

Laryngopharyngeal Reflux: Diagnosis, Treatment, and Latest Research

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Abstract

Keywords

- ▶ laryngopharyngeal reflux
- ▶ laryngoscopy
- ▶ esophageal pH monitoring
- ▶ proton pump inhibitors
- ▶ biomarkers
- ▶ pharmacologic

Introduction Laryngopharyngeal reflux (LPR) is a highly prevalent disease and commonly encountered in the otolaryngologist's office.

Objective To review the literature on the diagnosis and treatment of LPR.

Data Synthesis LPR is associated with symptoms of laryngeal irritation such as throat clearing, coughing, and hoarseness. The main diagnostic methods currently used are laryngoscopy and pH monitoring. The most common laryngoscopic signs are redness and swelling of the throat. However, these findings are not specific of LPR and may be related to other causes or can even be found in healthy individuals. Furthermore, the role of pH monitoring in the diagnosis of LPR is controversial. A therapeutic trial with proton pump inhibitors (PPIs) has been suggested to be cost-effective and useful for the diagnosis of LPR. However, the recommendations of PPI therapy for patients with a suspicion of LPR are based on the results of uncontrolled studies, and high placebo response rates suggest a much more complex and multifactorial pathophysiology of LPR than simple acid reflux. Molecular studies have tried to identify biomarkers of reflux such as interleukins, carbonic anhydrase, E-cadherin, and mucin.

Conclusion Laryngoscopy and pH monitoring have failed as reliable tests for the diagnosis of LPR. Empirical therapy with PPIs is widely accepted as a diagnostic test and for the treatment of LPR. However, further research is needed to develop a definitive diagnostic test for LPR.

Introduction

Laryngopharyngeal reflux (LPR) is defined as the retrograde flow of stomach content to the larynx and pharynx whereby this material comes in contact with the upper aerodigestive tract.¹ In contrast, gastroesophageal reflux disease (GERD) is the flow of stomach acids back into the esophagus. Acid reflux diseases are highly prevalent and GERD and LPR are epidemic.^{2–6} According to El-Serag,² the prevalence of reflux

diseases (GERD and LPR) has increased by 4% every year since 1976, and data from the National Cancer Institute of the United States show an increase in the prevalence of esophageal cancer of 600% since 1975.⁵ Altman et al reported a 500% increase in visits to the otolaryngologist due to LPR between 1990 and 2001.³ Moreover, it is estimated that LPR is present in more than 50% of patients with dysphonia.⁷

LPR has been implicated in the etiology of many laryngeal diseases such as reflux laryngitis, subglottic stenosis,

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laryngeal carcinoma, granulomas, contact ulcers, and vocal nodules.^{8,9} Patients with LPR may endure prolonged and exhaustive suffering if the physician is unable to establish a diagnosis because the signs and symptoms of the disease are nonspecific and can be manifestations of other etiologies, such as infection, vocal abuse, allergy, smoking, irritant inhalation, heavy drinking, or nonpathologic alterations. However, when presented together, the signs and symptoms are a strong indicator of reflux.¹

Literature Review

Harmful Events

Physiological Barriers

The physiological barriers to LPR include the lower esophageal sphincter, esophageal clearance influenced by esophageal peristalsis, saliva and gravity, and the upper esophageal sphincter. When these barriers fail, stomach content comes in contact with the laryngopharyngeal tissue, causing damage to the epithelium, ciliary dysfunction, inflammation, and altered sensitivity. It is believed that carbonic anhydrase type III exerts an important protective function in the epithelium of the larynx through the active secretion of bicarbonate, regulating pH in response to acid reflux. Supporting this hypothesis, this enzyme was found to be absent in 64% of laryngeal tissue biopsies from patients with LPR.¹

Acid

The pH of the pharynx is neutral (pH 7), whereas stomach acids range in pH from 1.5 to 2. Damage to the pharynx is the result of a decline in pH and exposure to reflux components such as pepsin, bile salts, and pancreatic enzymes.¹⁰ In the esophagus, 50 reflux episodes per day are considered to be normal, whereas in the larynx three episodes can already cause damage.¹¹ However, the effect of acids on the larynx is unclear and some studies suggest that the combination of acid and pepsin is necessary to cause laryngeal injury.¹²

Pepsin

Nonacid reflux has been associated with inflammation in both LPR and GERD. Impedance pH monitoring detected episodes of nonacid or weakly acid gastric reflux in symptomatic patients,¹³ suggesting that reflux components such as pepsin and bile salts can cause mucosal damage. Evidence indicates that pepsin is actively transported into laryngeal epithelial cells and remains stable at pH 7.4,¹⁴ but is irreversibly inactivated at pH 8. After pepsin is reactivated by a decline from pH 7.4 to pH 3, 72% of peptic activity remains.¹⁴ The activity of pepsin is optimal at pH 2.¹⁰ Recent studies suggest that pepsin is the causative agent of laryngeal injury in nonacid reflux.^{11,13} At an average pH of 6.8, the larynx may contain stable pepsin that can be reactivated during subsequent reflux episodes or by hydrogen ions from any source, including dietary sources.^{4,10} Furthermore, there is evidence showing that pepsin can cause intracellular damage because

cell components such as the Golgi complex and lysosomes have a low pH (5.0 and 4.0, respectively).¹⁴ In the study of Johnston et al,¹¹ intracellular pepsin was detected by Western blot analysis of laryngeal biopsies in 19 of 20 patients with LPR documented by pH monitoring, but in only 1 of 20 controls. The presence of pepsin in tissue is associated with the depletion of key protective proteins such as carbonic anhydrase, E-cadherin, and Sep 70 (an epithelial stress protein).^{11,15} A recent study demonstrated that pepsin increases the levels of genetic markers associated with cancer.¹⁶

Bile Acids

The reflux of duodenal-gastric juices contains bile acids and pancreatic secretions and can reach the larynx.¹⁷ The conjugated bile causes damage to the mucosa at low pH (1.2 to 1.5).¹⁸ The bile acid chenodeoxycholic acid is activated at pH 7 and not at pH 2. An experimental study showed that conjugated bile acids are more damaging to the mucosa at acid pH, whereas chenodeoxycholic acid is active at pH 5 to 8.¹⁷ In that study, the laryngeal mucosa of rats was exposed to taurocholic and chenodeoxycholic acid at pH 1.5 to 7.4 and the results were compared with control rats exposed to saline. Taurocholic acid was more damaging to the mucosa at pH 1.5, whereas chenodeoxycholic acid caused maximum inflammation at pH 7.4. The study suggested that bile can cause laryngeal inflammation at both acid and nonacid pH. However, there is no evidence that the same mechanism occurs in the human larynx.

Symptoms

According to Koufman,⁸ it is important to recognize LPR and GERD as distinct entities. In Kaufman's study including 899 patients, throat clearing was observed in 87% of patients with LPR versus 3% of patients with GERD. On the other hand, only 20% of the patients with LPR reported heartburn or a burning sensation compared with 83% in the group with GERD.

The most common symptoms of LPR are excessive throat clearing, coughing, hoarseness, and globus pharyngeus ("lump in the throat sensation").¹ Hoarseness is generally a fluctuating symptom that occurs in the morning and improves during the day.¹⁹ Belafsky et al developed a nine-item questionnaire (Reflux Symptom Index [RSI]) for the assessment of symptoms in patients with reflux disease that can be completed in less than 1 minute.⁹ The scale for each individual item ranges from 0 (no problem) to 5 (severe problem), with a maximum score of 45 (–Table 1). The authors concluded that the questionnaire shows high reproducibility and validity for the diagnosis of reflux if an RSI score > 13 is defined as abnormal. The RSI value was significantly higher in untreated LPR patients than in controls ($p < 0.001$). The authors concluded that the questionnaire shows high reproducibility and validity because the accuracy in documenting symptom improvement of patients with LPR. One challenge in diagnosing LPR is that the symptoms of the LPR disease lack sufficient specificity to confirm LPR and thus to rule out other causative agents. In fact, several studies have shown a poor correlation

Table 1 Reflux Symptom Index

How did the problems listed below affect you since the last month? Please circle the appropriate answer	0 = no problem 5 = severe problem					
	0	1	2	3	4	5
1. Hoarseness or voice problems	0	1	2	3	4	5
2. Throat clearing	0	1	2	3	4	5
3. Excess mucus or postnasal drip (descends behind the nose to the throat)	0	1	2	3	4	5
4. Difficulty in swallowing solids, fluids or tablets	0	1	2	3	4	5
5. Coughing after eating or lying down	0	1	2	3	4	5
6. Breathing difficulties or choking episodes	0	1	2	3	4	5
7. Annoying cough	0	1	2	3	4	5
8. Sensation of a lump or foreign body in the throat	0	1	2	3	4	5
9. Burning, heartburn, chest pain, indigestion, or stomach acid coming up (reflux)	0	1	2	3	4	5
	Total					

between LPR symptoms, laryngeal findings, and findings from hypopharyngeal pH registrations.^{20,21}

Diagnostic Methods

Laryngoscopy

The laryngoscopic findings used for the diagnosis of reflux are nonspecific signs of laryngeal irritation and inflammation. The laryngeal exam identifies edema and erythema, particularly in the posterior region.⁸ These are the main findings used by various investigators for the diagnosis of LPR.^{8,22} Granulomas, contact ulcers, and pseudosulcus (infraglottic edema) are also common findings, and the last has been observed in up to 90% of cases of LPR.¹ Laryngoscopy is important because an association seems to exist between cancer and LPR.^{1,23} Reflux has also been shown to be associated with subglottic stenosis, laryngospasm, obstructive sleep apnea, bronchiectasis, and rhinitis or chronic rhinosinusitis.^{19,23} Besides that, according to some investigators, these findings are also seen in healthy subjects, and the type of endoscope can influence the color of erythema.¹ Furthermore, because the exam depends on the examiner, variations may exist that make the precise diagnosis of LPR highly subjective.²⁴

In an attempt to identify the most specific laryngoscopic signs of LPR, Belafsky et al developed the Reflux Finding Score (RFS) based on the findings of fiberoptic laryngoscopy.²³ This scale evaluates eight items that comprise the most common laryngoscopic findings in patients with LPR: subglottic edema; ventricular obliteration; erythema or hyperemia; vocal fold edema; generalized laryngeal edema; posterior commissure hypertrophy; granuloma or granulation tissue; and excess mucus in the larynx. Each item is scored according to severity, location, and presence or absence, for a total score of 26. Patients presenting a score of 7 or higher are classified as having LPR. In that study, this scale showed excellent reproducibility and, although each item alone was unable to predict the presence or absence of LPR, the total RFS score was highly suggestive of LPR in a patient with a score higher

than 7. In addition, this scale is useful to evaluate the efficacy of treatment in patients with LPR (► **Table 2**).

The correlations between laryngeal findings, symptoms, and pH monitoring have been found to be weak.^{21,24} It has been reported that findings normally associated with LPR may also be found among up to 86% of healthy controls, as shown in the report by Hicks et al.²⁵

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. Regarding LPR, more studies are needed to reveal which signs are truly specific. In one study, vocal lesions were suggested to represent more specific signs for LPR, with 91% specificity and 88% response to proton pump inhibitor (PPI) therapy.²⁶

It should be emphasized, however, that a thorough medical history and laryngoscopy are important for the proper workup of cases of LPR, precisely because there is no gold standard for diagnosis.

pH Monitoring

Reflux events are best demonstrated by multichannel intraluminal impedance pH monitoring. This method is able to detect acid and nonacid or gaseous fluid.²⁰ Despite controversy, an LPR event occurs when the pH of the proximal sensor declines to < 4 during or immediately after distal acid exposure (near the lower esophageal sphincter) and LPR is confirmed when total acid exposure time (percentage of time during 24-hour monitoring when the sensor detected pH < 4) is > 1%.²⁰ Multichannel intraluminal impedance pH monitoring is useful for the diagnosis of LPR, but the methods tested vary widely and there is no consensus regarding the definition of abnormal pH.²⁷ Sataloff et al described a biological variation among individuals.²⁸ The diagnostic sensitivity of hypopharyngeal pH monitoring is only 40%.¹⁶ Furthermore, pH monitoring has been shown to be a weak indicator of the severity of signs and symptoms in affected patients.²⁰ A meta-analysis of 16 studies demonstrated that the number of pharynges with positive reflux

Table 2 Reflux Finding Score

Subglottic edema (pseudosulcus)	0 = absent
	2 = present
Ventricular obliteration	0 = absent
	2 = partial
	4 = complete
Erythema/hyperemia	0 = absent
	2 = only in the arytenoid
	4 = diffuse
Vocal fold edema	0 = absent
	1 = mild
	2 = moderate
	3 = severe
	4 = polypoid
Diffuse laryngeal edema	0 = absent
	1 = mild
	2 = moderate
	3 = severe
	4 = obstruction
Posterior commissure hypertrophy	0 = absent
	1 = mild
	2 = moderate
	3 = severe
	4 = obstruction
Granuloma/granulation tissue	0 = absent
	2 = present
Thick endolaryngeal mucus	0 = absent
	2 = present
Total	

submitted to 24-hour pH monitoring differed significantly between patients with LPR and controls.²¹ When used in combination with laryngoscopy and RFS, pH monitoring may contribute to identify patients with a potential response to PPIs.²³ However, another meta-analysis including 11 studies found no difference in the prevalence of pharyngeal reflux measured by pH monitoring between patients with LPR and controls, and only a small proportion of the patients with clinically diagnosed reflux laryngitis had pharyngeal reflux.²⁹

Empirical Treatment

In view of the controversial diagnostic criteria for LPR, empirical treatment with PPIs has been used as an alternative diagnostic modality in which a favorable response is defined as diagnostic confirmation.^{10,27,28} The empirical treatment preconized consist of PPI twice a daily for 2 to 3 months.³⁰ Most studies consider a favorable response to PPI when the patient reports resolution of symptoms related to LPR.^{27,31}

Treatment

Treatment of LPR consists of dietary changes and changes in habits such as weight loss, quitting smoking, avoiding alcohol, and not eating immediately before bedtime. Dietary restrictions include caffeine, chocolate, gasified beverages, fat, tomato sauce, and red wine.^{1,19} These modifications have been shown to be a significant independent determinant of the response to medicamentous treatment.³²

At present, the drugs most commonly used for the treatment of LPR are PPIs, which suppress acid production by directly acting on the H⁺-K⁺ATPase of parietal cells. PPIs not only prevent exposure of the upper aerodigestive tract, but also reduce the damage resulting from the enzymatic activity of pepsin, which requires an acid medium for activation.³³

Clinical evidence indicates that pharmacologic intervention should comprise a minimum of 3 months of treatment with PPIs administered twice a day (40 mg omeprazole or an equivalent PPI), 30 to 60 minutes before a meal. This period is important because it provides the highest concentration of the drug during the period of stimulation of the proton pump by food consumption.^{1,19}

In contrast to GERD, the therapeutic response of patients with LPR to PPIs is variable,²² in part because LPR requires more aggressive and prolonged therapy than GERD.²⁶ Although most patients show improvement of symptoms within 3 months, the resolution of symptoms and laryngeal findings generally takes 6 months.^{1,19} This variability in response is also due to the failure of studies to standardize inclusion criteria and to stratify groups according to severity, lack of adequate controls, and differences in therapeutic duration and dose.

Studies have tried to establish some standards. Significant failure rates have been reported when a single daily dose of the PPI was used, and most studies suggest adopting a regimen of two daily doses.^{34,35} In the study of Park et al,²⁶ a response to the regimen consisting of two daily doses of PPI was observed in 50% of the patients after 2 months of treatment, whereas only 28% of the patients receiving a single daily dose responded to treatment. In the single-dose group, 54% of the patients who had not improved showed improvement of symptoms after an additional 2 months of treatment with two daily doses. After 4 months of treatment with two daily doses, an additional 22% of the patients had improved, resulting in a response rate of 70% after 4 months of treatment with two daily doses.

Maximum antireflux treatment consists of the combined administration of a PPI two times per day (before breakfast and dinner) and of an H₂ receptor antagonist before bedtime.^{4,36} Although this regimen results in greater acid suppression than previous medical treatments, the failure rate is still significant (10 to 17%).³⁵

Studies analyzing the efficacy of PPI therapy in patients with LPR have provided different patterns of response, probably because of variations in the inclusion criteria and the true prevalence of LPR. Most uncontrolled studies suggest a response rate of almost 70% to PPIs.²² In contrast, most controlled trials found no beneficial effect of PPIs when compared with placebo.³⁷ Divergent results have been reported in the three

most recent controlled studies. Fass et al observed no difference in acoustic parameters or voice perception between patients with LPR treated with esomeprazole and the placebo group.³⁸ Similarly, Shaheen et al found no difference in chronic cough between patients without burning sensation who used esomeprazole and placebo.³⁹ In contrast, in the study of Lam et al involving 24 patients with LPR, rabeprazole was superior to placebo in terms of symptom improvement after 12 weeks of treatment.⁴⁰ In a randomized controlled study including patients with postnasal drip as main symptom, PPI treatment was superior to placebo.⁴¹

In view of the divergent results and the heterogeneity of patients, many patients may not have LPR, a fact that could explain the high response rate to placebo as observed in other inflammatory diseases or functional gastrointestinal disorders.⁴² However, general consensus suggests initial empirical treatment with PPIs twice a day for 2 to 3 months.³⁰

PPIs reduce the volume of acid reflux, but nonacid reflux may still occur. Orally ingested liquid alginate reacts with the acid in the stomach to produce a "raft" that acts as physical barrier to reflux. This is the only nonsurgical treatment that physically prevents acid and nonacid reflux disease. Alginates act rapidly, are long-lasting and inexpensive, and have no known side effects.

Surgery

Laparoscopic or Nissen fundoplication is a well-established surgical treatment for GERD and produces reliable and reproducible results.⁴³ However, its role in the management of LPR is uncertain. A recent study revised an extensive series of patients undergoing fundoplication and found similar improvement in patients with laryngeal findings and typical symptoms of GERD and those with exclusive typical symptoms. In contrast, poor results were obtained for patients with exclusive laryngeal symptoms, but a positive pH monitoring test for reflux, indicating the possibility that the cause of symptoms is not related to reflux in many of these patients.⁴³

It has been suggested that Nissen fundoplication should not be performed in patients resistant to PPIs.²⁷ Furthermore, one study showed that only 10% of patients respond to Nissen fundoplication after failure of PPI therapy, and this response rate did not differ from the group who continued to use PPIs (7%).⁴⁴ Sataloff et al reported positive results after surgery in symptomatic patients due to nonacid reflux.²⁸

Latest Research

Nonacid Diet and Alkaline Water

Koufman suggested that pepsin, which is deposited in laryngeal tissue, can be activated by exogenous hydrogen ions derived from any source, including diet.⁴ On the basis of this suggestion, the author conducted a study including patients with LPR who were resistant to PPI treatment. The patients received a restricted nonacid diet for 2 weeks and symptoms improved in 95% of them. This author also demonstrated that pepsin is irreversibly inactivated in alkaline water at pH 8.8, suggesting therapeutic benefits of alkaline water in patients with reflux disease.⁶

Biomarkers of Reflux

Inflammatory Cytokines

Multiple markers have been implicated in inflammation of the esophageal mucosa caused by reflux. GERD alters the expression of interleukin (IL)-6, a cytokine involved in mucosal inflammation induced by reflux.⁴⁵ IL-6 is known to play a role in acute inflammation and the body's immune response.⁴⁶ Esophageal IL-6 levels increase according to the degree of reflux and decrease after treatment of GERD. IL-6 seems to be an indicator of mucosal inflammation related to reflux.⁴⁶ Increased expression of IL-8 has also been associated with reflux, especially in esophageal mucosa with Barrett's dysplasia and adenocarcinoma. A decrease in IL-8 levels was observed after anti-reflux surgery.⁴⁷ An in vitro study demonstrated increased expression of IL-8 and other inflammatory markers when exposed to pepsin.¹³

Carbonic Anhydrase

Carbonic anhydrase is a defense component of the mucosa that catalyzes the hydration of carbon dioxide, producing bicarbonate, which neutralizes acid reflux in the extracellular space. In the esophagus, carbonic anhydrase neutralizes acid reflux to almost neutrality.⁴⁸ An increase in the expression of carbonic anhydrase III may be a consequence of epithelial hyperplasia, which is a histopathologic sign of esophagitis.⁴⁹ In patients with LPR, differences in the expression of carbonic anhydrase III were observed between different biopsy sites.⁴⁹ In the presence of LPR and pepsin, the expression of carbonic anhydrase III decreases in the vocal folds, worsening acid-induced damage, and increases in the posterior commissure of the larynx, with the observation of a correlation between the severity of symptoms and levels of this enzyme.¹¹

E-Cadherin

E-cadherin plays an important role in the maintenance of integrity and barrier function of the epithelium.¹⁰ Pepsin digests the intracellular structures responsible for intercellular cohesion.¹⁰ E-cadherin levels have been shown to decline in response to LPR,⁵⁰ but it remains unclear whether this decrease is due to reflux components (acid or pepsin) or to the reflux-associated inflammatory response. There is strong evidence that E-cadherin is a tumor suppressor and that the loss of expression of this protein is the first step to tumor invasion.⁵¹

Mucins

Mucins are glycoproteins expressed by different types of epithelial cells at sites exposed to oscillations in pH, ion concentration, hydration, and oxygenation. The functions of mucins include protection, lubrication, transport, renewal and differentiation of the epithelium, cell cycle modulation, adhesion, and cell signal transduction.⁵² LPR reduces the secretion of mucins, impairing epithelial protection. Reduced secretion of esophageal mucins has been observed in patients with reflux esophagitis.⁵²

Discussion

LPR has become a frequent disease in the otorhinolaryngologist's office. A large number of studies have been published in the medical literature over the last few years, but controversies regarding LPR still exist.⁴⁹ Although nonspecific, the combination of symptoms and characteristic laryngoscopic findings may be more suggestive of LPR. However, investigators highlight the wide variability in the laryngoscopic findings of reflux among examiners.⁵³

The reliability of 24-hour pH monitoring has been questioned, and there is no consensus on the adequate site of the upper probe and interpretation of the results.⁵⁴ At present, the combination of symptoms, laryngoscopic findings, and empirical PPI therapy resulting in symptomatic improvement is used for the diagnosis of LPR. However, if the therapeutic test fails, other diseases should be investigated or it should be considered that reflux components other than acids are the cause of signs and symptoms in the patient.⁵³ Studies have demonstrated that not only acid reflux causes damage in LPR, but pepsin and bile acids are also causative agents of inflammation.^{11,14} Particularly pepsin has been increasingly implicated in the damage caused by reflux disease, with studies showing its intracellular presence and ability to remain stable in laryngeal tissues, where it can be reactivated by endogenous hydrogen ions (acid reflux) or by exogenous hydrogen ions derived from any source, including diet.^{4,13}

Molecular studies have tried to identify biomarkers of reflux, such as ILs, carbonic anhydrase, E-cadherin, and mucins. The data emerging from these studies explain the role of biomarkers not only in mucosal defense mechanisms but also in tumor progression.¹¹

Data from controlled studies demonstrate that the outcomes of PPI therapy are comparable to those of placebo treatment. Nevertheless, empirical treatment with PPIs for 2 to 3 months continues to be recommended in the medical literature as a cost-effective and useful therapy for the initial diagnosis of LPR.¹ In addition to the difficulty in demonstrating the efficacy of PPIs, the diagnosis of LPR remains a challenge in view of the nonspecific signs and symptoms of the condition and the controversial role of pH monitoring. The result would be an unreal increase in the diagnosis of LPR in patients who do not respond to acid suppression therapy.⁴²

Controlled studies have shown low response rates and no significant differences between PPI and placebo treatment, a fact suggesting that patients without typical symptoms of GERD (heartburn or burning sensation) will not benefit from treatment with PPIs.¹⁶ In contrast to what is seen in GERD, the response to treatment with PPIs varies widely among patients with LPR. Some authors believe that treatment of LPR requires higher doses and longer treatment when compared with GERD.²⁶ The recommendation is that empirical therapy should use the full dose of PPIs for a minimum period of 2 to 3 months.^{1,19} In this respect, the results of controlled studies and meta-analyses suggest that the lack of a response to empirical treatment should not lead to an increase of the dose or duration of treatment, but rather to revision of the diagnosis.²⁷ Recommendations for PPI treatment in patients with a suspicion of LPR are based on the results of uncon-

trolled studies, and the high response rates to placebo treatment suggest a much more complex and multifactorial pathophysiology of LPR than simple acid reflux.¹⁰ Further studies are needed to characterize subgroups of patients with symptoms of LPR who would benefit from treatment with PPIs.

Conclusion

LPR is a disease commonly diagnosed in otorhinolaryngologic practice in the presence of a set of nonspecific laryngeal signs and symptoms. The cause of laryngeal damage is uncertain but is likely to comprise a combination of acid and reflux components, particularly pepsin. Pepsin is associated with nonacid or weakly acid reflux. This enzyme remains stable in laryngeal tissues and is reactivated by subsequent reflux or by dietary acids.

There is no specific test for LPR. Laryngoscopy and pH monitoring have failed as reliable tests for the diagnosis of this condition. Empirical therapy with PPIs has been widely accepted as a diagnostic test and for the treatment of LPR. Other treatment options include lifestyle and dietary changes (quitting smoking and drinking, weight loss, avoiding caffeine, etc.).

Molecular studies have been conducted in an attempt to identify biomarkers of reflux, such as ILs, carbonic anhydrase, E-cadherin, and mucins. However, further investigation is needed to establish a definitive diagnostic test for LPR and to determine the mechanism underlying mucosal damage, which would contribute to the development of new treatments and the understanding of the physiopathology of LPR.

References

- 1 Ford CN. Evaluation and management of laryngopharyngeal reflux. *JAMA* 2005;294:1534-1540
- 2 El-Serag HB. Time trends of gastroesophageal reflux disease: a systematic review. *Clin Gastroenterol Hepatol* 2007;5:17-26
- 3 Altman KW, Stephens RM, Lyttle CS, Weiss KB. Changing impact of gastroesophageal reflux in medical and otolaryngology practice. *Laryngoscope* 2005;115:1145-1153
- 4 Koufman JA. Low-acid diet for recalcitrant laryngopharyngeal reflux: therapeutic benefits and their implications. *Ann Otol Rhinol Laryngol* 2011;120:281-287
- 5 Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. *J Natl Cancer Inst* 2005;97:142-146
- 6 Koufman JA, Johnston N. Potential benefits of pH 8.8 alkaline drinking water as an adjunct in the treatment of reflux disease. *Ann Otol Rhinol Laryngol* 2012;121:431-434
- 7 Fraser AG. Review article: gastro-oesophageal reflux and laryngeal symptoms. *Aliment Pharmacol Ther* 1994;8:265-272
- 8 Koufman JA. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24-hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. *Laryngoscope* 1991; 101(4 Pt 2, Suppl 53):1-78
- 9 Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptom index (RSI). *J Voice* 2002;16:274-277

- 10 Wood JM, Hussey DJ, Woods CM, Watson DI, Carney AS. Biomarkers and laryngopharyngeal reflux. *J Laryngol Otol* 2011;125:1218–1224
- 11 Johnston N, Knight J, Dettmar PW, Lively MO, Koufman J. Pepsin and carbonic anhydrase isoenzyme III as diagnostic markers for laryngopharyngeal reflux disease. *Laryngoscope* 2004;114:2129–2134
- 12 Johnston N, Yan JC, Hoekzema CR, et al. Pepsin promotes proliferation of laryngeal and pharyngeal epithelial cells. *Laryngoscope* 2012;122:1317–1325
- 13 Samuels TL, Johnston N. Pepsin as a causal agent of inflammation during nonacidic reflux. *Otolaryngol Head Neck Surg* 2009;141:559–563
- 14 Johnston N, Wells CW, Blumin JH, Toohill RJ, Merati AL. Receptor-mediated uptake of pepsin by laryngeal epithelial cells. *Ann Otol Rhinol Laryngol* 2007;116:934–938
- 15 Johnston N, Dettmar PW, Lively MO, et al. Effect of pepsin on laryngeal stress protein (Sep70, Sep53, and Hsp70) response: role in laryngopharyngeal reflux disease. *Ann Otol Rhinol Laryngol* 2006;115:47–58
- 16 Vaezi MF. We should learn from important negative results. *Laryngoscope* 2009;116:1718
- 17 Sasaki CT, Marotta J, Hundal J, Chow J, Eisen RN. Bile-induced laryngitis: is there a basis in evidence? *Ann Otol Rhinol Laryngol* 2005;114:192–197
- 18 Lillemo KD, Johnson LF, Harmon JW. Role of the components of the gastroduodenal contents in experimental acid esophagitis. *Surgery* 1982;92:276–284
- 19 Bove MJ, Rosen C. Diagnosis and management of laryngopharyngeal reflux disease. *Curr Opin Otolaryngol Head Neck Surg* 2006;14:116–123
- 20 Noordzij JP, Khidr A, Desper E, Meek RB, Reibel JF, Levine PA. Correlation of pH probe-measured laryngopharyngeal reflux with symptoms and signs of reflux laryngitis. *Laryngoscope* 2002;112:2192–2195
- 21 Merati AL, Lim HJ, Ulualp SO, Toohill RJ. Meta-analysis of upper probe measurements in normal subjects and patients with laryngopharyngeal reflux. *Ann Otol Rhinol Laryngol* 2005;114:177–182
- 22 Vaezi MF, Hicks DM, Abelson TI, Richter JE. Laryngeal signs and symptoms and gastroesophageal reflux disease (GERD): a critical assessment of cause and effect association. *Clin Gastroenterol Hepatol* 2003;1:333–344
- 23 Belafsky PC, Postma GN, Koufman JA. The validity and reliability of the reflux finding score (RFS). *Laryngoscope* 2001;111:1313–1317
- 24 Branski RC, Bhattacharyya N, Shapiro J. The reliability of the assessment of endoscopic laryngeal findings associated with laryngopharyngeal reflux disease. *Laryngoscope* 2002;112:1019–1024
- 25 Hicks DM, Ours TM, Abelson TI, Vaezi MF, Richter JE. The prevalence of hypopharynx findings associated with gastroesophageal reflux in normal volunteers. *J Voice* 2002;16:564–579
- 26 Park W, Hicks DM, Khandwala F, et al. Laryngopharyngeal reflux: prospective cohort study evaluating optimal dose of proton-pump inhibitor therapy and pretherapy predictors of response. *Laryngoscope* 2005;115:1230–1238
- 27 Abou-Ismaïl A, Vaezi MF. Evaluation of patients with suspected laryngopharyngeal reflux: a practical approach. *Curr Gastroenterol Rep* 2011;13:213–218
- 28 Sataloff RT, Hawkshaw MJ, Gupta R. Laryngopharyngeal reflux and voice disorders: an overview on disease mechanisms, treatments, and research advances. *Discov Med* 2010;10:213–224
- 29 Joniau S, Bradshaw A, Esterman A, Carney AS. Reflux and laryngitis: a systematic review. *Otolaryngol Head Neck Surg* 2007;136:686–692
- 30 Kahrilas PJ, Shaheen NJ, Vaezi MF; American Gastroenterological Association Institute; Clinical Practice and Quality Management Committee. American Gastroenterological Association Institute technical review on the management of gastroesophageal reflux disease. *Gastroenterology* 2008;135:1392–1413, e1–e5
- 31 Reimer C, Bytzer P. Management of laryngopharyngeal reflux with proton pump inhibitors. *Ther Clin Risk Manag* 2008;4:225–233
- 32 Steward DL, Wilson KM, Kelly DH, et al. Proton pump inhibitor therapy for chronic laryngo-pharyngitis: a randomized placebo-control trial. *Otolaryngol Head Neck Surg* 2004;131:342–350
- 33 Dobhan R, Castell DO. Normal and abnormal proximal esophageal acid exposure: results of ambulatory dual-probe pH monitoring. *Am J Gastroenterol* 1993;88:25–29
- 34 Leite LP, Johnston BT, Just RJ, Castell DO. Persistent acid secretion during omeprazole therapy: a study of gastric acid profiles in patients demonstrating failure of omeprazole therapy. *Am J Gastroenterol* 1996;91:1527–1531
- 35 Amin MR, Postma GN, Johnson P, Digges N, Koufman JA. Proton pump inhibitor resistance in the treatment of laryngopharyngeal reflux. *Otolaryngol Head Neck Surg* 2001;125:374–378
- 36 Koufman JA, Aviv JE, Casiano RR, Shaw GY. Laryngopharyngeal reflux: position statement of the committee on speech, voice, and swallowing disorders of the American Academy of Otolaryngology-Head and Neck Surgery. *Otolaryngol Head Neck Surg* 2002;127:32–35
- 37 Qadeer MA, Phillips CO, Lopez AR, et al. Proton pump inhibitor therapy for suspected GERD-related chronic laryngitis: a meta-analysis of randomized controlled trials. *Am J Gastroenterol* 2006;101:2646–2654
- 38 Fass R, Noelck N, Willis MR, et al. The effect of esomeprazole 20 mg twice daily on acoustic and perception parameters of the voice in laryngopharyngeal reflux. *Neurogastroenterol Motil* 2010;22:134–141, e44–e45
- 39 Shaheen NJ, Crockett SD, Bright SD, et al. Randomised clinical trial: high-dose acid suppression for chronic cough—a double-blind, placebo-controlled study. *Aliment Pharmacol Ther* 2011;33:225–234
- 40 Lam PK, Ng ML, Cheung TK, et al. Rabeprazole is effective in treating laryngopharyngeal reflux in a randomized placebo-controlled trial. *Clin Gastroenterol Hepatol* 2010;8:770–776
- 41 Vaezi MF, Hagaman DD, Slaughter JC, et al. Proton pump inhibitor therapy improves symptoms in postnasal drainage. *Gastroenterology* 2010;139:1887–1893, e1, quiz e11
- 42 Patel SM, Stason WB, Legedza A, et al. The placebo effect in irritable bowel syndrome trials: a meta-analysis. *Neurogastroenterol Motil* 2005;17:332–340
- 43 Ratnasingham D, Irvine T, Thompson SK, Watson DI. Laparoscopic antireflux surgery in patients with throat symptoms: a word of caution. *World J Surg* 2011;35:342–348
- 44 Swoger J, Ponsky J, Hicks DM, et al. Surgical fundoplication in laryngopharyngeal reflux unresponsive to aggressive acid suppression: a controlled study. *Clin Gastroenterol Hepatol* 2006;4:433–441
- 45 van Roon AH, Mayne GC, Wijnhoven BP, et al. Impact of gastroesophageal reflux on mucin mRNA expression in the esophageal mucosa. *J Gastrointest Surg* 2008;12:1331–1340
- 46 Hirano T. Interleukin 6 in autoimmune and inflammatory diseases: a personal memoir. *Proc Jpn Acad, Ser B, Phys Biol Sci* 2010;86:717–730
- 47 Oh DS, DeMaester SR, Vallbohmer D, et al. Reduction of interleukin 8 gene expression in reflux esophagitis and Barrett's esophagus with antireflux surgery. *Arch Surg* 2007;142:554–559, discussion 559–560
- 48 Tobey NA, Powell DW, Schreiner VJ, Orlando RC. Serosal bicarbonate protects against acid injury to rabbit esophagus. *Gastroenterology* 1989;96:1466–1477
- 49 Axford SE, Sharp N, Ross PE, et al. Cell biology of laryngeal epithelial defenses in health and disease: preliminary studies. *Ann Otol Rhinol Laryngol* 2001;110:1099–1108
- 50 Reichel O, Mayr D, Durst F, Berghaus A. E-cadherin but not β -catenin expression is decreased in laryngeal biopsies from patients with laryngopharyngeal reflux. *Eur Arch Otorhinolaryngol* 2008;265:937–942

- 51 Kurtz KA, Hoffman HT, Zimmerman MB, Robinson RA. Decreased E-cadherin but not beta-catenin expression is associated with vascular invasion and decreased survival in head and neck squamous carcinomas. *Otolaryngol Head Neck Surg* 2006;134:142–146
- 52 Samuels TL, Handler E, Syring ML, et al. Mucin gene expression in human laryngeal epithelia: effect of laryngopharyngeal reflux. *Ann Otol Rhinol Laryngol* 2008;117:688–695
- 53 Mahieu HF. Review article: the laryngological manifestations of reflux disease; why the scepticism? *Aliment Pharmacol Ther* 2007;26(Suppl 2):17–24
- 54 Sato K, Umeno H, Chitose S, Nakashima T. Tetra-probe, 24-hour pH monitoring for laryngopharyngeal reflux: a technique for simultaneous study of hypopharynx, oesophagus and stomach. *J Laryngol Otol* 2009;123(Suppl 31):117–122