000 and July 2001, 1,209 patients underwent 1,311 upper gastrointestinal endoscopies and were enrolled in this study. The structured examination of the laryngopharyngeal area during upper gastrointestinal endoscopy was videotaped for review by three gastroenterologists and one otorhinolaryngologist, blinded to the endoscopic esophageal findings. From the 1,209 patients enrolled in this prospective study, all patients (group I, N = 132) with typical endoscopic esophageal findings of GERD (Savary–Miller I–IV) were selected. The sex- and age-matched control group II (N = 132) underwent upper gastrointestinal endoscopy for different reasons, had no reflux symptoms, and had normal esophagoscopy

**RESULTS:** In the two groups of patients, we found no difference in the prevalence of abnormal interarytenoid bar findings (32% vs 32%), arytenoid medial wall erythema (47% vs 43%), posterior commissure changes (36% vs 34%), or posterior cricoid wall edema (1% vs 3%). The only difference was noted in the posterior pharyngeal wall cobblestoning (66% vs 50%,  $P = 0.004$ ).

**CONCLUSION:** The results of this large systematic investigation challenge the diagnostic specificity of laryngopharyngeal findings attributed to gastroesophageal reflux.

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## INTRODUCTION

Gastroesophageal reflux disease (GERD) is defined by esophageal symptoms or mucosal damage produced by abnormal reflux of gastric contents into the esophagus (1). There has been an increasing number of reports describing ear, nose, and throat (ENT) changes secondary to GERD (2–9). There have been conflicting reports on the frequency of these associations. Contact ulcers in the larynx were the first laryngeal signs associated with GERD (10), and since then, many other findings in the larynx and pharynx region have been attributed to GERD (11–21). GERD occurs in 35–40% of the population in the western world on a daily or monthly basis (22, 23). At least 4–10% of patients seeking help from ENT physicians are perceived as suffering from acid-based complaints (24). Studies using 24-h pH monitoring in patients with unresponsive hoarseness find that 55–79% have acid reflux (25). GERD is the third leading cause of chronic cough, after sinus

problems and asthma, accounting for 20% of cases (26–28). Chronic laryngitis and a difficult-to-treat sore throat are associated with acid reflux in as many as 60% of patients (2–7, 24). During upper gastrointestinal endoscopy, routine laryngopharyngeal examination often reveals findings thought to result from gastroesophageal reflux. The direct association between these mucosal findings and GERD, however, is not well established.

Most ENT specialists treat patients with suspected GERD-related complaints and associated signs in the larynx and pharynx region with an empiric therapy using proton pump inhibitors (PPIs). There are no large, placebo-controlled studies to evaluate the validity of clinical improvement gained from acid suppressive therapy in patients with ENT manifestations of GERD. Only few patients undergo 24-h pH monitoring to test for GERD before starting treatment. Therefore, it seems not surprising that up to 50% of patients with laryngoscopic findings suggesting GERD do not respond

to aggressive acid suppression and do not have abnormal esophageal acid reflux on pH testing (8). Establishing the specific relationship among symptoms, signs, and etiology in this population is necessary for correct diagnosis and optimal treatment. The aim of this controlled prospective study was to compare the prevalence of laryngopharyngeal changes associated with GERD in patients with typical GERD findings on upper gastroesophageal endoscopy with patients without typical GERD.

## PATIENTS AND METHODS

All patients undergoing an elective upper gastrointestinal endoscopy at the University Hospital of Zurich between July 2000 and July 2001 were included in this prospective study (29). All patients undergoing emergency endoscopy were excluded. Before starting the study, all endoscopists from our unit attended a teaching session, taught by the study otorhinolaryngologist, who gave instructions on how to examine the laryngopharyngeal area and reviewed the most common pathological findings. The most commonly used endoscopes were the Olympus GIF-XQ 140 or -Q20 140 video endoscopes (Olympus, Hamburg, Germany). Premedication varied according to the preference of the individual endoscopist but consisted mostly of topical anesthesia in combination with midazolam 2.5–5 mg and/or meperidine 25–50 mg intravenously. All examinations were performed in the left lateral decubitus position. Examination of the laryngopharyngeal area was performed at the beginning or the end of the examination. The instrument was advanced under direct vision. First the base of the tongue, the vallecula, and the epiglottis were inspected. Further advancement of the instrument with anterior flexion allowed visualization of the arytenoids and aryepiglottis folds. The pyriform sinus was inspected with minimal lateral deflection. If inspection of the laryngopharyngeal area was not successful initially, it was repeated in reverse order at the end of the upper gastrointestinal endoscopy. If an adequate examination of the laryngopharyngeal area was not possible, the patient was excluded from further analysis. The whole examination of the laryngopharyngeal area was recorded on videotape for later review by an experienced study otorhinolaryngologist (CAS), and three gastroenterologists (SRV, SMW, NW), blinded to the endoscopic findings and to each other's ratings. The laryngopharyngeal region was divided into 10 specific areas (Fig. 1). These areas are believed by ENT physicians and voice clinicians to represent typical regions where reflux can be detected (30). The specific structures included posterior pharyngeal wall, interarytenoid bar, posterior commissure, posterior cricoid wall, arytenoid complex, true and false vocal folds, anterior commissure, epiglottis, and aryepiglottic folds. Findings of erythema, edema, redundant tissue, surface irregularities, and other lesions were further distinctions under each structure.

Patients were classified as GERD patients (group I) if the endoscopic examination of the esophagus revealed single, erosive, or exudative lesions (Savary–Miller I), noncircular

multiple erosions or exudative lesions taking not more than one longitudinal fold (Savary–Miller II), circular erosions or exudative lesions (Savary–Miller III), or ulcers/strictures (Savary–Miller IV). Patients were classified as non-GERD patients (group II) if they had normal esophageal findings and no typical (heartburn, regurgitation) or atypical (chronic hoarseness, sore or burning throat, cough, globus sensation, acid taste) GERD symptoms while not taking acid suppressive therapy (PPIs or histamine 2 receptor antagonists [H2RAs]). Patients in the second group were age and gender matched to those in the first group. In both groups, patients with a possible contributing or cooccurring association with reflux-like smoking or history of asthma, seasonal allergies, chronic nasal congestion, sinusitis, postnasal drip, or recent viral illness were excluded. In both groups, we excluded patients in whom prior or concomitant use of PPIs/H2RAs was documented in their electronic medical records.

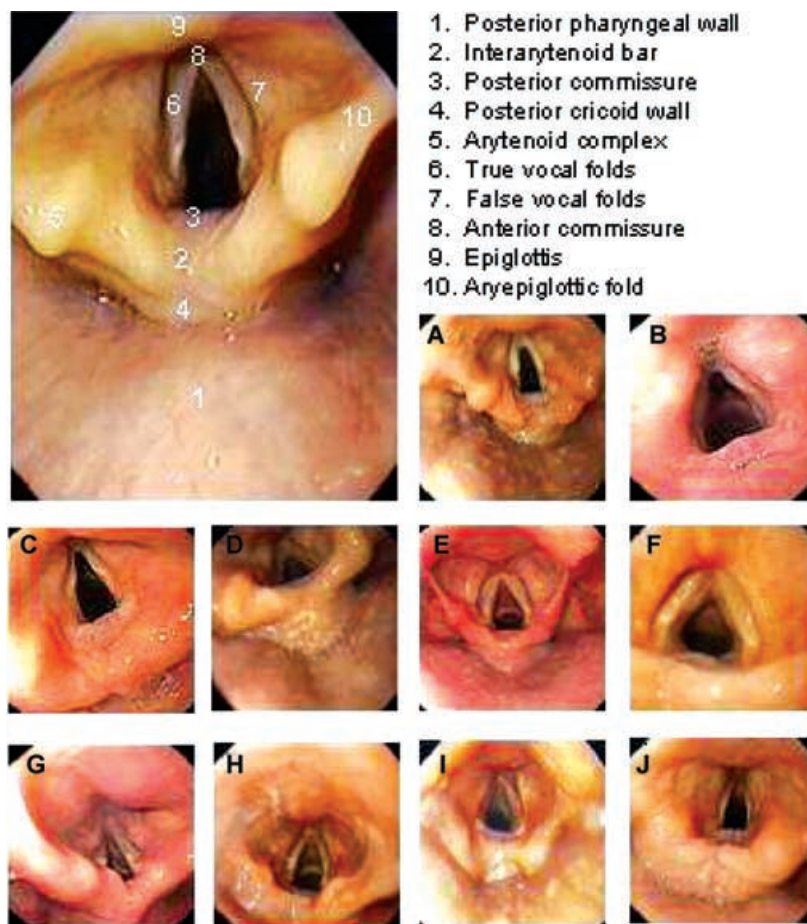
### Statistical Analysis

Statistical calculations were done using InStat version 3.05 (GraphPad, San Diego, CA). Continuous parameters are reported as median (range) and proportions as percentages. A *P* value of <0.05 was considered statistically significant. To characterize the level of agreement among different raters, kappa statistics were calculated (31, 32). The kappa statistic can be interpreted as reflecting the proportion of agreement after chance agreement is removed from consideration. The kappa statistic is highly sensitive to prevalence of findings. A kappa value ( $\kappa$ ) >0.75 represents excellent agreement, a  $\kappa$  value of 0.4–0.75 a fair to good agreement, and a  $\kappa$  value <0.4 poor agreement.

## RESULTS

### Demographics

During the study period, 1,311 endoscopies were performed in 1,209 patients. A thorough videoscopic examination of the laryngopharyngeal area was possible in 1,076 patients (82%). Of these, 571 were men and 505 women. Median age was 52.1 yr (range 16–94). In the remaining 18% of patients, the area could not be examined because of excessive gagging or because the quality of the examination was not sufficient for a thorough evaluation. The two groups of patients were identified based on the results of the 1,076 video recordings. Group I consisted of 132 patients with reflux esophagitis lesions on upper gastrointestinal endoscopy (UGIE) and no prior PPI intake. Group II was age and sex matched and consisted of 132 patients who underwent UGIE for reasons not related to GERD, were nonsmokers, had no prior PPI intake, and had normal esophagoscopy (Table 1). The most commonly reported indication for gastroscopy was epigastric pain (33%) in group I and iron deficiency anemia (18%) in group II. The most common endoscopic finding in group I was mild reflux esophagitis Savary–Miller I (58%). The only abnormal findings in group II were hiatal hernia (11%) and PEG removal/insertion (2%).



**Figure 1.** The laryngopharyngeal region was divided into 10 specific structures, representing a comprehensive profile of tissue irritation locations and which are believed by ENT physicians and voice clinicians to represent typical regions where reflux can be detected (30). The specific structures included posterior pharyngeal wall, interarytenoid bar, posterior commissure, posterior cricoid wall, arytenoid complex, true and false vocal folds, anterior commissure, epiglottis, and aryepiglottic folds. Findings of erythema, edema, redundant tissue, surface irregularities, and other lesions were further distinctions under each structure. Shown are: (A) posterior pharyngeal wall cobblestoning, (B) interarytenoid bar with erythema, (C) posterior commissure with erythema and surface irregularity, (D) posterior cricoid wall edema, (E) arytenoid complex with apex edema, erythema, and medial wall erythema, (F) true vocal folds with edema, (G) false vocal folds erythema, (H) anterior commissure erythema, (I) epiglottis erythema, and (J) aryepiglottic fold edema.

### Prevalence of Laryngopharyngeal Findings

At least one tissue irritation sign was detected in 85% of the study population. Examining the 10 distinct larynx/pharynx sites in patients with reflux esophagitis (group I), posterior pharyngeal wall with cobblestoning, erythema, and edema was the most prevalent finding (65.5%) and anterior commissure erythema was the least prevalent finding (1.1%). In the control group II with normal upper GI endoscopy, the prevalence of findings ranged from 64.7% (posterior pharyngeal wall with cobblestoning, erythema, and edema) to 2.6% (anterior commissure erythema). Figure 2 displays the prevalence of mucosal changes in the 10 different laryngopharyngeal areas attributed to GERD in groups I and II. With the exception of posterior wall edema, erythema, and cobblestoning, there was no difference in the prevalence of laryngopharyngeal findings between GERD (group I) and non-GERD (group II) patients.

### Interobserver Agreement

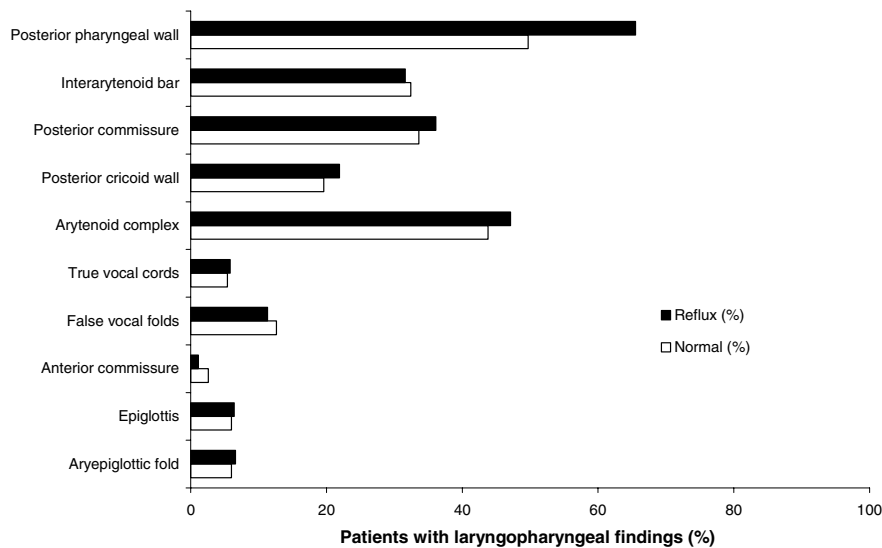
The prevalence of findings identified by the four blinded raters are summarized in Table 2 along with the kappa scores for the 10 findings. The agreement was fair–good for posterior pharyngeal wall and posterior commissure lesions. Regions with low prevalence had poor agreement among raters (arytenoid complex, anterior commissure, epiglottis, and aryepiglottic fold).

### DISCUSSION

In this large controlled study, we explored the presence and prevalence of tissue changes in the laryngopharyngeal region in patients with and without endoscopic esophageal findings of GERD. Some authors refer to the ENT symptoms and findings as laryngopharyngeal reflux (LPR) (7). Of particular interest is that these findings were observed during upper

**Table 1.** Demographics, Indications for Endoscopy, and Endoscopic Esophageal Findings in Patients With and Without GERD

	Group I Reflux (N = 132)	Group II Normal (N = 132)	P Value
Age (mean years) ± SD	52.1 ± 16.7	52.1 ± 16.1	ns
Age range	17–90	17–83	ns
Gender (M/F)	76/56	76/56	ns
Indication for endoscopy			
Epigastric pain	44 (33%)	20 (15%)	0.001
Reflux symptoms	42 (32%)	0 (0%)	<0.001
Heartburn	39 (30%)	0 (0%)	<0.001
Retrosternal chest pain	27 (20%)	10 (8%)	0.01
Nausea/vomiting	23 (17%)	17 (13%)	ns
Iron-deficiency anemia	8 (6%)	24 (18%)	0.01
Control duodenal/gastric ulcer	8 (6%)	9 (7%)	ns
Dysphagia	7 (5%)	3 (2%)	ns
Hematemesis/melena	7 (5%)	19 (14%)	0.03
Meteorism	0 (0%)	12 (9%)	0.001
Diarrhea	0 (0%)	12 (9%)	0.001
Screening for tumor	0 (0%)	14 (11%)	0.001
Halitosis	0 (0%)	8 (6%)	0.01
Constipation	0 (0%)	9 (7%)	0.01
Endoscopic findings			
Normal	0 (0%)	115 (87%)	<0.001
PEG insertion/removal	0 (0%)	3 (2%)	ns
Reflux Savary I	76 (58%)	0 (0%)	0.001
Reflux Savary II	46 (35%)	0 (0%)	0.001
Reflux Savary III	6 (5%)	0 (0%)	0.025
Reflux Savary IV	4 (3%)	0 (0%)	0.05
Hiatus hernia	45 (34%)	14 (11%)	0.001
Antral erosions/ulcers	20 (15%)	0 (0%)	0.001
Barrett's	9 (7%)	0 (0%)	0.01
Erosive bulbitis	9 (7%)	0 (0%)	0.01
Portal hypert. gastropathy	3 (2%)	0 (0%)	ns
Bilroth II operation	2 (2%)	0 (0%)	ns



**Figure 2.** Prevalence of laryngopharyngeal signs in the two groups. Group I consisted of 132 patients with reflux esophagitis on UGIE, group II was age and sex matched and consisted of 132 patients who underwent UGIE for reasons not related to GERD. The most prevalent sign in group I and II was posterior pharyngeal wall erythema, edema, and cobblestoning (65.5% vs 49.7%,  $P = 0.004$ ).

**Table 2.** Measure of Agreement (Kappa Score) Among Raters

Region	Finding	Finding Reported by Individual Raters					Kappa	Agreement
		4/4	3/4	2/4	1/4	0/4		
Posterior pharyngeal wall	Erythema, edema, cobblestoning	45%	10%	5%	9%	31%	0.734	fair-good
Interarytenoid bar	Present, erythema, blanched, irregular	12%	20%	70%	80%	53%	0.568	fair-good
Posterior commissure	Erythema, edema, surface irregularity	26%	6%	3%	14%	51%	0.729	fair-good
Posterior cricoid wall	Erythema, edema, redundant tissue	10%	9%	6%	40%	71%	0.690	fair-good
Arytenoid complex	Apex edema, apex erythema, medial wall erythema, medial wall erosion, medial wall granularity	17%	20%	14%	28%	21%	0.314	poor
True vocal folds	Erythema, edema, surface irregularity, mass lesions (polyp)	2%	2%	2%	7%	87%	0.446	fair-good
False vocal folds	Erythema, edema, surface irregularity	1%	9%	4%	10%	76%	0.424	fair-good
Anterior commissure	Erythema	0%	0%	1%	4%	95%	0.286	poor
Epiglottis	Erythema (laryngeal surface), Erythema (petiole)	1%	0%	3%	16%	80%	0.149	poor
Aryepiglottic fold	Erythema, edema	0%	1%	3%	17%	79%	0.081	poor

4/4—all raters reporting the finding is present.

3/4—three out of four raters reporting the finding is present; one out of four raters reporting the finding is not present.

2/4—two out of four raters reporting the finding is present; two raters reporting the finding is not present.

1/4—one out of four raters reporting the finding is present; three out of four raters reporting the finding is not present.

0/4—all raters reporting the finding is not present.

GI endoscopy and not as part of a laryngoscopic evaluation. Although some authors emphasize these signs in the larynx and pharynx area being specific for acid-related problems, others argue that these changes may be secondary to smoking, allergies, asthma, viral illness, or voice abuse (2, 11–13, 33). The role of smoking and asthma in GERD has been discussed in the literature (34). Our exclusion of patients with smoking, asthma, and prior PPI intake reduces concern that our results are biased by unrecognized reflux.

The results of the present study document a high prevalence of several changes in the ENT region in patients undergoing upper GI endoscopy. Until recently, these signs have been considered pathognomonic for GERD-related laryngeal and pharyngeal lesions. We found the same prevalence of most laryngopharyngeal lesions assumed to be related to GERD in patients with and without endoscopically documented GERD. These results suggest that most laryngopharyngeal lesions supposed to be acid related have causes other than reflux disease. Similar results have been published by others in healthy volunteers (30, 35). In these studies the prevalence of lesions in the laryngopharyngeal area attributed to GERD was as high as 78–87%, raising concerns about the specificity of the changes for GERD. Koufmann studied 46 patients with suspected reflux laryngitis and found that edema and erythema of the larynx contributed to 89% and 87% of the abnormal findings, respectively (2). More recently, in a study surveying 415 patients, the most commonly associated laryngoscopic signs of reflux were erythema or edema of the arytenoids or the vocal cords (33). The importance of our results is best appreciated in the context of current clinical practice, whereby certain signs of tissue irritation in the laryngopharyngeal region are presumed to be associated with uncontrolled GERD and are treated accordingly with PPIs. Hence, given the poor specificity of laryngeal erythema and edema for GERD, it is not surprising that many patients told to have GERD do not

respond to aggressive acid suppression (36). Therefore, it is of paramount importance to identify more specific signs for reflux. It has been suggested that three sites, especially the posterior pharyngeal wall, true vocal folds, and arytenoid medial wall show a higher prevalence of tissue irritation in GERD patients as compared with healthy controls (8, 30). In the present study, only the posterior pharyngeal wall (erythema, edema, and especially cobblestoning) showed a slightly higher prevalence in GERD patients as compared with the control group. Although this finding was statistically significant, the clinical relevance of posterior wall cobblestoning is limited given its high prevalence in both groups. The most prevalent sign was posterior pharyngeal wall cobblestoning. An additional dilemma in diagnosing GERD-related laryngeal and pharyngeal abnormalities is that the examination is subjective and based on physicians' experience in identifying these potentially acid-related laryngeal and vocal fold lesions. Intuitively, this approach may result in considerable variations among physicians' definitions of reflux laryngitis.

Another important finding of our study is the interobserver agreement in identifying these lesions. There was a fairly good agreement among observers on findings with a high prevalence; the agreement for posterior wall, posterior commissure, and posterior cricoid wall lesion almost reached an excellent agreement rating. Because the kappa statistic depends very much on the prevalence, it is not surprising that in regions where changes are infrequent, the interobserver agreement is poor. Our data are actually better compared with recent publications reporting a poor correlation ( $r = 0.16$ – $0.46$ ) in the laryngoscopic assessment of changes related to reflux disease (37). This might be explained by the good teaching of the participating physicians before the study and a standardized evaluation protocol of assessing the lesions.

One limitation of our study is that we did not specifically exclude patients with potential endoscopy-negative reflux disease (ENRD) using 24-h pH monitoring. Because ENRD is the most common presentation of GERD, affecting up to 70% of these individuals (38, 39), one might argue that we have included ENRD patients in the control group (group II). Although we did not perform pH monitoring or PPI trials, we did not include any patients with symptoms suggestive of GERD in group II, therefore minimizing the chance of ENRD patients being part of the control group. Still, ENRD patients without symptoms but ENT findings might have been included in group II, thereby narrowing the difference between the two groups.

The limited training of gastroenterologists to recognize reflux-induced ENT findings could be considered a further limitation of our study because there are no studies validating the accuracy of one training session by an ENT specialist. Still, the experience of the four trained raters reflects the experience most endoscopists have in this field.

In conclusion, given the similar prevalence of laryngopharyngeal findings in patients with and without erosive esophagitis, our data challenge the current clinical trend of attributing several laryngopharyngeal lesions to gastroesophageal reflux. Until diagnostic criteria with a better specificity become available, clinicians should be aware that over-diagnosing reflux laryngitis can lead to unnecessary patient concerns and futile treatments.

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### STUDY HIGHLIGHTS

#### What Is Current Knowledge

- Gastroesophageal reflux is a recognized cause of laryngopharyngeal symptoms.
- The sensitivity and specificity of reflux-induced ear, nose, and throat (ENT) findings are debated.

#### What Is New Here

- The prevalence of most ENT findings in patients with erosive esophagitis and patients with normal endoscopy and no reflux symptoms were similar.
- Posterior pharyngeal wall cobblestoning was more prevalent in patients with reflux esophagitis as compared with the control group; this finding was highly prevalent in the control group making its clinical relevance questionable.
- These findings challenge the diagnostic accuracy of laryngopharyngeal findings attributed to gastroesophageal reflux.

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#### CONFLICT OF INTEREST

The authors have declared no potential conflicts of interest.

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