INTRODUCTION

Gastroesophageal reflux disease (GERD) is implicated in many patients with chronic laryngitis. Ear, nose and throat (ENT) physicians often refer to this condition as laryngopharyngeal reflux (LPR) representing the retrograde movement of gastric contents, including acid, pepsin as well as bile acids, into the laryngopharynx (1,2). Typical LPR symptoms include dysphonia, globus pharyngeus (sensation of lump in throat), mild dysphagia, chronic cough, and non-productive throat clearing (Table 1). There are many synonyms for LPR including extraesophageal reflux, reflux laryngitis, and laryngeal reflux.

There is currently no gold-standard in the diagnosis of LPR, and hence data on its epidemiology is limited. One study of 105 normal, healthy, adults revealed at least one finding associated with reflux during a laryngoscopy in 86% of the volunteers (3). In a meta-analysis which reviewed the data of pH probe readings in patients with LPR and in controls, 10% to 60% of the control patients (totaling 264 in number) demonstrated reflux (4). Studies such as these reveal that LPR or what is thought to be LPR is a common occurrence in the general population; however, it may be overdiagnosed in some patients.

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

PATHOPHYSIOLOGY

The upper esophageal sphincter and to some extent the larynx act as a sphincters to protect the lower airways from aspiration of swallowed contents. The larynx is highly innervated and in a normal individual, any reflux would be sensed and a protective cough would be elicited. In patients with LPR, this “safety mechanism” may fail. For example, a study conducted by Aviv, et al proposed that a sensory deficit may play a role in LPR. The authors found decreased laryngeal adductor reflexes in response to endoscopic administration of air pulses in patients with documented LPR (5). Another study using immuno-histochemical staining of two cadaveric larynges, illustrated that there are numerous alpha and beta subunits of the H+/K+ ATPase in the larynx. It was concluded that larynges of LPR patients may produce higher levels of acid via proton pumps. Although intriguing findings, the clinical significance of these studies are yet to be elucidated which further complicates an already controversial field.

The two predominant pathophysiologic mechanisms for LPR accepted by most experts is thought to be direct or indirect laryngeal exposure to various injurious contents of the stomach. The direct mechanism simply results from the actions of caustic gastric contents such as acid, pepsin and/or bile acids inter-

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acting with mucosa in the laryngopharynx. The indirect mechanism is thought to result from reflux material interacting with structures more distal to the larynx. It is thought that this irritation evokes a vagally-mediated response of bronchoconstriction; possibly causing the commonly associated non-productive cough (6). In LPR the former mechanism may be more important.

The delicate ciliated respiratory epithelium of the posterior larynx which normally functions to clear mucus secretions from the trachea fails when directly affected by the caustic gastroduodenal chemicals which may result in mucus stasis. This in turn, promotes the sensation of post-nasal drip and furthermore, throat clearing (6). Recently, it is proposed that the bicarbonate-producing enzyme carbonic anhydrase protects the laryngeal tissues from reflux and that this protective mechanism may be present less often in laryngeal tissues of patients with LPR (7).

The specific agent(s) responsible for producing ENT symptoms and laryngeal pathology including laryngitis, vocal cord lesions and even laryngeal carcinoma are currently unknown and the subject of many debates. Potential candidates include gastric contents, acid and pepsin, and duodenal contents, both bile acids and the pancreatic enzyme trypsin. Previous animal studies suggested injurious potential for both acid and pepsin, reporting a significant role for both agents in causing laryngeal lesions (8). A recent study extended the above 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 (9). 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 since some reports implicate the reflux of non-acidic duodenal contents as the cause of persistent laryngitis in patients unresponsive to aggressive acid suppression.

In humans, it is difficult to isolate the injurious potential of each of the above listed agents, mainly because the gastric milieu refluxing into the esophagus is commonly a mixture of gastric and duodenal contents. Although laryngeal injury may occur with intermittent acid/pepsin exposure in animals, this area is not well studied in humans and is subject to controversy. The advent of impedance/pH monitoring as the indirect marker for the reflux of gastroduodenal contents have recently shed some important light into the possible contribution of acid and non-acid reflux in patients with LPR who continue to be symptomatic despite acid suppressive therapy.

**CLINICAL MANIFESTATIONS**

Most patients diagnosed with LPR may not have the classic symptoms of GERD. One series of patients with otolaryngologic symptoms who were found to have LPR complained of the following symptoms: Dysphonia (71%), cough (51%), globus pharyngeus (47%), throat clearing (42%), and dysphagia (35%) (10). These symptoms were often intermittent. Additionally, heartburn and regurgitation which are hallmark symptoms suggesting the presence of GERD were not present in most of these patients. It is estimated that up to 50% of patients with laryngeal and voice disorders have reflux (11).

Based on a study of pH-confirmed LPR patients, some have advocated the use of the Reflux Symptom Index (RSI). This is a self-administered tool that helps clinicians assess the clinical severity of LPR symptoms at diagnosis and then after treatment. Patients rate nine symptoms such as throat clearing, hoarseness, and difficulty swallowing on a scale from 0-to-5 (Table 2). The RSI is significantly higher in untreated LPR patients than in controls (21.2 versus 11.6, p < .001). Any score greater than 13 is considered...
abnormal (12). However, this index is seldom used by the general ENT practitioners (13).

**DIAGNOSIS**

The diagnosis of LPR is most commonly suspected on the basis of combination of chronic throat symptoms and laryngeal findings. However, given lack of specificity of symptoms and signs for GERD many patients initially diagnosed with LPR do not respond to treatment for GERD and will need evaluation for other potential causes. Other potential causes for patient’s persistent symptoms and laryngeal signs may include tobacco, alcohol, allergies, vocal trauma, vocal cord overuse or abuse, infections or postnasal discharge.

The two most commonly used diagnostic tools in LPR include laryngoscopy and pH monitoring. There are numerous signs on laryngoscopy that are attributed to reflux disease: edema and erythema of the larynx, granuloma, contact ulcers, polyps, subglottic stenosis, tumors, cobblestoning of posterior pharynx (hyperemia and lymphoid hyperplasia) (14) (Table 3). However, a survey of 2,000 ENT physicians revealed that the two signs most likely to be used to diagnose laryngitis associated with reflux were erythema and edema of the larynx (13). These signs are highly non-specific and many healthy adults have laryngeal changes without any throat symptoms (3). This suggests 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. More specific signs need to be identified to increase the rate of correct diagnoses of LPR. In one study, vocal cord lesions were suggested to represent more specific signs for LPR with 91% specificity and 88% response to PPI therapy (15).

In addition to the non-specificity of the currently employed signs in LPR, an additional problem is the inter- and intra-observer variability of laryngoscopic exam. One study which recorded ENT physician’s independent ratings of laryngeal images of 120 patients revealed poor inter- and intra-rater reliability (16). Additionally, there is poor correlation between symptoms and laryngoscopic findings. This was evidenced in a recent study where patients with LPR symptoms who were refractory to aggressive PPI therapy underwent a Nissen fundoplication. One year post-fundoplication, laryngeal symptoms improved in only 10% of patients, whereas signs improved in 80% (17).

Reflux Finding Score (RFS) (18) 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 (Table 4). Each of the eight items are ranked from either 0-to-2 or 0-to-4 with a Reflux Finding Score of seven or more indicating a 95% chance that the patient indeed does have LPR. Initial studies found good inter- and intra-observer reproducibility for this tool in assessment and follow-up of LPR patients (18). However, similar to RSI, RFS is seldom

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used in clinical or academic practice. Additionally, the clinical relevance of this score is in question.

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 in LPR. Compared with physical exam findings, dual pH probe monitoring does have superior sensitivity and specificity (10). However, there is much variability in testing methods and lack of agreement on what pH value is considered abnormal. Additionally, one study determined that it was a poor predictor of the severity of patients’ symptoms and signs (19). A more recent meta-analysis involving 16 studies and 793 subjects who underwent 24-hour pH monitoring (264 controls, 529 LPR patients) found that the number of positive pharyngeal reflux events for normal subjects and for subjects with LPR differed significantly. There was also a significant difference in acid exposure times between these two groups. The conclusion from this study was that the “upper probe gives accurate and consistent information in normal subjects and patients with LPR” and that the acid exposure time and number of reflux events are most important in distinguishing normal subjects from patients with LPR (4).

However, there are numerous problems with using pH data to diagnose LPR. First, several studies have shown that proximal esophageal and hypopharyngeal acid exposure occurs in normal subjects as well (from 7% to 17%) (20-22). Second, there are no universally accepted diagnostic criteria for hypopharyngeal pH monitoring (normal pH limits, number of events, and probe placement). Finally, proximal and hypopharyngeal probes have poor sensitivity in detecting reflux of gastric acid, 50% and 40%, respectively (23,24).

Given poor specificity of laryngoscopic exam and poor sensitivity of pH monitoring, the most accepted method employed in clinical practice to suggest the diagnosis of LPR is an empiric trial of a proton pump inhibitor. Other diagnostic tests, such as barium esophagography 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 is recently gaining some popularity (25-28). Employing 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 distinction to be made between acid, weakly acidic and weakly alkaline reflux (26). Impedance works by measuring changes in resistance to alternating current between a series of metal electrodes produced by gas, liquid, or bolus. Metal rings are placed on a catheter to determine the impedance (increased by gas and decreased by liquid). Measuring impedance at multiple sites (multichannel) allows for determination of the direction of the esophageal bolus (antegrade versus retrograde).

A recent multi-center trial, which used impedance—pH-metry in healthy adults, has provided normal values which can be used in clinical and research settings for comparison with reflux patients (29). Recent data from a single center (30) and multicenter (27) studies in a group of patients with heartburn and regurgitation as well as those with extraesophageal symptoms suggested that 10% to 40% of patients on BID PPI therapy may have continued non-acid reflux. However, the causal association between these reflux events and patients’ continued reflux symptoms are difficult to establish. Preliminary outcomes data on response of this group of patients to surgical fundoplication (28) is encouraging and await validation by large scale multicenter controlled trials.

**TREATMENT**

Initial treatment of LPR patients should include education about the disorder and recommendations regard-
ing diet and behavioral changes that may play a role in the pathophysiology. Ideally, foods and beverages containing caffeine, alcohol, chocolate, and peppermints which are thought to weaken the esophageal sphincters and possibly increase acid secretion, should be eliminated. Carbonated beverages, with or without caffeine, are thought to worsen reflux as it often prompts belching, allowing gastric contents to bypass the protective esophageal sphincters. Additionally, acidic foods (pH below 4.6) should be limited. This includes citrus fruits, tomatoes, and red wines. Other lifestyle modifications that may improve LPR symptoms, as well as other symptoms of extra-esophageal reflux, include smoking cessation and weight loss. A study by Steward, et al (31), revealed that lifestyle modification for two months, with or without PPI therapy, significantly improved chronic laryngitis symptoms.

Drug therapy usually consists of acid suppression with proton pump inhibitors (PPI’s). As both laryngoscopy and pH monitoring are not 100% accurate in diagnosis, empiric therapy with a PPI is warranted, especially since it may aid in diagnosis. To date, studies examining the efficacy of PPI therapy in LPR patients has produced a broad range of responses. This is most likely due to selection biases and the true prevalence of reflux induced laryngeal disease. Most uncontrolled studies suggest near 70% response rate with PPI’s (32). However, nearly all controlled studies disappointingly do not suggest a major benefit of PPI’s over placebo. An earlier controlled trial involving treatment with lanoprazole 30mg twice daily for three months in 22 patients with idiopathic chronic laryngitis revealed that 50% of the treatment group had a complete response versus 10% in the control group (33). However, another study using the same medicine regimen, found no difference in response rates in patients with posterior pharyngolaryngitis (34). The most recent large scale multi center study of 145 patients suspected of having LPR did not show a benefit in those treated for four-months with esomeprazole 40 mg BID compared to placebo (35). Although, a disappointing result, once again this study highlights the difficulty in certainty of the LPR diagnosis in most patients.

Given the negative findings of controlled trials, currently uncontrolled studies are the basis for the treatment recommendations in patients with LPR. Two studies which both examined use of omeprazole 40 mg (initially once daily dosing which was changed to twice daily dosing in non-responders) reported response rates of 67% and 92% (36,37). All of the above studies were limited by small numbers and short duration. The most recent study involving 85 subjects determined that twice daily PPI therapy was more efficacious than once daily therapy and that extending therapy to four months from two months resulted in more responses (38). Overall, the general consensus supports the use of twice daily PPI therapy for two-to-three months. Unlike GERD, the variable efficacy of PPI therapy for LPR suggest the multifactorial nature of the disease process.

The role of combination therapy of PPI’s with histamine 2 receptor antagonists (H2RA) was initially raised by Peghini, et al in 1998 when it was determined that three-fourths of patients experienced a return of pH <4 for greater than one hour within 12 hours of their evening PPI dose (39). A follow-up study by Peghini, et al examined whether a bedtime Histamine 2 receptor antagonist (H2RA, ranitidine) or a bedtime PPI dose would be beneficial in patients on BID dosing of a PPI with nocturnal acid breakthrough (NAB) (40). It was determined that a bedtime ranitidine rather than a third dose of a PPI at bedtime was more effective on NAB. However, two later studies examining the role of H2RA’s for NAB concluded that H2RA’s provide no additional benefit over PPI therapy alone (41,42). The current recommendations do not suggest the use of nocturnal H2RA in addition to PPI’s in patients suspected of LPR. To achieve best results, PPI’s should be taken on an empty stomach, about 30 minutes before a meal.

Treatment with a PPI usually will result in improving patient symptoms within one month of therapy (43) but laryngeal signs my take up to six months to resolve (12). Patients who do not improve after two-to-three months of therapy most likely do not have GERD as the cause of their laryngeal signs and throat symptoms. However, they may need to be tested for non-acid reflux using the combined impedance/pH monitoring while on BID PPI therapy.

The role of surgical fundoplication in those poorly responsive to BID PPI therapy is still somewhat con-
troversial. A recent study (17) evaluated 12-month symptomatic response of 10 patients who despite lack of response to PPI therapy underwent fundoplication compared to 12 PPI unresponsive patients who continued on their therapy. They showed that only 10% of patients responded to surgical fundoplication and this response rate was not any different than the group who continued on their PPI therapy (7%). Thus they suggested that surgical fundoplication does not reliably relieve symptoms in LPR patients who were unresponsive to medical management. However, the role of surgical intervention in the subgroup of PPI unresponsive patients who have abnormal non-acid reflux detected by impedance monitoring suggests that these patients can be successfully treated by laparoscopic Nissen fundoplication (28). A large scale randomized, controlled outcome study is currently underway to assess the efficacy of surgical fundoplication in symptomatic patients on therapy who have abnormal non-acid reflux on impedance monitoring.

CONCLUSIONS

Common clinical manifestations of LPR include dysphonia, cough, globus pharyngeus, throat clearing, and dysphagia. Unless they report warning symptoms, this group of patients should be treated empirically consisting of lifestyle modification as well as twice-daily PPI therapy for two-to-three months. Patients whose symptoms resolve should have tapering of the medication to minimum acid suppression that keeps them in the asymptomatic state. Patients who show minimal or no sign of improvement after adequate trial of PPI’s, will require physiologic assessment to ensure adequate acid and non-acid reflux as the contributing factors. Etiologies other than reflux should be investigated in most patients unresponsive to PPI’s.

References

Chronic Laryngitis and GERD

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