

# Extraesophageal Manifestations of Gastroesophageal Reflux Disease: A Focus on Laryngeal Manifestation of GERD

Michael F. Vaezi

Center for Swallowing and Esophageal Disorders, Division of Gastroenterology and Hepatology, Vanderbilt University Medical Center, Nashville, Tennessee

## ABSTRACT

Extraesophageal manifestations for GERD refers to patients in whom gastroesophageal reflux disease (GERD) presents with symptoms not typical of this disease. These include symptoms relating to chronic laryngitis, such as hoarseness, sore or burning throat and throat clearing, as well as asthma, chronic cough, or noncardiac chest pain. The diagnosis of these supraesophageal manifestations may be difficult since most patients do not have heartburn or regurgitation. Diagnostic tests have low specificity and cause and effect association between GERD and supraesophageal symptoms is difficult to establish. A few published studies in 2005 increased our understanding of this difficult to diagnose and manage field. However, controversies continue due to lack of a gold standard diagnostic modality.

## INTRODUCTION

Gastroesophageal reflux disease (GERD) is a common disorder affecting close to 40% of the population.<sup>1</sup> The most common presenting symptoms of GERD are heartburn and regurgitation. This pattern of presentation is often referred to as “typical GERD.” In addition to heartburn and regurgitation, GERD may present with other less typical symptoms. Most common “atypical” or extraesophageal manifestations may include ear, nose, throat (ENT), pulmonary (chronic cough or asthma), or cardiac (noncardiac chest pain) symptoms (Figure 1).<sup>2</sup> Patients with extraesophageal manifestations often do not complain of the “typical” GERD symptoms. Classic reflux symptoms are absent in 40%–60% of asthmatics, in 57%–94% of patients with ENT complaints, and in 43%–75% of patients with chronic cough. This “silent” nature of reflux contributes to the difficulty in establishing the diagnosis. This is made more difficult by the less than optimal sensitivity of the currently available diagnostic tests. Empiric therapy is usually

employed; however, in those unresponsive to such therapies GERD continues to be implicated.

Two possible mechanisms may be responsible for GERD-related extraesophageal symptoms.<sup>3</sup> Microaspiration of gastric contents or vagally mediated mechanisms. A disturbance in any of the normal protective mechanisms may allow direct contact of noxious gastroduodenal contents with the larynx or the airway resulting in laryngitis, chronic cough, or asthma. As to the indirect mechanisms, embryologic studies show that the esophagus and bronchial tree share a common embryologic origin and neural innervation via the vagus nerve. Acidification of the distal esophagus can stimulate acid sensitive receptors resulting in noncardiac chest pain, cough, or bronchoconstriction and asthma. The difficulty in patients with extraesophageal symptom is not knowing in whom GERD is the cause and in whom it is an innocent bystander.

In 2005, several studies increased our understanding in the field of extraesophageal GERD. Given recent exciting developments in the field of chronic laryngitis, cough, and GERD, in this review we will focus on four publications<sup>4-7</sup> in the area of diagnosis and management of this difficult group of patients. First, we will review results of a study questioning the specificity of laryngoscopic exam<sup>4</sup> followed by discussion of the results of an open-labeled study with proton pump inhibitors (PPIs) in patients initially suspected of having chronic laryngitis due to GERD.<sup>5</sup> We will next evaluate the conflicting results in two studies on the role of prolonged ambulatory pH<sup>6</sup> and impedance monitoring<sup>7</sup> in extraesophageal GERD and patients with unexplained cough.

## State of the Art at the Beginning of 2005

There is increasing evidence that GERD causes laryngeal signs and symptoms.<sup>8,9</sup> This is often referred to as “reflux laryngitis,” “ENT reflux,” or recently as “laryngopharyngeal reflux (LPR).” Many laryngeal symptoms are associated with GERD including hoarseness, throat clearing, cough, sore or burning throat, dysphagia, and globus (Table 1). Hoarseness is caused by GERD in an estimated 10% of all cases. Chronic laryngitis and difficult to treat sore throat are associated with acid reflux in as many as

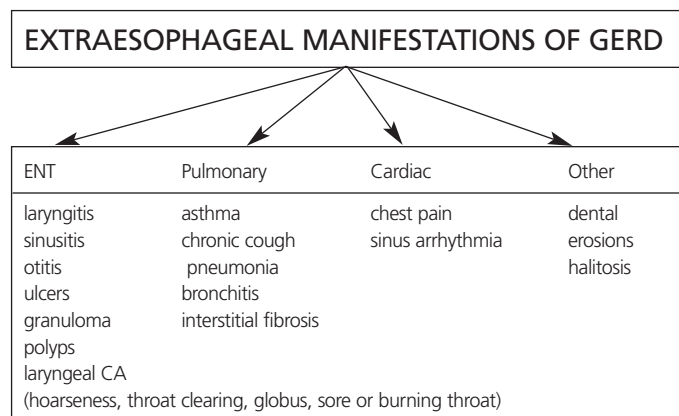


Figure 1. Extraesophageal GERD. ENT = ears, nose, and throat.

**Table 1: Symptoms Associated with Laryngopharyngeal Reflux**

Hoarseness	Globus
Dysphonia	Dysphagia
Sore or burning throat	Postnasal drip
Otalgia	Apnea
Excessive throat clearing	Laryngospasm
Chronic cough	

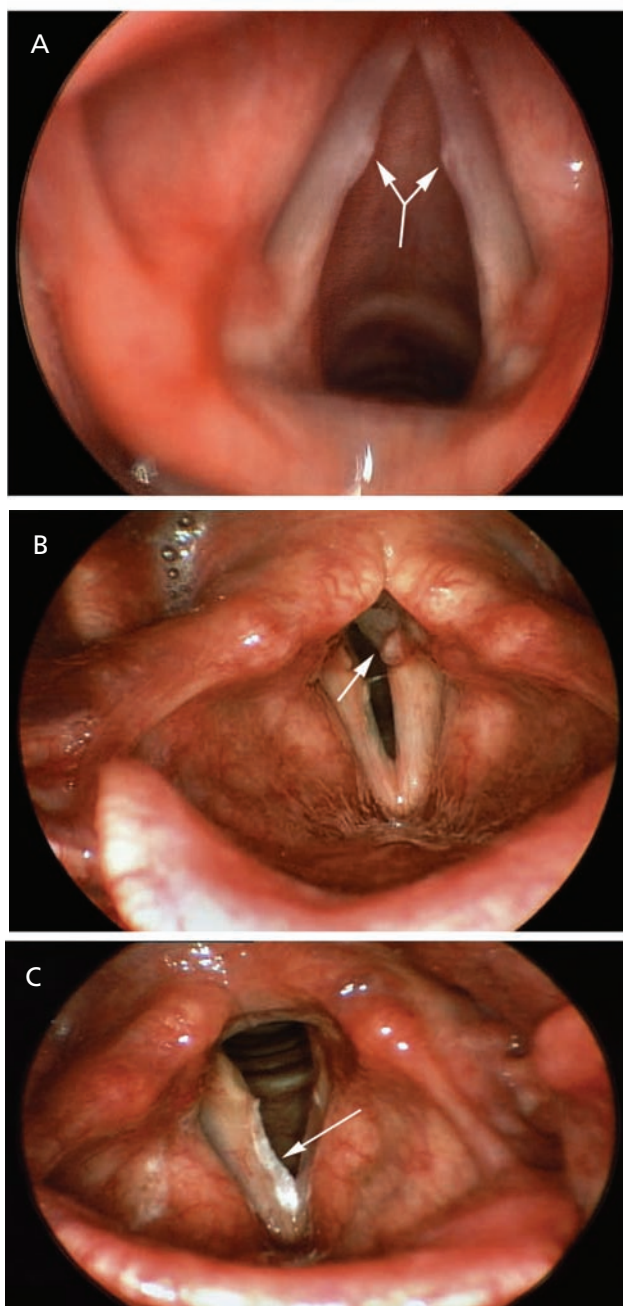
60% of patients. Globus sensation (a feeling of choking or a lump in the throat more prominent between meals and generally disappearing at night) may be caused by GERD in 25% to 50% of cases. Finally, laryngeal cancer has recently been associated with GERD. The most common mechanism for laryngeal irritation from GERD is direct contact with the gastroduodenal contents. A recent study showed that pepsin and conjugated bile acids in acidic pH ranges result in laryngeal tissue inflammation, while nonacid exposure of any gastroduodenal agents do not cause injury.<sup>10</sup>

Clinically, patients are initially evaluated by primary care physicians and subsequently referred to ENT physicians for laryngoscopy. Laryngoscopic evaluation is usually the initial test

suspecting GERD. Normal laryngeal tissue is often smooth and glistening in nature; however, GERD may be responsible for causing laryngeal pathology such as ulcerations, vocal cord nodules, granuloma, or even leukoplakia and cancer (Figure 2). Many laryngeal signs have been attributed to GERD including erythema and edema of the posterior larynx, vocal cord polyps, and granuloma and subglottic stenosis (Table 2). However, most signs are not specific for GERD and may also occur as a result of other laryngeal irritants such as smoking, alcohol, postnasal drip, viral illness, voice overuse, or environmental allergens.<sup>8,11</sup> This may explain why many patients with laryngeal signs do not respond to GERD therapy. Therapeutically, it is recommended that patients take twice daily PPI therapy;<sup>8</sup> however, until recently patient response was not compared between once or twice daily therapies. Additionally, the role of ambulatory esophageal pH or impedance monitoring in this group of patients was not well studied.

#### Important New Information Published in 2005

The nonspecific nature of laryngeal evaluation was highlighted by Milstein et al.<sup>4</sup> who evaluated 52 nonsmoker volunteers with no history of ENT abnormalities or GERD, with both rigid and flexible videolaryngoscopy. Three examiners independently evaluated all videotaped evaluations for the presence of any laryngeal irritation or structural abnormalities. The authors found that in this asymptomatic normal population there was at least one sign of tissue irritation in 93% of flexible and 83% of rigid laryngoscopic evaluations. Additionally, the findings were dependent on the laryngoscopic technique. Laryngeal signs were more commonly reported on flexible transnasal laryngoscopy than with the rigid transoral examination (Table 3). Finally, kappa scores indicated an overall agreement which was poor to moderate at best suggesting high degree of interobserver vari-



**Figure 2.** Abnormal larynx. A: Vocal cord nodule. B: Vocal cord granuloma. C: Leukoplakia.

**Table 2:** Potential Laryngopharyngeal Signs Associated with GERD

Edema and hyperemia of larynx	Laryngeal polyps
Hyperemia and lymphoid hyperplasia of posterior pharynx (cobblestoning)	Reinke's edema
Interarytenoid changes	Tumors
Granuloma	Subglottic stenosis
Contact ulcers	Posterior glottic stenosis
	Strictures

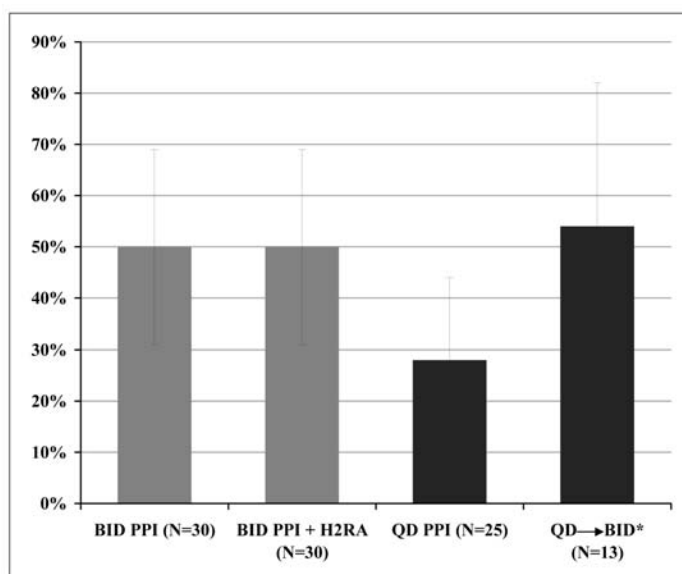
**Table 3:** Laryngeal Signs in Normal Volunteers Detected by Flexible and Rigid Laryngoscopy

Signs	Flexible	Rigid	P
Arytenoid complex	76.3%	53.2%	<.01
Pseudosulcus	37.2%	7.7%	<.01
Interarytenoid mucosa	16.7%	6.4%	<.01
Posterior pharyngeal wall	10.9%	0.6%	<.01
Ventricular obliteration	9.6%	0%	<.01

Adapted from Milstein.<sup>4</sup>

ability. This important study further highlights the nonspecific nature of the laryngoscopic diagnosis of GERD-suspected chronic laryngitis. This may be an important reason why there is great variability in patient response to GERD therapy. In many such patients GERD, as initially suspected, may not be the cause of laryngeal signs or symptoms. Given the nonspecific nature of laryngoscopic diagnosis, the authors correctly suggested that “for those unresponsive to PPI therapy, other causes of laryngitis should be investigated.”

A large-scale cohort study assessing optimal dose of PPI therapy in patients with suspected GERD-related laryngitis was published in 2005 by Park et al.<sup>5</sup> In this 8-year prospective study the authors enrolled 85 patients with suspected GERD-related chronic laryngitis, and separate groups were treated over time with three different PPI dosing regimen for 4 months. This included lansoprazole (30 mg bid), omeprazole (20 mg bid) plus H<sub>2</sub>-receptor antagonist (H<sub>2</sub>RA) at nighttime (ranitidine, 300 mg qhs), or esomeprazole (40 mg once daily) for 2 months with doubling of the PPI dose for an additional 2 months of therapy if patients were unresponsive. Objective and subjective improvement were assessed by laryngoscopy and symptom questionnaire at 2 and 4 months of therapy. Primary study outcome was greater than 50% symptom improvement at 2 and 4 months. The authors showed that there was no significant difference in patient response at 2 months of therapy in those receiving twice daily PPI therapy with or without H<sub>2</sub>RAs (50% and 50%, respectively) while there was only 28% response in those receiving once daily PPI therapy (Figure 3). At 4 months of therapy the response rates remained similar between the first two therapies (63% vs. 80%) suggesting that the addition of H<sub>2</sub>RAs did not affect the primary outcome, while the response rate increased from 28% to 54% ( $P < .05$ ) in those initially receiving once daily PPI therapy whose medication dose was increased to a twice daily regimen. The study suggested that twice daily dos-



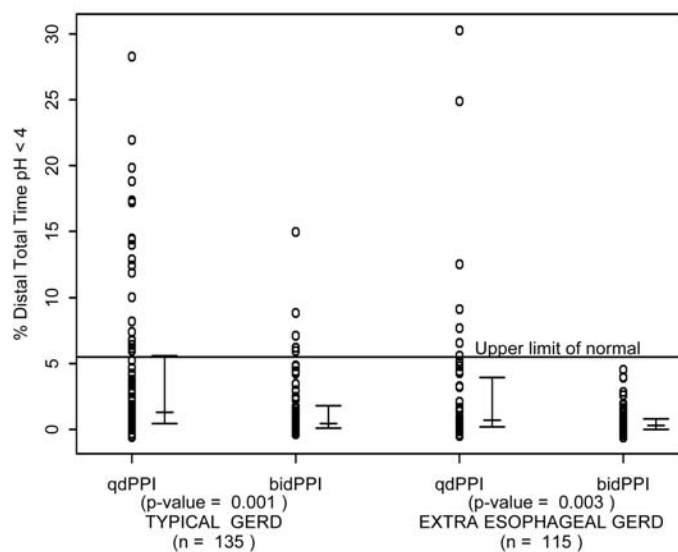
\* Response at two month after dose increased from QD to BID PPI.

**Figure 3.** Symptomatic response after 8 weeks of proton pump inhibitor (PPI) therapy. BID = two times a day. QD = every day. H<sub>2</sub>RA = H<sub>2</sub>-receptor antagonist.

ing of PPI's was the optimal option in the empiric therapy of patients initially suspected of GERD-related laryngitis. The importance of this study was that for the first time patients' response to once daily therapy was compared to twice daily dosing. However, since it was not a randomized, placebo-controlled study it suffered from the pitfalls of open-label study design. Thus, the true therapeutic gain could not be determined from the results of this study.

Ambulatory pH monitoring on therapy has been recommended in patients with extraesophageal GERD who do not respond to therapy in order to assess the relationship between continued symptoms and possible acid reflux.<sup>8</sup> However, the justification for this recommendation was not well studied. In 2005, Charbel et al.<sup>6</sup> published their data on 250 patients with continued typical or atypical GERD symptoms who had undergone pH monitoring on once or twice daily PPI therapy. They found that patients were likely to have continued abnormal esophageal acid exposure on once daily PPI therapy and less likely to reflux on twice daily PPIs (Figure 4). In fact, 99% of patients with extraesophageal GERD had normal findings when tested on twice daily PPI therapy. Similarly, in patients with typical GERD symptoms 93% had normal pH findings on this dose of PPI. Thus, based on these data, in patients who continue to have symptoms while on twice daily PPIs, the likelihood of finding abnormal pH is low and patients' continued symptoms may not be related to acid reflux. Although, Charbel et al. showed that the pretest probability of normal findings in these patients is high there is still value in performing this test. Normative pH data help objectively convince the patients and the referring physicians that acid reflux may not be the cause of patients' continued symptoms.

The role of nonacid (weakly acidic) reflux in patients with extraesophageal reflux continues to be debated. In 2005, Sifrim et al.<sup>7</sup> published their well-conducted study on 28 patients with chronic cough using 24-hour ambulatory impedance/pH monitoring. Patients with daily cough of unknown etiology were tested off



**Figure 4.** Individual and group distal esophageal percentage of time pH < 4 for patients with atypical and extraesophageal GERD symptoms as a function of proton pump inhibitor (PPI) dose. qd = every day. bid = twice a day.

therapy to determine the temporal association between acid or weakly acidic esophageal reflux and patients' cough. Impedance/pH probe was positioned 5-cm above the LES and cough episodes were identified through analysis of the simultaneously monitored manometric tracings during the study. Acid reflux was defined by pH drop below 4 and weakly acidic reflux as a drop of at least 1 pH unit sustained for at least 4 seconds with basal pH remaining between 7 and 4. Reflux was determined to induce cough if cough episodes occurred within 2 minutes after a reflux event. The authors reported completed data in 22 of the 28 studied patients finding that the majority of the cough events (69%) were independent of reflux. Of the remaining 31% of the cough episodes which occurred within 2 minutes of reflux episodes, nearly half (49%) were considered to be induced by reflux events of which 29% were related to weakly acid reflux events. Thus, only 4% of this groups' unexplained cough episodes were considered related to weakly acidic reflux. The authors found that 3 of the 22 (13.6%) patients with unexplained cough had positive symptom association probability with weakly acid reflux events. These findings suggest that reflux events with pH values between 4 and 7 could indeed be associated with symptom occurrence in a subgroup of patients with unexplained cough. However, one could argue that the association of unexplained cough and weakly acidic reflux was only 4% of the cough episodes, which is less than enthusiastic prevalence. Furthermore, the important clinical question in this group of patients is the role of nonacid or weakly acid reflux in those on PPI therapy who continue to have symptoms. This issue is less than settled and is the subject of future ongoing studies.

### Looking Ahead

In 2005, two additional important studies were presented at Digestive Disease Week which have been accepted for publication in 2006.<sup>12,13</sup> The first was a multicenter, randomized, placebo-controlled study assessing treatment response to esomeprazole (40mg bid) versus placebo in 145 patients with chronic laryngitis suspected GERD-related.<sup>12</sup> The study found a similar response rate between placebo and aggressive acid suppression with esomeprazole after 4 months of therapy (40% vs. 46%;  $P = .6$ ). This has further complicated an already difficult area of patient management. The study was criticized for including patients with normal hypopharyngeal acid exposure, which may have diluted the prevalence of patients with true GERD related disease. However, given the low sensitivity of hypopharyngeal pH monitoring this criticism is somewhat shortsighted. The finding however does point to the nonspecificity of laryngeal findings since suspicion of GERD and enrollment was based on laryngoscopic findings. This study combined with those discussed above by Milstein et al.<sup>4</sup> further emphasize the need for finding more specific laryngeal signs for GERD.

The second study in the area of chronic laryngitis and GERD presented in 2005 to be published in 2006 was performed by Swoger et al.,<sup>13</sup> assessing the role of surgical fundoplication in patients suspected of having GERD-related laryngitis who do not respond to aggressive acid suppression. In this study patients suspected of GERD-related laryngitis were initially treated aggressively with twice daily PPIs for 4 months and were offered surgical fundoplication if they had less than 50% symptom improvement. The subjective and objective improvement of 10 patients electing

to undergo surgery was compared to 15 patients who continued on twice daily PPIs after 12 months. Only 1 of 10 (10%) patients in the surgery group reported improvement of laryngeal symptoms at 1 year post therapy compared to 1 of 15 in the control group (15%;  $P = 1.0$ ). Thus, the authors concluded that surgical fundoplication would not result in symptom improvement in the absence of response to medical therapy.

### CONCLUSIONS

In 2005, studies provided information on the nonspecific nature of laryngeal evaluation by laryngoscopy, which help explain why nearly 50% of patients initially suspected of having GERD-related chronic laryngitis do not respond to aggressive acid suppression. We also learned that optimal initial therapy for such patients should be twice daily dosing of PPIs to optimize response to therapy and better control esophageal acid. We also learned that if patients continue to be symptomatic after such a therapy, diagnostic testing with pH monitoring will most likely be normal if performed on therapy but can be useful to "close the door" on continually blaming GERD as the cause of patients' symptoms. Finally, we learned that nonacid or weakly acidic reflux may be associated with chronic cough in patients with symptoms off PPI therapy, and future studies are on the way to help determine their role in patients who continue to have symptoms while on PPI therapy.

### REFERENCES

1. Locke GR, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ. Prevalence and clinical spectrum of gastroesophageal reflux: a population based study in Olmstead County, Minnesota. *Gastroenterology* 1997;112:1448-1456.
2. Vaezi MF. Extraesophageal manifestations of gastroesophageal reflux disease. *Clinical Cornerstones* 2003;5:32-38.
3. Shaker R. Protective mechanisms against supraesophageal GERD. *J Clin Gastroenterol* 2000;30:53-58.
4. Milstein CF, Charbel S, Hicks DM, Abelson TI, Richter JE, Vaezi MF. Prevalence of laryngeal irritation signs associated with reflux in asymptomatic volunteers: impact of endoscopic technique (Rigid vs flexible laryngoscope). *Laryngoscope* 2005;115:2256-2261.
5. Park W, Hicks DM, Khandwala F, Richer JE, Abelson, TI, Milstein C, Vaezi MF. Laryngopharyngeal reflux: prospective cohort study evaluating optimal dose of proton pump inhibitor therapy and pre-therapy predictors of response. *Laryngoscope* 2005;115:1230-1238.
6. Charbel S, Khandwala F, Vaezi MF. The role of esophageal pH monitoring in symptomatic patients on PPI therapy. *Am J Gastroenterol* 2005;100:283-289.
7. Sifrim D, Dupont L, Blondeau K, Zhang X, Tack J, Janssen J. Weakly acidic reflux in patients with chronic unexplained cough during 24-hour pressure, pH and impedance monitoring. *Gut* 2005;54:449-454.
8. Vaezi MF, Hicks DM, Abelson TI, Richter JE. Laryngeal signs and symptoms and GERD: a critical assessment of cause and effect association. *Clin Gastroenterol Hepatol* 2003;1:333-344.
9. Koufman JA. The otolaryngologic manifestation of gastroesophageal reflux disease. *Laryngoscope* 1991;101:1-78.
10. Adhami T, Goldblum JR, Richter JE, Vaezi MF. The role of gastric and duodenal agents in laryngeal injury: an experimental canine model. *Am J Gastroenterol* 2004;99:2098-2106.
11. Hicks DM, Vaezi MF, Ours TM, Richter JE. ENT signs of GERD. *J Voice* 2002;16:564-579.
12. Vaezi MF, Richter JE, Stasney R, et al. Treatment of chronic posterior laryngitis with esomeprazole. *Laryngoscope* 2006;116:254-260.
13. Swoger J, Ponsky J, Hicks DM, Richter JE, Abelson TI, Milstein C, Qadeer M, Vaezi MF. Surgical fundoplication in laryngopharyngeal reflux unresponsive to aggressive acid suppression: a controlled study. *Clin Gastroenterol Hepatol*. In press.