

Evaluation of Patients with Suspected Laryngopharyngeal Reflux: A Practical Approach

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Abstract Laryngopharyngeal reflux (LPR) is associated with symptoms of laryngeal irritation such as throat pain, cough, and voice change. Currently, the two main diagnostic tools are laryngoscopy and reflux monitoring. On laryngoscopy, the signs most commonly used to diagnose LPR are erythema and edema of the larynx; however, these signs are not specific for LPR, may be associated with other causes, and may even be found in healthy individuals. In addition, pH testing has low sensitivity in diagnosing gastroesophageal reflux disease-related laryngeal findings. Proton pump inhibitor (PPI) therapy remains the cornerstone of treatment. The current management recommendation for this group of patients is empiric therapy with twice-daily PPIs for 1 to 2 months. In the majority of those who are unresponsive to such therapy, other causes of laryngeal irritation are considered. Surgical fundoplication is most effective in those who are responsive to acid-suppressive therapy.

Keywords Cough · Chronic laryngitis · Dysphonia · Extraesophageal reflux · Globus · Laryngoscopy · pH monitoring · Proton pump inhibitors · Reflux

Introduction

Gastroesophageal reflux disease (GERD) is defined as a condition that develops when reflux of the stomach

contents causes troublesome symptoms, according to the Montreal definition and classification of GERD [1]. Typically, GERD presents with heartburn and regurgitation, but it can also present atypically as chronic cough, chronic laryngitis, and asthma. Chronic laryngitis is an inflammation of the larynx lasting more than a few weeks, and typically presenting with hoarseness, throat pain, globus, and throat clearing, among other possible symptoms [2, 3]. Causes of chronic laryngitis include smoking, alcohol use, asthma, and GERD. Reflux of gastroduodenal contents in a patient with chronic laryngitis is often referred to as laryngopharyngeal reflux (LPR), chronic laryngitis from GERD, or GERD-related laryngitis. Typical LPR symptoms include dysphonia, globus pharyngeus (sensation of lump in throat), mild dysphagia, chronic cough, and nonproductive throat clearing (Table 1).

Up to 15% of all visits to otolaryngology offices can be related to LPR [4]. More specifically, at least 50% of patients with laryngeal or voice disorders on presentation may have LPR [5]. However, the estimates may be inflated because of the lack of a gold standard in diagnosing LPR. Numerous etiologies can be associated with chronic laryngeal inflammation and the patient's presenting symptoms. In most cases, acid reflux is the initial diagnosis because of the high prevalence of GERD in the population and the ease of prescribing acid-suppressive therapy. Thus, an important question that naturally arises is how much clinical or diagnostic evidence is needed before initiating treatment for someone with suspected LPR. In addition, if the patient does not respond to treatment, what could be done and how aggressive should we be in reaching a conclusive diagnosis?

In this review, we highlight the current knowledge and controversy in LPR, and discuss current treatment options.

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Table 1 Symptoms attributed to laryngopharyngeal reflux

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- Hoarseness
 - Dysphonia
 - Sore or burning throat
 - Excessive throat clearing
 - Chronic cough
 - Globus pharyngeus
 - Dysphagia
 - Postnasal drip
 - Laryngospasm
-

Pathophysiology

Reflux of stomach contents can be associated with LPR via two main mechanisms. The first is the result of direct exposure of the laryngopharyngeal mucosa to gastric contents (eg, acid, pepsin, and bile acids). The second is an indirect mechanism, in which the interaction between the reflux material and structures more distal to the larynx leads to bronchoconstriction via a vagally mediated response [3, 6]. In LPR, the former mechanism may be more important.

The specific agents responsible for producing ear, nose, and throat (ENT) symptoms and laryngeal pathology, including laryngitis and vocal cord lesions, are currently unknown. Potential candidates include gastric contents (acid and pepsin) and duodenal contents (bile acids and the pancreatic enzyme trypsin). Previous animal studies suggested injurious potential for acid and pepsin, reporting a significant role for both agents in causing laryngeal lesions [7]. A later study extended those observations, and showed that the bile constituents—conjugated and unconjugated bile acids as well as trypsin—at different pH values (pH 1–7) caused no histological laryngeal injury in a dog model [8]. The most injurious agents were acid and pepsin in an acidic pH. This finding highlights the importance of acidic refluxate in causing laryngeal inflammation and casts doubt on the significance of bile constituents in this region. This finding is clinically important because some reports implicate the reflux of nonacidic duodenal contents as the cause of persistent laryngitis in patients unresponsive to aggressive acid suppression.

Symptoms and Signs

The most common clinical manifestations of LPR are hoarseness, cough, globus (the sensation of a lump in the throat), and throat clearing (Table 1). Other presenting symptoms may include sore throat, burning throat, dysphagia, postnasal drip, and laryngospasm [3, 4]. The diagnosis of LPR is challenging because many of these patients do not present with typical symptoms of GERD (eg, heartburn and

regurgitation) [7]. Thus, the diagnosis of GERD-related laryngeal signs and symptoms is often based on a constellation of atypical symptoms and laryngoscopic findings that are usually not specific for GERD.

Based on a study of pH-confirmed LPR patients, some have advocated the use of the Reflux Symptom Index (RSI) [9]. The RSI is a self-administered tool that helps clinicians to assess the clinical severity of LPR symptoms at diagnosis and after treatment. This nine-item survey assesses the following symptoms on a scale from 0 to 5: hoarseness, throat clearing, throat mucus, difficulty swallowing, coughing after eating or lying down, troublesome cough, choking episodes or difficulty breathing, sensation of lump in the throat, and heartburn or chest pain. The RSI was significantly higher in untreated LPR patients than in controls (21.2 vs 11.6, $P < .001$). Any score greater than 13 is considered abnormal [9]. However, this index is seldom used by the general ENT practitioner [9], and it does not predict response to therapy. Thus, at this time, the diagnosis of possible GERD-related throat symptoms is based on clinical impression and not on a specific constellation of presenting symptoms.

Diagnosis

The two most commonly used diagnostic tools in LPR are laryngoscopy and reflux monitoring.

Laryngoscopy

Numerous signs on laryngoscopy are attributed to reflux disease: edema and erythema of the larynx, granuloma, contact ulcers, polyps, subglottic stenosis, tumors, and cobblestoning of posterior pharynx (hyperemia and lymphoid hyperplasia) (Table 2) [3]. A survey of 2000 ENT physicians revealed that erythema and edema of the larynx were the

Table 2 Laryngopharyngeal signs attributed to laryngopharyngeal reflux

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

two signs most commonly used to diagnose LPR in patients with symptoms of laryngitis [10]. These signs are highly nonspecific, and many healthy adults have laryngeal changes without any throat symptoms [11]. More than 80% of healthy adults without throat symptoms have laryngeal examination results reported as “abnormal,” which strongly argues for the nonspecificity of this mode of testing. Additionally, “abnormal” laryngeal signs are more likely to be suspected with flexible than with rigid laryngoscopes, suggesting that flexible laryngoscopy is more sensitive but less specific in identifying laryngeal tissue irritation [12]. Finally, a recent study evaluated the prevalence of laryngeal signs in GERD versus non-GERD controls, and found no difference among most laryngeal signs between the groups, suggesting lack of diagnostic specificity of laryngeal signs for GERD [13]. In the two groups of patients (GERD vs non-GERD), the authors 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%, $P=0.004$).

The Reflux Finding Score (RFS) [14] is a laryngoscopic evaluation tool developed to improve the reliability between ENT physicians. It consists of an eight-item, semi-objective, clinical severity scale for ENT physicians to use when evaluating findings at laryngoscopy. Each of the eight items is ranked from either 0 to 2 or 0 to 4, with a score of 7 or more indicating a 95% chance that the patient has LPR. Initial studies found good inter- and intraobserver reproducibility for this tool in assessment and follow-up of LPR patients [14]. However, similar to the RSI, the RFS is seldom used in clinical or academic practice. Additionally, the clinical relevance of this score is in question. The reliability of this score was recently questioned [15, 16].

Therefore, it appears that laryngeal signs are poorly specific for LPR, which can explain why patients initially diagnosed with reflux-related laryngitis often do not respond to appropriate treatment. That being said, a proper head and neck examination and laryngoscopy are important in the initial evaluation of the patient with laryngeal symptoms to rule out other, more serious, causes; however, regarding LPR, more studies are needed to reveal which signs are truly specific. In one study, vocal cord lesions were suggested to represent more specific signs for LPR, with 91% specificity and 88% response to proton pump inhibitor (PPI) therapy [17].

pH Monitoring

When the diagnosis is in question, ambulatory 24-hour double-probe (simultaneous esophageal and pharyngeal)

monitoring is believed by some to be useful in the diagnosis of LPR. However, there is much variability in testing methods and lack of agreement on what pH value is considered abnormal. Additionally, one study showed that pH testing was a poor predictor of the severity of patients' symptoms and signs [18]. One meta-analysis of 16 studies revealed that the number of positive pharyngeal exposures in those who underwent 24-hour pH monitoring differed significantly between patients with LPR and controls [19]. Additionally, it is suggested that when pH monitoring is performed in conjunction with a laryngoscopic evaluation using the RFS, it could be easier to predict who is more likely to respond to PPI therapy [14, 20]. However, another systematic review used 11 studies to investigate the results of 24-hour double-probe pH monitoring in controls and in patients with LPR; this review found no significant difference in the prevalence of pharyngeal reflux between the two groups, and only a minority of those with clinically diagnosed reflux laryngitis had pharyngeal reflux events [21].

The use of pH monitoring prior to PPI therapy in LPR remains controversial, but monitoring can be used after therapy to assess whether the therapy was successful in normalizing acid exposure. Although pH monitoring could be useful in diagnosis, it is not an ideal gold standard [22, 23]. This is because several problems exist with using pH data to diagnose LPR, such as the presence of hypopharyngeal acid exposure in normal subjects, the lack of clear diagnostic criteria for hypopharyngeal pH monitoring, and the poor sensitivity of the probes in detecting gastric acid in the hypopharynx. [3, 4, 23–26]. Some studies even suggest that abnormal pH findings in the hypopharynx do not predict a better response to acid-suppression therapy when compared to those with normal pH findings [27].

Given the poor specificity of laryngoscopic examination and poor sensitivity of pH monitoring, the most accepted method used in clinical practice to suggest the diagnosis of LPR is an empiric trial of a PPI. Other diagnostic tests (eg, barium esophagogram or esophagoscopy) are far less sensitive for LPR than laryngoscopy or pH monitoring, and thus offer little in the diagnosis and management of this group of patients.

The role of non-acid reflux in those who remain symptomatic on PPI therapy recently gained some popularity [28–31]. Using the newly developed combined impedance and pH monitoring may shed light on this possible mechanism of disease. Combining these two techniques allows for the detection of all reflux events, and permits distinctions to be made among acid, weakly acidic, and weakly alkaline reflux [32•]. Recent data from a group of patients with heartburn and regurgitation, as well as extraesophageal symptoms, suggested that 10% to 40% of patients on twice-daily PPI therapy may experience

continued non-acid reflux [28, 33]. However, the causal associations between these reflux events and patients' continued reflux symptoms are difficult to establish. Preliminary outcomes data on the response of this group of patients to surgical fundoplication [29] is encouraging, and awaits validation by large-scale, multicenter, controlled trials. In this uncontrolled study, 19 patients were contacted by telephone after surgery to inquire about symptom response to surgical fundoplication. The authors found that 16 of 17 patients with positive symptom index on impedance monitoring were asymptomatic or markedly improved on follow-up [29]. Most recently, a study of 71 chronic cough patients with impedance monitoring and an acoustic cough monitoring device found that acidity of refluxed material may not be important in triggering cough, and that degree and proximal extent of reflux were not associated with cough episodes [34••]. However, this study focused on cough; whether the findings are applicable to other LPR symptoms is unknown.

Finally, the role of minimal mucosal change in chronic laryngitis was investigated by Vaezi et al. [35••]. In a prospective blinded study, 53 participants (15 controls, 20 with GERD, and 18 with suspected LPR) underwent distal esophageal and laryngeal biopsies before and after PPI therapy. The authors found no increase in the esophageal or laryngeal epithelium intercellular space among the three groups pre- or post-therapy, suggesting that the use of electron microscopy and dilated intercellular space would not be useful in identifying GERD-related laryngeal findings. Another study with a less vigorous study design found that patients with LPR diagnosis based on laryngeal examination had increased intercellular space measurements [36]. The divergent findings between these two studies further highlight the difficulty in using dilated intercellular space measurement as markers for reflux-related disease.

Therapy

Anti-reflux measures are a valuable tool in treatment, and even in diagnosis, of LPR. As with typical symptoms of GERD, patients with suspected LPR should be advised to avoid stimuli that aggravate acid reflux (eg, fatty meals, acidic foods, alcohol, and caffeine). Head elevation in bed, smoking cessation, and weight loss should also be advised, if applicable. A double-blind, randomized trial showed that lifestyle modification for a period of 2 months significantly improved symptoms of LPR, with or without the use of PPIs [37]. However, the role of lifestyle modification in GERD therapy remains controversial [38••].

Proton pump inhibitors are the basis for treatment of patients suspected of having GERD-related laryngeal symptoms and signs. To date, studies examining the

efficacy of PPI therapy in LPR patients have produced a broad range of responses. This is most likely from selection biases and the true prevalence of reflux-induced laryngeal disease. Most uncontrolled studies suggest a response rate of almost 70% with PPIs [3]. Disappointingly, however, most controlled studies do not suggest a major benefit of PPIs over placebo [39]. The results from the three most recent controlled studies in this area are mixed. Fass et al. [40] could not find a difference between esomeprazole-treated patients and those receiving placebo on acoustic and perception parameters of the voice in LPR findings. Similarly, Shaheen et al. [41] reported no symptom improvement difference between high-dose esomeprazole versus placebo in patients with chronic cough and no concomitant baseline heartburn. However, Lam et al. [42], in a study of 24 patients with LPR, showed that 12 weeks of treatment with rabeprazole was superior to placebo for symptom improvement. In this study, the authors used RSI and RFS as objective criteria for symptom and laryngeal sign measurements. In a randomized, controlled study of patients with a chief complaint of postnasal drainage, Vaezi et al. [43] found a benefit for treatment with PPIs, suggesting that PPIs may do more than just suppress reflux.

The mixed treatment results suggest the heterogeneity of the studied patient population and the fact that many patients who are treated with PPI for suspected LPR, may not in fact have LPR. In many patients, other factors may be involved in creating the bothersome symptoms and the laryngeal irritation. Interestingly, the high placebo response rate in LPR is similar to inflammatory bowel syndrome and other functional gastrointestinal disorders [44], suggesting the complexity and multifactorial nature of the disease. However, the overall consensus supports the initial empiric trial of twice-daily PPI therapy for 2 to 3 months [38••]. Twice-daily therapy was shown to be more effective than once-daily therapy in significantly reducing esophageal acid exposure [45]. In patients who do not respond to twice-daily PPI therapy, other causes of laryngitis should be investigated.

Nissen fundoplication should not be offered to patients who are resistant to PPI therapy. One study showed that only 10% of patients responded to Nissen fundoplication after failing to respond to PPI therapy, and this response rate was not any different than the group who continued on their PPI therapy (7%) [46]. Thus, they suggested that surgical fundoplication does not reliably relieve symptoms in LPR patients who were unresponsive to medical management.

Conclusions

Common clinical manifestations of LPR include dysphonia, cough, globus, throat clearing, and dysphagia. No clear gold standard exists for the diagnosis of LPR, and reflux monitoring

and laryngoscopy have generally failed as reliable tools in diagnosing LPR. Given the lack of a diagnostic test, empiric therapy is the most accepted means of testing and treating for suspected GERD-related laryngeal findings. The first step in approaching the patient with suspected LPR is a thorough history and physical examination, including a careful head and neck examination to rule out more ominous causes for the patient's symptoms. Although most laryngeal signs are not specific enough to diagnose LPR, laryngeal evaluation is often important for ruling out other diagnoses. Unless they report warning symptoms (eg, dysphagia, weight loss, anemia, or chest pain), this group of patients should be treated empirically with lifestyle modification and twice-daily PPI therapy for 1 to 2 months. Patients should be advised regarding weight loss (if applicable), smoking cessation, avoiding laryngeal overuse, and other changes in diet and sleep habits that may help decrease laryngeal irritation. If symptoms resolve at the end of that period, tapering of PPIs to the lowest dose of acid suppression should be implemented. If symptoms do not resolve, then further diagnostic studies could be pursued. Other potentially useful studies are 24-hour pH monitoring and impedance studies to investigate whether reflux (acidic or nonacidic) is the cause of the symptoms. In addition, this would be a good time to investigate possible etiologies more assertively by looking for pulmonary, cardiac, psychogenic, or other possible causes. There is no evidence that increasing the dose of PPI therapy would make a difference.

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- Of major importance

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