Review Article

Laryngo-pharyngeal reflux- A review

Harkare Vivek[1]

Abstract:

Laryngo-pharyngeal reflux or atypical gastro-esophageal reflux disease (GERD) syndrome commonly known as extra-esophageal reflux is a controversial subject. The available literature remains non-conclusive regarding the patho-physiology, investigations and management of patients presenting with symptoms of extra-esophageal disease. It remains unknown whether symptoms are caused by direct exposure to refluxate or are via a referred sensation or cough reflex or both. Mucosal changes are not specific to laryngo-pharyngeal reflux although laryngeal pseudo-sulcus has a positive predictive value of 67- 90 % for laryngo-pharyngeal reflux. The symptoms of laryngo-pharyngeal reflux include hoarseness of voice, throat clearing, dysphagia, increased phlegm and globus sensation; patients may also have asthma like symptoms. Physical findings which may be secondary to associated smoking, alcohol, allergic, asthma, viral illness and vocal abuse, include laryngeal edema, erythema, leukoplakia, granulation or even malignancy. The aims of the treatment include decreasing reflux, improving esophageal clearance and protecting esophageal and laryngo-pharyngeal mucosa. Lifestyle modification like weight loss, avoiding sweets, tomatoes, onions, alcohol and caffeine and finishing dinner 3 hours before going to bed may help. Antacids, H2 receptor antagonists, proton pump inhibitors, prokinetic drugs and anti-reflux surgery like fundoplication and injection of biopolymers in lower esophageal sphincter are used.

Key words : Laryngopharygeal reflux, laryngeal pseudosulcus, H2 receptor antagonists, prokinetic drugs.

[1]Professor & HOD
Department Of ENT
NKPSIMS & RC, Digdoh Hills,
Hingna Road, Nagpur-440019
viv_harkare@rediffmail.com

Laryngo-pharyngeal reflux

Laryngo-pharyngeal reflux (LPR), also extra-esophageal reflux disease (EERD) refers to retrograde flow of gastric contents to the upper aero-digestive tract, which causes a variety of symptoms, such as cough, hoarseness, and asthma, among others (1).

Although heartburn is a primary symptom among people with gastro-esophageal reflux disease (GERD), heartburn is present in fewer than 50% of the patients with LPR. Other terms used to describe this condition include atypical reflux, and supra-esophageal reflux (2).

Gastro-esophageal reflux disease (GERD) was recognized as a clinical entity in the mid-1930s and now is the most prevalent upper gastrointestinal (GI) disorder in clinical practice. Acid-related laryngeal ulcerations and granulomas were first reported by Chery in 1968 (3). Subsequent studies suggested that acid reflux might be a contributory factor in other laryngeal and respiratory conditions. In 1979, Pellegrini and DeMeester (4) were the first to document the link between these airway symptoms and reflux of gastric contents. They also proved that treatment of reflux disease results in elimination of these airway symptoms.

Laryngo-pharyngeal reflux or a typical GERD syndrome or commonly known as extra esophageal reflux is a controversial subject. The available literature remains controversial regarding the pathophysiology, investigations and management of patients presenting with symptoms of extra-esophageal disease. The terms acid laryngitis was coined 40 years ago as most of the extra-esophageal reflux manifestations affect the laryngopharynx (1). The recent research work shows the possibility of cellular mechanisms, whereby reflux might affect the upper airway. Acidified pepsin damages inter cellular spaces and pepsin is taken by human laryngeal ephithelial cells by receptor mediated endocytosis (5).

Pathogenesis

Laryngo-pharyngeal reflux differs from gastro-esophageal reflux disease (GERD) in that it is often not associated with heartburn and regurgitation symptoms. The larynx is vulnerable to gastric reflux, so patients often present with laryngo-pharyngeal symptoms in the absence of heartburn and regurgitation (6). There are 4 physiological barriers protecting the upper aero-digestive tract from reflux injury: the lower esophageal sphincter, esophageal motor function with acid clearance, esophageal mucosal tissue resistance, and the upper esophageal sphincter. The delicate ciliated respiratory epithelium of the posterior larynx that normally functions to clear mucus from the tracheo-bronchial tree is altered when these barriers fail, and the resultant ciliary dysfunction causes mucus stasis (7). The subsequent accumulation of mucus produces postnasal drip sensation and provokes throat clearing. Direct refluxate irritation can cause coughing and choking (laryngospasm) because sensitivity in laryngeal sensory endings is up-regulated by local inflammation (8). This combination of factors can lead to vocal fold edema, contact ulcers, and granulomas that cause other LPR-associated symptoms: hoarseness, globus pharyngeus, and sore throat (2,9).

Recent investigations suggest that vulnerable laryngeal tissues are protected from reflux damage by the pH-

regulating effect of carbonic anhydrase in the mucosa of the posterior larynx (10). Carbonic anhydrase catalyzes hydration of carbon dioxide to produce bicarbonate; this protects tissues from acid refluxate. In the esophagus, there is active production of bicarbonate in the extracellular space that functions to neutralize refluxed gastric acid. There is no active pumping of bicarbonate in laryngeal epithelium and carbonic anhydrase isoenzyme III, expressed at high levels in normal laryngeal epithelium, was absent in 64% (47/75) of biopsy specimens from laryngeal tissues of LPR patients (11).

Measurement of exposure to refluxate- It remains unknown whether symptoms are caused by direct exposure to refluxate or are via referred sensation or cough reflex or both. Upto 50% controls have measurable pH drop to < pH 4, 2cm above the upper esophageal sphincter. Techniques of measuring refluxate exit are varied and yet not standardized across specialties (10).

Mucosal Changes- Mucosal changes are not specific to laryngo-pharyngeal reflux although laryngeal pseudo-sulcus has a positive predictive value of 67 -90% for laryngo-pharyngeal reflux. Exposure of laryngeal mucosa to biliary secretions for many years post gastrectomy appears to be carcinogenic. The role of Helicobacter pylori is not clear. Treating reflux may reduce the risk of recurrence of laryngeal cancer, but there is no prospective evidence (12).

Clinical Features

The symptoms of laryngo-pharyngeal reflux includes hoarseness of voice, throat clearing, dysphagia, increased phlegm and globus sensation. Many patients may have asthma like symptoms. Laryngo-pharyngeal reflux may be suspected if the onset of asthma comes in adults without any family history and heart burn precedes onset of asthma.

Physical finding which may be secondary to associated smoking, alcohol, allergic asthma, viral illness and vocal abuse, include laryngeal edema, erythema, leukoplakia, granulation or even malignancy. Laryngoscopic findings such as erythema, edema, laryngeal granulomas, and inter-arytenoid hypertrophy have been used to establish the diagnosis, but these findings are very nonspecific, and have been described in the majority of asymptomatic subjects undergoing laryngoscopy (9,11).

Response to acid suppression therapy has been suggested as a diagnostic tool to confirm diagnosis of LPR, but studies have shown that the response to empirical trials of such therapy (as with proton-pump inhibitors) in these patients is often disappointing. Several studies have emphasized the importance of measuring proximal esophageal, or, ideally, pharyngeal acid exposure in patients with clinical symptoms of LPR, to document reflux as the cause of the symptoms (10).

Diagnosis of Laryngopharyngeal Reflux

History- It is important for physicians to appreciate the potential significance of hoarseness and the relative non-specificity of laryngitis. Laryngitis is a nonspecific designation of laryngeal inflammation. Often, it is mild and resolves spontaneously. When persistent, laryngitis must be further defined based on probable etiologic factors: viral or bacterial infection, allergy, vocal trauma, postnasal discharge or LPR. Persistent or progressive hoarseness lasting beyond 2 to 3 weeks requires examination of the laryngopharynx to rule out cancer and other serious conditions. This is generally considered good practice; however, laryngeal examination is particularly important in suspected LPR because of the apparent known association of LPR and upper aerodigestive tract cancer (12).

Laryngopharyngeal reflux should be suspected when clinical history and initial findings are suggestive. Failure to appreciate LPR as different from GERD has been a major source of skepticism about the diagnosis in the past. Koufman was the first to clearly distinguish LPR from GERD, noting that in a combined reported series of 899 patients, throat clearing was a complaint of 87% of LPR patients vs 3% of those with GERD, while only 20% of LPR patients complained of heartburn vs 83% in the GERD group(6). An international survey of American Broncho-esophagological Association members revealed that the most common LPR symptoms were throat clearing (98%), persistent cough (97%), globus pharyngeus (95%), and hoarseness (95%) (11).

Since there is no pathognomonic LPR finding, Belafsky et al (13) developed an 8-item clinical severity scale for judging laryngoscopic findings, the Reflux Finding Score, which appears to be useful for assessment and follow-up of LPR patients. They rated 8 LPR-associated findings on a variably weighted scale from 0 to 4: subglottic edema, ventricular obliteration, erythema/hyperemia, vocal fold edema, diffuse laryngeal edema, posterior commissure hypertrophy, granuloma, and thick endolaryngeal edema. The results could range from 0 (normal) to 26 (worst possible score). Based on their analysis, one can be 95% certain that a patient with a Reflux Finding Score of 7 or more will have LPR (14).

Management

Patient Education and Lifestyle Changes- Patients with LPR should be educated as to the nature of the problem and counseled on helpful behavioral and dietary changes (15). Important behavioral changes include weight loss, smoking cessation, and alcohol avoidance. Ideal dietary changes would restrict chocolate, fats, citrus fruits, carbonated beverages, spicy tomato-based products, red wines, caffeine, and late-night meals. Such behavioral changes appear to be an independently significant variable in

determining response to medical therapy. Education should include the optimal schedule for taking PPI medications (omeprazole, esomeprazole, rabeprazole, lansoprazole, and pantoprazole), which work best when taken 30 to 60 minutes before meals (16).

Medical Management- There are 4 categories of drugs used in treating LPR: PPIs, H2-receptor antagonists, prokinetic agents, and mucosal cytoprotectants. Proton pump inhibitors are considered the mainstay of medical treatment, although there is some controversy regarding their efficacy. A 3-month empirical trial is a cost-effective approach for initial assessment and management. Responders can be weaned, while non-responders should undergo studies to confirm LPR (17).

Other drugs have been used to treat LPR. Ranitidine has proved to be a more potent inhibitor of gastric secretion than cimetidine and is the H2-receptor antagonist of choice, although it has been found to be of limited value in treating LPR (18). Prokinetic agents that accelerate esophageal clearance and increase lower esophageal sphincter pressure have fallen out of favor because of reported adverse effects of ventricular arrhythmias and diarrhea (19). Cisapride has been discontinued because of such serious adverse effects. Tegaserod is a prokinetic agent that was recently demonstrated to decrease reflux and lower esophageal sphincter relaxation events, and that was found useful in treating some LPR cases with associated esophageal dyskinesia. Sucralfate is a polysulfated salt of sucrose that may be helpful as an adjunct in protecting injured mucosa from harmful effects of pepsin and acid. Antacids (sodium bicarbonate–, aluminum-, and magnesium-containing over-the-counter antacids) may relieve GERD symptoms but do not play a role in LPR management (15).

The aims of the treatment include decreasing reflux, improving esophageal clearance and protecting esophageal and laryngo-pharyngeal mucosa.

Anti reflux surgical management- When medical management fails, patients with demonstrable high-volume liquid reflux and lower sphincter incompetence are often candidates for surgical intervention. Fundoplication, either complete (Nissen or Rossetti) or partial (Toupet or Bore), is the most common procedure performed, and the laparoscopic approach is preferred (20). The goal of surgery is to restore competence of the lower esophageal sphincter, and the outcome measures for LPR include demonstration of reduced pharyngeal reflux episodes. Excellent results have been reported in 85% to 95% of reflux cases, but results with LPR are not as impressive (21). Focusing on a carefully screened group of patients with demonstrable extraesophageal reflux (LPR), Oelschlager et al reported a significant decrease in pharyngeal reflux (7.9 to 1.6 episodes per 24 hours; P<.05) and esophageal acid exposure (7.5% to 2.1%; P<.05) following basic laparoscopic Nissen fundoplication surgery (21). In Nissen's fundoplication, fundus of stomach is wrapped around LES. Fundoplication appears superior to medical management in preventing Barrett metaplasia (22).

Recent developments

Although there is interest in recent nonfundoplication endoscopic techniques like Bard EndoCinch System for endoluminal plication, System for radiofrequency-induced thermal injury and Enteryx liquid polymer injection, to improve lower esophageal sphincteric function, there are no controlled studies and there is no long-term follow-up evidence to support their use.

References

1. Delahunty J E. Acid laryngitis. J. Laryngol. 1972; Otol. 86: 335-342.
2. Chheda N N, Seybt M W, Schade R R et al. Normal values for pharyngeal pH monitoring. Ann. Otol. Rhinol. Laryngol. 2009; 118: 166-171.
3. Cherry J, Margulies S I. 'Contact ulcer of the larynx.' Laryngoscope. 1968; 78 (11): 122-125.
4. Pellegrini C A, DeMeester T R. et al. " Gastroesophageal reflux and pulmonary aspiration: incidence, functional abnormality, and results of surgical therapy." Surgery. 1979; 86(1): 110 – 114.
5. Johnston N. Review article: Uptake of pepsin at pH 7- in non-acid reflux – causes inflammatory, and perhaps even neoplastic, changes in the laryngopharynx, Aliment. Pharmacol Ther. 2011; 33: 13-20.
6. 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
7. Koufman J, Sataloff RT, Toohill R. Laryngopharyngeal reflux: consensus conference report. J Voice. 1996; 10215-216 Hanson DG, Jiang JJ. Diagnosis and management of chronic laryngitis associated with reflux. Am J Med. 2000;108(suppl 4a) 112S-119S
8. 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;1101099-1108.
9. Ylitalo R, Ramel S. Extraesophageal reflux in patients with contact granuloma: a prospective controlled study. Ann Otol Rhinol Laryngol. 2002;111441-446
10. Postma GN. Ambulatory pH monitoring methodology. Ann Otol Rhinol Laryngol Suppl. 2000;18410-14
11. Ford CN, Inagi K, Khidr A, Bless DM, Gilchrist KW. Sulcus vocalis:A rational analytical approach to diagnosis and management. Ann Otol Rhinol Laryngol. 1996;105189-200.
12. Morrison MD. Is chronic gastroesophageal reflux a causative factor in glottic carcinoma? Otolaryngol Head Neck Surg.

1988;99, 370-373
13. Belafsky PC, Postma GN, Koufman JA. The validity and reliability of the Reflux Finding Score (RFS). Laryngoscope. 2001;111, 1313-1317
14. Vaezi MF. Extraesophageal manifestations of gastresophageal reflux disease. Clin Cornerstone. 2003;532-38
15. Katz PO, Castell DO. Medical therapy of supraesophageal gastresophageal reflux disease. Am J Med. 2000;108(suppl 4a) 170S-177S
16. 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
17. Williams RB, Szczesniak MM, Maclean JC, Brake HM, Cole IE, Cook IJ. Predictors of outcome in an open label, therapeutic trial of high-dose omeprazole in laryngitis. Am J Gastroenterol. 2004;99, 777-785
18. Fackler WK, Ours TM, Vaezi MF, Richter JE. Long-term effect of H2RA therapy on nocturnalgastric acid breakthrough. Gastroenterology. 2002;122625-632
19. Castell DO. Future medical therapy of reflux esophagitis. J Clin Gastroenterol. 1986;8(suppl 1) 81-85.
20. Fuchs KH, Breithaupt W, Fein M, Maroske J, Hammer I. Laparoscopic Nissen repair: Indications, techniques and long-term benefits. Langenbecks Arch Surg. 2005;390197-202
21. Oelschlager BK, Eubanks TR, Oleynikov D, Pope C, Pellegrini CA. Symptomatic and physiologic outcomes after operative treatment for extraesophageal reflux. Surg Endosc. 2002;16, 1032-1036.
22. Charles N. Ford, MD. Evaluation and management of laryngopharyngeal reflux. JAMA 2005, 294(12) 1534-1540.