Laryngopharyngeal reflux disease (LPRD) – Review article

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Abstract

Laryngopharyngeal reflux disease (LPRD) is caused by the back-flow of stomach contents and/or gastric acid into the laryngopharynx. Symptoms of laryngopharyngeal reflux (LPR) include hoarseness, sore throat, throat-clearing, chronic cough, globus sensation, dysphagia, and postnasal drip. LPRD is diagnosed in approximately 10% of patients presenting to outpatient otolaryngology clinics and in more than 50% of patients presenting with voice complaints. Gastroesophageal reflux disease (GERD) and LPRD may be associated with periodontitis, sleep disorders, and otolaryngology disease. Gastric acid reflux with LPRD is thought to cause laryngeal granulomas. The most useful endolaryngeal signs for diagnosing LPRD are erythema, edema, and interarytenoid hypertrophy. Ambulatory 24-h dual-probe pH monitoring can be misleading; false-positive outcomes may occur due to artifacts in the upper probe, and false-negative outcomes can occur as a result of the intermittent character of reflux episodes. In patients with LPRD, proton pump inhibitors (PPIs) have been shown to significantly improve reflux laryngitis. However, some patients are resistant to antacid therapy. Nocturnal acid breakthrough (NAB) on PPI has been suggested as one reason for resistance to PPI therapy. Administration of a PPI with the additional bedtime administration of a histamine-2 receptor antagonist has been shown to be an effective treatment of LPRD with NAB. Recently, potassium-competitive acid blockers have been proposed as an effective treatment of antacid-resistant disease.

1. Introduction

Gastroesophageal reflux (GER), defined as the entry of gastric contents into the esophagus, is a common disorder encountered in clinical practice and is usually treated with proton pump inhibitors (PPIs). Laryngopharyngeal reflux disease (LPRD) is similarly common, particularly in patients with vocal disorders (1). Several studies have reported that PPI treatment of LPRD can improve ear, nose, and throat (ENT) symptoms, although symptom improvement usually requires higher doses of PPIs and a longer treatment time than for typical reflux symptoms (2,3,4,5).

The current management of LPRD includes life style changes, Histamine-2 receptor antagonist (H2RA) therapy, PPI therapy, or a combination of H2RA and PPI therapies, with treatment duration of 1-6 months (6).

LPRD has a significant impact on health-related quality of life (HRQOL). In addition to suffering from heartburn and abdominal pain, patients may worry that these symptoms represent an early warning sign of cancer (7). Hence, the effect of PPI therapy on HRQOL is an important component of treatment (5).

In this article, we review the definition, epidemiology, pathophysiology, symptoms, examination, diagnosis, and treatment of LPRD.

2. Definition

Gastroesophageal reflux disease (GERD) is a common disorder characterized by acid regurgitation and heartburn. Gastric reflux can affect organs other than the esophagus; subsets of gastric reflux include atypical reflux, extraesophageal reflux, reflux laryngitis, and LPR. LPRD is caused by the back-flow of stomach contents and/or gastric acid into the laryngopharynx (8). Common presenting symptoms of LPR include hoarseness, sore throat, throat-clearing, chronic cough, globus sensation, dysphagia, and postnasal drip (3,9). The effects of gastric reflux on the larynx include direct exposure to gastric contents, a vagal-mediated reflex, a

secondary increase in throat-clearing, and increased laryngeal muscle tone (10).

3. Epidemiology

It has been estimated that 15 to 20% of patients presenting to an otolaryngologist complain of chronic cough, globus sensation, dysphonia, or sore throat (11). LPRD is diagnosed in approximately 10% of patients presenting to outpatient otolaryngology clinics, and in more than 50% of patients presenting with voice complaints (12). Fewer than 40% of LPRD patients report typical symptoms of GERD, such as heartburn (3,13,14). In contrast, 44% of the adult US population report GERD symptoms at least once a month, 20% report at least once a week, and 7% report daily symptoms (15). Although there is significant overlap between LPRD symptoms and other disease processes,

LPRD should be suspected when laryngeal edema or erythema is observed in a patient with classic LPRD symptoms.

4. Pathophysiology

In LPRD, gastric acid reflux is thought to cause laryngeal granuloma formation (16) (Figure 1-a). Mechanical stimulation, such as vocal cord abuse, endotracheal intubation, and coughing, may also contribute to granuloma formation (17). LPRD patients have significantly longer acid reflux time in the upper esophagus than do control patients. An upper esophageal pH of 5 is an appropriate cutoff for the diagnosis of LPRD (18). Nocturnal acid breakthrough (NAB) also appears to contribute to LPRD pathophysiology, and may be one of the causes of LPRD resistance to PPI therapy (19).
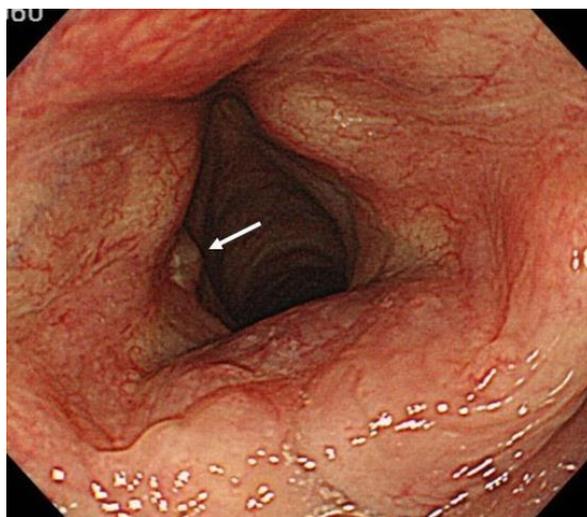
Figure 1-a. Endoscopic view of vocal fold granuloma. Granuloma visualized with White Light Endoscopy (WLE)

5. Examination

Ambulatory 24-h dual-probe pH monitoring is considered the gold standard for LPR diagnosis. However, this method can be misleading; false-positive outcomes can occur due to artifacts in the upper probe, and false-negative outcomes can occur as a result of the intermittent character of reflux episodes (20, 21).

Endoscopic findings and quantification of esophageal acid exposure may help to predict the long-term outcome of medical therapy in LPRD (3). The endolaryngeal signs considered most useful in diagnosing LPRD include erythema, edema, and interarytenoid hypertrophy (6,22). An accurate clinical assessment of endoscopic laryngeal findings can be difficult (23), but a combination of white light endoscopy (WLE) and Narrow Band Imaging (NBI) may enable easier detection of benign vocal fold lesions (24) (Figure 1-b).

Figure 1-b: Endoscopic view of vocal fold granuloma. Granuloma visualized with Narrow Band Imaging (NBI)

6. Symptoms and Diagnosis

The diagnosis of LPRD is based on a combination of the patient's history, symptoms, and laryngeal signs observed during laryngoscopy. The more signs and symptoms a patient has, in the absence of other potential causes, the more likely the diagnosis of LPRD. As such, LPRD can be considered a "diagnosis of exclusion". A positive response to a 4-month trial of 40mg PPI twice-daily confirms the diagnosis of LPRD. However, non-response does not exclude LPRD (6, 25).

Ambulatory 24-h esophageal pH monitoring, once considered the "gold standard" for diagnosing reflux (26,27,28), is less sensitive for diagnosing extraesophageal manifestations of reflux, such as GERD-related laryngitis. pH monitoring of the distal esophagus, the proximal esophagus, and the hypopharynx was only 70%, 50%, and 40% sensitive, respectively, for detecting reflux (29,30). Emerging data suggest that pH monitoring has a poor sensitivity for establishing cause and effect associations between reflux and laryngeal signs. For example, abnormal pH findings do not predict responses to therapy (31,32), and patients with or without proximal or hypopharyngeal acid reflux report

improvement in laryngeal symptoms following medical treatment. Despite this, many gastroenterologists report that pH monitoring remains among the most useful tests for evaluating patients with GERD-related laryngitis.

Many symptoms have been associaтeд with LPRD, including abnormal voice characteristics such as musculoskeletal tension, hard glottal attack, glottal fry, restricted tone placement, and hoarseness (33).

Digital laryngeal videostroboscopy (LVS) has revealed that PPI therapy improves LPRD findings, including supraglottic edema and erythema, glottis edema, and subglottic edema and erythema. Notably, a clinical grading scale for LPRD was found to be a valid clinical tool for following response to PPI therapy (34).

7. Complications

7.1. Periodontitis

GERD has been shown to be an independent risk factor for chronic periodontitis, regardless of the presence of other established risk factors such as dental caries, tobacco use, or a history of calcium channel blocker, cyclosporine, or phenytoin use (35). Significant associations between GERD, tooth loss, and functional dyspepsia (FD) have been observed in women, but not in men. Furthermore, a significant relationship exists between tooth loss and components of FD, such as early satiety (36). However, the association between periodontitis and LPRD remains unclear.

7.2. Sleep disorders

Previous research has demonstrated an association between GERD and sleep disturbances, such as obstructive sleep apnea (OSA), daytime sleepiness, and insomnia (37). In patients with OSA, LPR is accompanied by both respiratory and spontaneous arousals (38).

7.3. Otolaryngology disease

A higher incidence of pharyngeal acid reflux has been observed in patients with chronic rhinosinusitis (CRS) compared with control patients. Results from fluorometric pepsin assays correlate

with results of 24-hour dual-probe monitoring in patients with LPR. Furthermore, LPR is frequently noted in children with otitis media with effusion (OME) (39). These data suggest an association between CRS and LPR (40).

8. Treatment

Patients with extraesophageal manifestations of GERD may require higher doses of acid suppressive therapy and longer treatment duration to control their symptoms (41). PPI therapy may aid in the diagnosis and treatment of atypical GERD affecting the larynx when used as a therapeutic trial in patients with symptoms suggesting LPR (28,42,43,44). Placebo-controlled studies of PPIs in LPRD demonstrated a significant improvement in reflux laryngitis following PPI treatment (45,46). However, several recent reviews have concluded that, to date, the data are insufficient to support the regular use of PPIs in LPRD (47,48,49). An alternative therapeutic strategy is anti-reflux surgery, such as Nissen fundoplication (50).

Some LPRD patients are resistant to antacid therapy (51). One reasons for PPI resistance in LPRD may be mutations in cytochrome P450, which can lead to altered metabolism of PPIs (52,53,54). Recently, potassium-competitive acid blockers (P-CABs) have been shown to be an effective treatment for acid-related diseases (ARDs), and are particularly effective in healing reflux esophagitis. P-CABs inhibit gastric acid secretion, exhibit a rapid onset of action, and lead to prolonged control of gastric acidity. P-CABs may improve the management of ARDs in the near future (55).

Adding a H2RA to PPI therapy is a common practice in patients with NAB. Pharyngeal, laryngeal, and esophageal symptoms improve after taking the additional bedtime dose of H2RA. Hence, the administration of a PPI with an additional bedtime dose of H2RA was thought to be an effective treatment of LPRD (19). Unfortunately, the combination of PPI and H2RA therapy only reduces NAB during the introduction of therapy (56); the efficacy of the H2RA

decreases with continuous administration (57).

The proton pump is present in seromucinous cells and in ducts within the human larynx. The presence of the proton pump in human laryngeal seromucinous glands may explain the heightened laryngeal sensitivity in patients with chronic laryngitis due to LPRD. In these patients, PPIs may exert their effects in the larynx, which may explain some of the treatment controversies surrounding LPRD (58).

9. Conclusions

LPRD is a gastric acid-related disease that is usually diagnosed by otolaryngologists and gastroenterologists. LPRD is related to periodontitis, sleep disorders, and otolaryngeal disease. Future studies are required to clarify the pathophysiology and treatment of LPRD.

Conflict of Interest

The authors have no conflicts of interest in connection with the publication of this manuscript.

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