

Laryngopharyngeal reflux: diagnosis and treatment of a controversial disease

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Purpose of review

Laryngopharyngeal reflux is a well-recognized and widely used term in ear, nose and throat practice. However, the symptoms and signs attributed to laryngopharyngeal reflux are non-specific and treatment is usually empirical. This review discusses current knowledge on diagnosis and treatment of laryngopharyngeal reflux.

Recent findings

Information is evolving regarding the implications of laryngopharyngeal reflux in the development of pathological conditions affecting the upper aerodigestive tract epithelium such as chronic laryngitis, otitis media with effusion and chronic sinusitis. However, there is still much to learn about the pathophysiologic mechanisms of laryngopharyngeal reflux and their role in its related disease conditions and there is still considerable controversy on diagnostic as well as therapeutic parameters for this condition. There is no consensus on the diagnosis and treatment of laryngopharyngeal reflux and the majority of clinicians depend mainly on clinical findings and empirical therapeutic tests rather than more specific investigations.

Summary

The concept of laryngopharyngeal reflux is still controversial. The current practice of empirical treatment with proton-pump inhibitors is based on weak evidence. However, this practice seems to be widely accepted and will not change until further clinical and laboratory studies improve our understanding of this common and well-recognized condition.

Keywords

laryngitis, laryngopharyngeal reflux, otitis media with effusion, pH, proton-pump inhibitor, sinusitis

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Introduction

Laryngopharyngeal reflux (LPR) is the back flow of gastric contents (refluxate) to the laryngopharynx and upper aerodigestive tract. This term was adopted by the American Academy of Otolaryngology–Head and Neck Surgery in its 2002 Position Statement on LPR [1]. The term is widely used by otolaryngologists who, in most circumstances, diagnose LPR depending on clinical manifestations rather than specific diagnostic investigations. This review aims to discuss current knowledge on the pathology, diagnosis and treatment of LPR as a common ear, nose and throat (ENT) condition.

Laryngopharyngeal and gastroesophageal reflux

Koufman [2] first reported LPR to be an entity distinct from classic gastroesophageal reflux disease (GERD) in its complexity of symptoms, presumed pathophysiology,

and physical sequelae. Most patients with LPR-related laryngitis deny classic symptoms of GERD, particularly heartburn (silent reflux). At least 50% of LPR patients reported lack of endoscopic reflux esophagitis and rather have endoscopic-negative GERD, and the severity of endoscopic esophagitis does not predict the level of LPR symptoms and signs [3].

As the upper-airway epithelium is far more susceptible to the injurious effect of gastric refluxate than the esophageal epithelium, LPR has been implicated in the pathogenesis of a multitude of diseases involving the larynx, pharynx, middle ears and paranasal sinuses (Table 1).

Most of these symptoms and signs can be referred to as laryngitis due to chemical injury by gastric refluxate. These symptoms and signs are, however, non-specific and can develop in different ENT conditions such as excessive voice abuse, smoking, alcohol abuse, asthma, allergy, and infections. Some of these signs have been

Table 1 Symptoms and signs of laryngopharyngeal reflux

Laryngopharyngeal symptoms	Signs	Extrapharyngeal symptoms
Globus pharyngeus	Common	Middle ear effusion (glue ear)
Dysphonia	Vocal fold edema/polyps	Chronic sinusitis
Postnasal drip	Ventricular edema (obliteration)	Dental erosion
Chronic cough	Subglottic edema	
Dysphagia	Excessive laryngeal mucus	
Throat irritation and clearing	Vocal cord nodules	
Laryngospasm	Laryngeal granuloma	
	Rare	
	Paradoxical vocal cord movements	
	Contact ulcer and (peptic)	
	Recurrent laryngeal spasms	
	Laryngeal stenosis	
	Laryngeal carcinoma	
	Cricoid joint fixation	
	Pharyngeal pouch	

reported in up to 86% of the asymptomatic population [4,5].

Pathophysiology of laryngopharyngeal reflux

Although the exact mechanisms for LPR have not been conclusively described, it has been associated with the upright position and a possible dysfunction of the upper esophageal sphincter, whereas GERD tends to occur in the supine position and involves a dysfunction of the lower esophageal sphincter. Additionally, patients with GERD have longer periods of acid exposure and dysmotility [1]. LPR manifestations are due to the direct effect of gastric refluxate, including gastric HCl and pepsin, on the hypopharynx. These two injurious factors can result in local inflammatory reactions. Pepsin was detected in the laryngeal epithelium of LPR patients and absent in normal controls [6]. Pepsin retains some of its peptic activity at pH levels as high as 6.5 [7] and the injurious effect of pepsin and gastric HCl together is significantly more than that of gastric HCl alone. Carbonic anhydrase isoenzyme III (CA-III) was depleted in the vocal folds and laryngeal ventricles and increased in the posterior commissure. CA-III catalyses the production of bicarbonate which neutralizes refluxed gastric acids resulting in a reduction of peptic activity. This depletion might predispose vocal cords and laryngeal ventricles to reflux-related inflammatory damage [6]. The role of *Helicobacter pylori* in LPR is unclear. Oridate *et al.* [3] suggested that *H. pylori* toxins in gastric refluxate may aggravate airway hyper-responsiveness, leading to reflex cough and globus pharyngeal sensations. Tezer *et al.* [8^{*}] reported a significant correlation between signs of laryngitis, grades of esophagitis and *H. pylori* colonization in the stomach. However, Ercan *et al.* [9] found no relationship between *H. pylori* and the number of LPR reflux episodes or hypopharyngeal acid exposure time.

Laryngopharyngeal reflux and otitis media with effusion

Several studies have indicated LPR as a potential factor in the development of otitis media with effusion (OME), the most common cause of deafness in children [10,11]. Gastric acid and pepsin can disturb Eustachian tube functions [12]. Pepsin, which retains some proteolytic activity up to pH 6.5, could be the main damaging factor rather than gastric HCl [7]. Tasker *et al.* [13] has found high levels of pepsinogen in middle ear effusions up to 1000 times higher than pepsinogen levels in serum. A direct chemical inflammatory effect on the mucosal lining of the Eustachian tubes, impairment of middle ear ventilation and the direct access of gastric refluxate to the middle ear could pave the way for the development of OME [13]. In adults, high pepsinogen levels of up to 95 times higher than that in serum were reported by Sone *et al.* [14^{*}]. Abd El-Fattah *et al.* [15^{**}] reported LPR in 71% of children with OME. They detected high levels of pepsinogen in middle ear effusions up to 231 times higher than serum levels, with a significant positive correlation between pepsinogen levels in the effusion and the number of LPR events.

Chronic sinusitis

Chambers and Davis [16] found that a history of gastroesophageal reflux was the only historic factor that predicts poor outcome after endoscopic sinus surgery (ESS). Ulualp and Toohill [17] reported significantly higher prevalence of pharyngeal acid reflux in patients with chronic sinusitis. Treating reflux in patients with gastroesophageal reflux and refractory chronic sinusitis resulted in improvement of their chronic sinusitis symptoms more than in patients with chronic sinusitis without gastroesophageal reflux [18]. LPR was considered as a contributory factor of the failure of chronic sinusitis to respond to

medical treatment [19] as well as ESS [20]. In a prospective controlled study, patients with refractory sinusitis after ESS had significantly more LPR compared with two control groups, including patients with chronic sinusitis who responded to ESS and non-sinusitis individuals.

Diagnosis of laryngopharyngeal reflux

Ambulatory 24 h double-probe (pharyngeal and esophageal) pH monitoring is considered by many authorities to be the gold standard for diagnosing LPR. The distal probe is placed 5 cm above the lower esophageal sphincter and the proximal probe is placed in the hypopharynx within 2 cm of the upper esophageal sphincter. This is usually done under manometric or flexible fiberoptic endoscopic guidance. Probes with variable intersensor distances are used. Alternatively, the proximal probe can be placed just above the upper esophageal sphincter guided by a flexible laryngoscope. The distance between the proximal and distal probe is fixed at 15 cm for adults and 5 cm for infants [21]. The fixed distance between the two probes, however, cannot guarantee a precise placement of the distal probe.

The normal pH values for the hypopharynx are not well defined. There is no generally accepted validated cut-off pH value for the definition of LPR. However, the most commonly used parameters to evaluate LPR are the number of reflux episodes with a drop to pH 4 in 24 h and the percentage of time the pH is below 4 (reflux index). Other parameters with different weights in different studies include total duration of reflux episodes under pH 4, number of reflux episodes with pH <5, longest reflux episode, acid clearance (time from the start of reflux until pH returns to baseline level), mean pH value and reflux area index (RAI; the sum of the area below the curve for pH episodes <4 corrected for study duration).

The choice of pH 4 as a threshold parameter for LPR is arbitrary. Based on the mean pH at the upper esophageal sphincter in asymptomatic controls, Panetti *et al.* [7] proposed pH 5 as a threshold for LPR. Whether this would pick up more reflux patients (increased sensitivity) or simply overestimate LPR prevalence and therefore reduce the test specificity is not clear.

There is no agreement on the cut-off number of pharyngeal reflux episodes diagnostic of pathological LPR. Earlier studies on LPR reported no pharyngeal reflux events in normal control subjects [2,22] and one reflux episode was then considered as a proof of LPR [2,15^{••},22,23]. Other researchers considered three episodes [24^{••}], four or more episodes [25–27] and seven or more episodes [28] diagnostic of LPR. These variations

depend on different methods of placing the proximal probe and different analysis protocols used.

LPR episodes have been reported in 30–50% of normal controls [28,29]. Probably, the determining factor for LPR causing symptoms is its severity. Brief LPR in some normal individuals with strong hypopharyngeal and upper esophageal protective mechanisms could be asymptomatic.

With careful clinical assessment and patient selection, one would expect a high yield of pH monitoring in the hypopharynx in patients suspected for LPR. However, a wide range of diagnostic yield has been reported in the literature, ranging from 14 to 83% [24^{••},30–33]. This could be due to various methods for testing pH [34], definition of normal values, patients selection and pH-monitoring artifacts. These artifacts include acidic foods, acidic beverages and loss of pH signals [24^{••}]. LPR events required antecedent esophageal reflux events of equal or greater value; drops in the pH value at the proximal probe without accompanying drops at the distal probe were ignored. ‘Pseudoreflux’, introduced by Wiener *et al.* [22] as a result of electrode drying or loss of mucosal contact, should also be identified and ignored.

In spite of the wide acceptance of double-probe pH monitoring as a gold standard for diagnosing LPR, pH monitoring is not widely used by otolaryngologists as a diagnostic modality. The reasons for this include patient resistance, expense, difficulty in quantifying intermittent episodes and, to some degree, its unavailability. The majority of otolaryngologists base initial diagnosis on physical findings. A polling of a select group of otolaryngologists (members of the American Broncho-Esophagological Association) revealed that the most commonly performed diagnostic procedure was fiberoptic laryngoscopy (75.7% of the responders) whereas 37.2% would order double-probe pH as an adjunctive test to diagnose LPR [35]. Questionnaires were e-mailed to members of the British Academy of Otolaryngology–Head and Neck Surgery, and the results showed that only 8% of the responders would consider referral to a gastroenterologist and/or order further investigations [36[•]]. Furthermore, a recent critical review of the studies of pharyngeal pH measurement in patients with clinically diagnosed LPR and normal controls found no significant difference in the prevalence of PR events between normal controls and LPR patients [37^{••}].

Scoring systems for laryngopharyngeal reflux symptoms and signs

Several scoring systems have been developed for the interpretation of normal and abnormal pH studies for children and adults [20,38,39]. The Reflux Symptom

Index (RSI) developed by Belafsky *et al.* [40] is widely used to analyze patient perception of possible LPR [41,42^{••}]. RSI is a validated self-administered scoring system which utilizes nine symptoms suggestive of LPR (hoarseness, throat clearing, throat mucus/postnasal drip, dysphagia, coughing after eating or after lying down, breathing difficulties, troublesome or annoying cough, globus pharyngeus, and heartburn). Each symptom is scaled from 0 to 5 with a maximum score of 45. The authors recommended that an RSI of 13 or more was abnormal and indicative of LPR. The RSI was criticized for not including throat pain, which was found in up to 40% of LPR patients [43] and for including heartburn which is a common symptom of esophageal reflux known to respond well to proton-pump inhibitors (PPIs) [44[•]]. The reason for giving cough the strength of two items is not clear.

The Reflux Finding Score (RFS) was also developed by Belafsky *et al.* [39] to document the severity of physical laryngeal findings associated with LPR. It includes eight laryngoscopic findings with various strengths (subglottic edema, ventricular obliteration, laryngeal erythema/hyperemia, vocal fold edema, diffuse laryngeal edema, posterior commissure hypertrophy, granuloma/granulation tissue, and excessive endolaryngeal mucus). The maximum score is 26 and a score of 7 or more was considered to be diagnostic of LPR [39].

The main criticism of the RFS is that it is subjective. Otolaryngologists vary significantly in their scoring of various laryngoscopic findings attributed to LPR and over/under diagnosis of LPR, based on clinical findings, cannot be avoided [45]. Even in 'ideal conditions', there is lack of agreement in scoring laryngeal findings between experienced coworkers devoted to their practice [42^{••}].

Treatment of laryngopharyngeal reflux

Treatment of LPR involves dietary and lifestyle modifications plus anti-acid medications. Lifestyle modifications include avoidance of heavy meals, smoking, excessive alcohol and meals at night time. Other measures include reducing body weight, avoiding tight clothes and adopting a higher head position in bed [46,47[•]]. Anti-acid medications include histamine H₂ receptor antagonists and PPIs, which are superior to other anti-acids in achieving gastric acid suppression [2]. PPIs are the most effective anti-reflux medicines available. These are used with variable doses (20–80 mg) for variable duration [46]. Initial reports on LPR recommended a twice-daily dose of PPI [1], which was also recommended for patients with severe or complicated LPR [48]. Treatment duration varies between 2 and 6 months. Whereas LPR symptoms might achieve maximal relief by 2 months [49], laryngeal reflux findings tend to resolve

more slowly and may take 6 months or longer to reverse [50]. A single daily dose of PPI together with lifestyle modifications for 8 weeks has been recommended for the majority of patients with LPR symptoms [49]. The PPI dose might be reduced after 8 weeks while maintaining lifestyle modifications [47[•]]. Reichel *et al.* [51[•]] reported adequate control of LPR symptoms after once-daily PPI for 13–54 days (mean, 28 days) with lifestyle modifications. They recommended higher doses twice daily for resistant cases.

PPIs and other acid-suppressing medications only alter the pH of gastric refluxate by reducing HCl formation. They do not stop the reflux process because of an incompetent lower esophageal sphincter and ineffective esophageal peristalsis. Therefore, some LPR patients require long-term medical treatment while others, who face a lifetime of anti-reflux treatment or failed medical therapy, require fundoplication to restore the competence of the lower esophageal sphincter.

There is a common practice among otolaryngologists to use a therapeutic test on patients clinically diagnosed with LPR, including acid-suppression medication, usually PPIs. In the view of the American Gastroenterological Association [52], pH-metry is reserved for patients who do not respond to initial empirical acid-suppression therapy. Therefore, pH monitoring has not gained widespread use in everyday clinical diagnosis and treatment of LPR.

In spite of the wide use of PPIs for treatment of LPR, randomized controlled studies have showed no clear evidence to demonstrate the superiority of PPIs over placebo for treatment of suspected LPR [44[•],46]. The response is based largely on a reported improvement in symptoms. The improvement of LPR symptoms and signs in placebo groups in the studies which used PPIs could mean that, in some patients, LPR is a self-limiting condition [26]. Lifestyle modifications are another significant factor which would be adopted by both placebo and treatment groups. As LPR manifestations are non-specific, even confirmation of LPR with pH measurements does not rule out other etiologies which could have diluted the effect of PPIs to control LPR [46]. Furthermore, as PPIs only reduce gastric acid formation, non-acid reflux would continue and this might explain, in part, why some individuals continue to have symptoms after PPI treatment [53[•]].

Conclusion

LPR is still largely controversial. It is essential to elucidate the molecular basis of pathophysiologic processes which develop in the upper esophageal sphincter and the upper airway mucosa leading to LPR and its various

manifestations. This would help the development of objective modalities for diagnosis, treatment and monitoring of LPR.

Immunoassay of pepsin as a biological marker for detection of LPR presents an objective and non-invasive diagnostic test. However, the precise role of pepsin in LPR pathogenesis needs further study to elucidate its clinical relevance. The role of non-acid reflux needs more exploration, particularly in patients who fail to respond to PPIs.

Intraluminal esophageal impedance measurement is a promising tool for investigating reflux events, particularly when combined with pH-metry. Its application is currently restricted to GERD and further studies are needed to elucidate its application in LPR.

If the diagnosis and treatment of LPR are to rely on rating physical findings as primary indicators, the sensitivity and specificity for various laryngoscopic findings should be determined. Further studies are needed to achieve greater independence and objectivity of ratings to verify and accurately assess inter- and intra-observer agreement.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 88).

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