Current perspectives on reflux laryngitis

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Abstract Laryngopharyngeal reflux (LPR) is an extraesophageal manifestation of gastroesophageal reflux disease (GERD). With the increase of GERD patients, the importance of LPR is acknowledged widely. However, the pathophysiology of LPR is not understood completely and the diagnostic criteria for LPR remain controversial. Unfortunately, a gold standard diagnostic test for reflux laryngitis is not available. Recently, an experimental animal model for reflux laryngitis was developed to investigate the pathophysiology of reflux laryngitis. An empirical trial of lifestyle modification and proton pump inhibitor therapy is a reasonable approach for LPR symptoms. Alternatives after failure with aggressive medical treatment are limited and multichannel intraluminal impedance and pH monitoring is currently the best alternative to detect nonacid reflux. Additional prospective and evidence-based research is anticipated.

Keywords Reflux laryngitis · Multichannel intraluminal impedance and pH (MII-pH) monitoring · Extraesophageal manifestation of GERD · Laryngopharyngeal reflux

Introduction

Recently, the incidence of gastroesophageal reflux disease (GERD) was reported to be increasing in Japan, as well as in Western countries [1], and the number of patients who are aware of unusual sensations in the laryngopharynx with

GERD is also increasing. Laryngopharyngeal reflux (LPR) is defined as an extraesophageal variant of GERD [2]. In one study, approximately 10 % of otolaryngology clinic patients overall and 50 % of patients with voice complaints were diagnosed with LPR [3]. LPR has been linked to several disorders, including reflux laryngitis and reflux cough. Symptoms associated with reflux laryngitis are hoarseness, throat clearing, choking sensation, dysphagia, dysphonia, globus, sore throat, and laryngospasm. However, LPR is not usually associated with esophagitis, heartburn, or regurgitation [4]. Since the typical LPR symptoms are nonspecific and can also be caused by infections, vocal abuse, allergy, smoking, inhaled environmental irritants, alcohol abuse, chronic sinusitis, laryngeal tumor, thyroid disorder, drugs, psychosomatic disorder, and depression, increased awareness of LPR can lead to overdiagnosis of the condition. Recently, an experimental animal model for reflux laryngitis was developed to investigate the pathophysiology of reflux laryngitis. This review addresses the current state of reflux laryngitis as an extraesophageal manifestation of GERD.

Pathophysiology

Most proposed pathophysiological mechanisms for LPR can be explained by reflux theory or reflex theory [5, 6]. Reflux theory is a direct mechanism involving aspiration that directly stimulates the pharynx or larynx. LPR symptoms result from direct contact between the laryngeal and pharyngeal epithelium and the retrograde flow of gastric contents. Compared to the esophageal mucosa, laryngeal and pharyngeal epithelium are significantly more vulnerable to damage, and even short exposure of direct contact with gastric refluxate can lead to laryngopharyngeal

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damage [6–8]. Although the lower esophageal sphincter (LES) is frequently breached by gastric contents in both physiological and pathophysiological states [10], the LES, esophageal motor function with acid clearance, esophageal mucosal tissue resistance, and the upper esophageal sphincter (UES) usually prevents gastroesophageal reflux [3]. UES pressure is increased by distal esophageal reflux and the esophagoglottic closure reflex, swallowing, and cough protect the pharynx and larynx from contact with proximal refluxate [9]. Pepsin has been shown to play a role in the pathogenesis of LPR. Pepsin is active maximally at a pH of 2, but it can cause tissue damage at a pH of ≤ 6.5 [11]. Johnson et al. showed that pepsin is found in human laryngeal epithelium collected from patients with LPR [8]. However, later studies suggest the co-importance of acid, pepsin, and bile acids [6].

Reflex theory involves distal esophageal reflux that produces LPR symptoms [12]. The reflexive mechanism is proposed by two potential reflexes. The first is laryngeal chemoreflex [13]—the reflex pathway consists of an afferent limb carried by the stimulated superior laryngeal nerve and an efferent limb carried by the recurrent laryngeal nerve [14]. The second reflexive mechanism is vagally mediated reflex [12]. Bauman et al. suggested that sensory stimulation of the distal esophagus in the absence of any laryngeal stimulation can cause laryngospasm via an afferent limb of the vagus nerve [15]. As a result of these reflex mechanisms, patients may experience LPR symptoms.

Experimental animal model

Since the ability to examine the pathophysiology of LPR in humans is limited, an experimental animal model for reflux laryngitis is required. In the past, some experimental animal models were established to clarify the relationship between gastric acid reflux and laryngopharynx lesions [16–18]. Adhami et al. [6] suggested that acidic refluxate, pepsin, and conjugated bile acids are the most injurious agents affecting laryngeal tissue. However, as these experimental animal models expose the pharynx directly to the acid solution, they are not physiological models. Few reports have investigated whether endogenous gastric acid can flow upward to the supraglottic larynx in a chronic reflux esophagitis model.

Shimazu et al. [19] established a rat model of reflux-induced esophagitis using the method of Omura et al. [20]. In this physiological model, reflux-induced esophagitis is caused by endogenous gastric acid reflux, and the model is accepted clinically. In the rat chronic acid reflux esophagitis model, studies reported that mucosal thickening and inflammatory cell infiltration were observed in the

hypopharynx at 8 weeks after surgery, and chronic inflammation with proliferation of fibroblasts, deposition of collagen fibers, and proliferation and dilatation of the capillaries were observed as time progressed. However, little macroscopic change was observed in the hypopharyngeal mucosa in this model. No consensus concerning histopathological findings in reflux laryngitis at the level of the subglottic larynx was attained, and Shimazu et al. failed to provide convincing evidence of laryngeal inflammation immediately after surgery. Moreover, there are no reports that investigate whether the damage to laryngeal epithelium by the endogenous gastric acid reflux was recovered using proton pump inhibitor (PPI) therapy.

We also established a rat reflux esophago-laryngitis model caused by endogenous gastric acid reflux on use of PPI by modifying our original model of chronic acid reflux esophagitis [21, 22]. Our reflux esophago-laryngitis model was developed only 2 weeks after surgery. The 14-day survival rate after surgery was 80 %, and all rats in this reflux esophago-laryngitis model showed macroscopic esophageal ulcers. In our study, laryngeal epithelial thickness and leukocyte infiltration in both the subglottic and supraglottic larynx were increased in rats with reflux esophago-laryngitis relative to controls. However, no macroscopic ulceration was seen in either the subglottic or supraglottic larynx. These results suggest that refluxed endogenous gastric acid can flow upward to the supraglottic larynx and beyond the glottis. The difference in epithelial defenses between the esophagus and larynx suggest that further investigation of the pathophysiology of reflux laryngitis using these experimental animal models is warranted.

Diagnosis

Laryngoscopy

Laryngoscopy is an important screening tool for the diagnosis of reflux laryngitis. However, laryngoscopic findings of LPR are often highly (Table 1) subjective and may be present in many normal subjects without GERD. Belafsky et al. [23] reported the reflux finding score (RFS), which is a standardized scoring system composed of an 8-item clinical severity score based on laryngoscopic examinations. The 8 components of the scoring system include subglottic edema, ventricular obliteration, erythema, vocal fold edema, diffuse laryngeal edema, posterior commissure hypertrophy, granuloma, and excessive endolaryngeal mucus. Results range from 0–26. Based on their analysis, there is 95 % chance that a patient with an RFS of ≥ 7 will have LPR. Although RFS is becoming widespread in the diagnostic process for LPR, some concerns have been

Table 1 Diagnosis and treatment of LPR

Diagnosis	Treatment
Laryngoscopy	Lifestyle modification
24-hour pH monitoring	Medical treatment
MII-pH monitoring	Surgery
Oropharyngeal pH monitoring	
Pepsin detection	
PPI test	

LPR Laryngopharyngeal reflux, *MII-pH* multichannel intraluminal impedance and pH monitoring, *PPI* proton pump inhibitor

raised about its subjectivity and inter-rater variability [24]. However, several laryngoscopic findings have been closely associated with LPR. One of these findings is pseudosulcus vocalis, which refers to infraglottic edema that passes posterior to the vocal process of the arytenoid cartilages. This pseudosulcus, as an independent laryngoscopic finding, has been strongly associated with LPR [25]. As a result of having scored the endoscopic images of the larynx and pharynx according to several variables associated with LPR before and after PPI therapy, Oridate et al. suggests that the finding of thick endolaryngeal mucus is useful for diagnosing LPR [26].

24-hour pH monitoring

The gold standard for diagnosing and quantifying GERD is the 24-h pH monitoring test. The probe senses fluctuations in pH between 2 and 7. For the duration of the test, the patients wear a data recorder that is connected to the probe and maintain a diary of events. At the end of the study, the pH tracing and the diary are compared to determine symptom correlation. However, the role of pH monitoring in establishing a relationship between GERD and reflux laryngitis syndrome is unclear. It was initially thought that patients with symptoms of reflux-related laryngitis would have more reflux events in the upper esophageal and hypopharyngeal regions. However, Joniau et al. reported that up to 43 % of normal subjects without LPR symptoms may have abnormal hypopharyngeal pH monitoring, and no statistical difference was found in the prevalence of pharyngeal reflux events between symptomatic patients and normal volunteers [27]. Other studies showed that only 54 % of patients with suspected LPR have abnormal esophageal acid exposure [28, 29]. Although correlating pharyngeal pH and aspiration is reasonable, measuring pH in the pharynx has limitations. There are no universally accepted diagnostic criteria such as normal pH limits, number of events, and probe placement for hypopharyngeal pH monitoring. Furthermore, reflux episodes may not be detected in the larger air-filled pharynx, and a reflux

episode may be diluted and buffered, resulting in a pH >4. In addition, there is a high frequency of artifacts in the recordings due to drying of the sensor and accumulation of mucus or foods on the sensor.

Multichannel intraluminal impedance and pH monitoring

The identification and quantification of nonacid refluxate is important in patients who continue to be symptomatic despite aggressive acid-suppressive therapy. The latest diagnostic tool for LPR is combined multichannel intraluminal impedance and pH (MII-pH) monitoring. This technique identifies the presence of any remaining physiological reflux regardless of pH, and can detect the frequency, location, and direction of any gas or liquid refluxate along the esophagus, as well as in the hypopharynx [30, 31]. After 24 h, ambulatory pharyngo-esophageal impedance and pH monitoring in patients with LPR-related chronic cough, Kawamura et al. [32] suggested that most patients with LPR-related chronic cough showed weakly acidic gas esophagopharyngeal reflux. However, no established normative values exist for all parameters acquired during MII-pH and the clinical significance of abnormal impedance findings in the patients with LPR awaits further study.

Oropharyngeal pH monitoring

The Restech pH probe (Respiratory Technology Corporation, San Diego, CA, USA) is a minimally invasive oropharyngeal pH monitoring device. It detects pH in either liquid or aerosolized droplets. The caliber of the probe is approximately 1 mm, and its placement does not require endoscopy. This device shows a faster detection rate compared with traditional pH catheters. A recent study showed that oropharyngeal pH monitoring is more sensitive than traditional pH monitoring in the evaluation of patients with extraesophageal reflux [33]. Ayazi et al. [34] studied this new device in asymptomatic volunteers, and suggested that discriminating pH thresholds were selected and normal values defined to identify patients with an abnormal pharyngeal pH environment. However, further controlled studies are needed to assess the role of this new device in patients with LPR.

Pepsin detection

Pepsin, which is activated in an acidic environment, has been important in the diagnosis of LPR. Pepsin is a proteolytic enzyme that takes its active form from pepsinogen secreted by the gastric chief cells. Pepsinogen is activated by hydrochloric acid in the stomach. A pepsin rapid test

(Peptest-Biomed) is used as a noninvasive tool to diagnose reflux laryngitis. Saritas et al. [35] suggested that the rapid lateral flow device for salivary pepsin has acceptable test characteristics in patients with GERD. However, further study of this diagnostic tool in LPR patients is needed.

PPI test

Due to the poor specificity of laryngoscopic examination and poor sensitivity of pH monitoring, the most accepted method in clinical practice to diagnose LPR is an empiric trial of PPI therapy [36]. As a diagnostic treatment, the PPI test is performed despite symptoms improving in suspected patients with reflux laryngitis. Altman et al. [37] suggested that empirical PPI therapy for a period of 1–2 months is a reasonable initial approach in patients with LPR symptoms. Patients unresponsive to PPI therapy have either nonreflux-related causes or may have a functional component to their symptoms.

Treatment

Lifestyle modification

Modification of daily lifestyle is critical to the management of reflux laryngitis. Patients with suspected LPR are advised to avoid stimuli that aggravate acid reflux, such as drinking alcohol, smoking, fatty foods, chocolate, acidic foods, spicy foods, and caffeine. A double-blind, randomized trial showed that lifestyle modification for a period of 2 months improved symptoms of LPR significantly, with or without the use of PPIs [38]. Koufman et al. [39] suggested that a strict low-acid diet may have beneficial effects on the symptoms and findings of recalcitrant LPR. Other lifestyle modifications are to raise the head of the bed during sleep and to avoid eating within 3 h of lying down.

Medical treatment

PPI therapy is the standard of care of extraesophageal GERD, such as reflux laryngitis syndrome. A randomized placebo-control study revealed that 12 weeks of treatment with rabeprazole improved reflux symptoms significantly in patients with LPR compared with placebo [40]. However, a recent meta-analysis of controlled studies in LPR showed that PPI therapy may offer a modest, but non-significant clinical benefit over placebo in suspected GERD-related chronic laryngitis [41]. In patients who do not respond to twice-daily PPI therapy, other causes of laryngitis should be investigated.

Surgery

Surgical intervention is an option for patients with LPR who have failed medical management. Anti-reflux surgery is usually a gastric fundoplication to create a new valve mechanism at the gastroesophageal junction to prevent gastroesophageal reflux. The most common method is a Nissen fundoplication. In this fundoplication, the fundus of the stomach is mobilized and the posterior aspect of the fundus is passed behind the esophagus. Deveney et al. [42] showed that 73 % of patients with reflux-induced laryngeal inflammatory lesion and voice disorders had resolution of symptoms after Nissen fundoplication. However, Swoger et al. [43] suggested that surgical fundoplication does not improve laryngeal symptoms reliably in patients unresponsive to aggressive PPI therapy.

Summary

Reflux laryngitis is an important extraesophageal symptom of LPR. However, the pathophysiology of LPR is not clear and the diagnostic criteria of LPR remain controversial. Diagnostic tools such as upper gastrointestinal endoscopy and pH monitoring are poor markers for diagnosing patients with reflux laryngitis and a gold standard diagnostic test for reflux laryngitis is needed. An empirical trial of lifestyle modification and PPI therapy is a reasonable approach only in patients with LPR symptoms. Cases that fail to improve substantially with aggressive medical treatment require definitive assessment. Although there are limitations, MII-pH monitoring is currently the best alternative to detect non-acid reflux. Additional prospective, evidence-based research is needed.

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