THE TRIBES AND TRIBULATIONS OF LARYNGOPHARYNGEAL REFLUX: A REVIEW OF RECENT STUDIES WITH IMPLICATIONS FOR INTERDISCIPLINARY COLLABORATIONS BETWEEN OTOLARYNGOLOGISTS AND GASTROENTEROLOGISTS

Oana-Bogdana Bărboi¹, Cristina Cîjeveschi Prelipcean¹, M.D. Cobzeanu², D. Palade², A. Albu-Soda¹, Mariana Floria³, I. Chirilă⁴, V.L. Drug⁵*, G. Bălan¹

University of Medicine and Pharmacy “Grigore T. Popa” - Iaşi
Faculty of Medicine
1. Department of Gastroenterology
2. Department of Otolaryngology
3. Department of Internal Medicine
4. Institute of Public Health

* Corresponding author. E-mail: vasidrug@email.com

Laryngopharyngeal reflux disease (LPR), also known as supraesophageal reflux disease, atypical gastroesophageal reflux disease (GERD) or reflux laryngitis, represents an extradigestive manifestation of GERD due to the reflux of gastric content through the esophageal/pharyngeal/laryngeal axis (1). Although GERD and LPR are considered to be part of a spectrum within the same disease, they are different clinical entities produced through different pathophysiological mechanisms. Reflux laryngitis is still a challenge for both gastroenterologists and otolaryngologists. Even though the cause-effect relationship assertion between GERD and LPR has been strengthened by more recent evidence, the causality, diagnosis and treatment remain controversial. Since Koufman coined the term "LPR" in the 90's, reflux laryngitis has been most frequently recognized by Ear, Neck and Throat (ENT) surgeons and gastroenterologists, but also by other medical specialists (pneumologists, cardiologists etc), even to the point of being over-diagnosed (2). For example, in the USA, during a period of 11 years, the number of ENT consultations for clinical conditions related to GERD in-
creased by over 300% and the prescription of proton pump inhibitor (PPI) also multiplied about 14 times (2).

**Epidemiology and pathophysiology.** The mechanisms involved in the pathophysiology of LPR may be related to the direct injury of the esophageal and pharyngolaryngeal mucosa by the gastro-duodenal content, with or without micro-aspiration in the respiratory airways. The larynx is an organ about a 100 times more sensitive than the esophagus and is at high risk of injury because of its immediate proximity to the digestive system (3). Thus, only a small amount of gastric content is sufficient to cause lesions of the larynx. The second mechanism that is incriminated in the pathophysiology of LPR is the tracheobronchial reflex mediated by the vagal nerve, produced by the acidification of the distal esophagus, and which determines cough, throat clearing and laryngospasm (3). The vocal folds are covered by stratified squamous epithelium which creates a barrier against external and internal factors, including reflux. Erickson and Sivasankar conducted a study using transepithelial electrical resistance (TER) for assessing the permeability of the epithelium of the vocal folds. They found that the exposure of vocal folds to refluxate determines the decrease of TER, making them more susceptible to injury (4). It has also been demonstrated that carbonic anhydrase type III plays a protective role of the epithelium of the larynx, as it regulates cellular pH when the larynx comes in contact with acid by producing bicarbonate (5). Ford (1) showed that this enzyme was absent in 64% of patients with LPR. The peptic injury was also associated with depletion of other key protective proteins such as E-cadherin and the stress proteins (e.g. Sep 70) (5).

The exact actual prevalence of reflux laryngitis is hard to determine because of the different clinical presentations of LPR, added to the lack of consensus regarding LPR diagnosis and treatment. It is estimated that 4-10% of patients who seek otorhinolaryngologic services suffer from reflux disease. At the same time, LPR was identified in more than 50% of dysphonic patients (6). In last decades, the prevalence of GERD and LPR has increased dramatically. Using a statistical model in an analysis of 17 studies, El-Serag (7) showed that the average increase rate of reflux disease since 1976 has been 4% per year (P <0.0001). An interview-based study on 656 subjects revealed unexpectedly high percentages of people living with GERD - 40% (22% with typical GERD and 18% with LPR) across the USA. In addition, many patients were young – 21-30 years old (37%). Regarding causality, food additives were now considered to play a significant role, apart from the historically acknowledged obesity (8).

**Clinical manifestations of LPR.** Despite the association between GERD and LPR, the diagnosis of reflux laryngitis remains a difficult task. First, a complete and accurate anamnesis is needed in order to diagnose this pathology. According to the study published by Koufman two decades ago we should discriminate between GERD and LPR as distinct clinical entities (3). The symptoms of LPR are diverse and many physicians may not link these symptoms to LPR. The most common manifestations of LPR are dysphonia/ hoarseness, throat clearing or pain, chronic cough and globus (9, 10). But it is known that these symptoms are nonspecific to LPR and can also be found in other diseases such as postnasal drip syndrome, exposure to dif-
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Different allergens or environmental irritants like smoke or vocal abuse. Because symptoms are not exclusive to LPR, the clinicians should rely on a combination of manifestations and diagnostic tools such as laryngoscopy exam, impedance-pH monitoring and empiric trial of proton pump inhibitors (PPI) to establish an accurate diagnosis. It is important to emphasize that patients with LPR do not usually present typical GERD symptoms (heartburn and regurgitation), which can make proper diagnosis more difficult (1).

Diagnostic methods. Laryngoscopy. The diagnosis of reflux laryngitis is usually performed by ENT surgeons. Transnasal fiberoptic laryngoscopy is the first-line method to be used by otolaryngologists to diagnose LPR. Laryngoscopic exams are essential for excluding neoplasms, but their role in detecting GERD-associated laryngitis remains uncertain. There is a low inter-rater reliability among ENT surgeons evaluating the same laryngeal signs, and that is the reason why LPR diagnosis may be subjective and inaccurate. The specificity of the laryngeal signs of LPR is still debated in the literature. The most frequent laryngoscopic lesions that have been found to be related to GERD were edema and erythema, particularly in the posterior region (9). These were the main findings used by different researchers for the diagnosis of LPR, while ulcers and ventricular obliteration, nodules, polyps and leukoplakia were reported to be less useful. In another study, pseudosulcus was found to have 70% sensitivity and 77% specificity in patients with LPR (11). In 2007, Vavricka et al. (12) evaluated the prevalence of specific laryngeal lesions thought to be GERD-related, both in patients with documented reflux and normal subjects. They found that the prevalence of laryngeal lesions was the same in both groups. Only posterior pharyngeal wall findings showed a statistically significant higher prevalence in GERD patients as compared to the control group. Furthermore, the study of Hicks et al. revealed that the most signs seen in patients suspected of LPR were also found in healthy, asymptomatic subjects (13). To improve the diagnostic accuracy, Belafsky et al. developed the Reflux Finding Score (RFS) based on the presence and severity of the lesions found in laryngoscopy (14). This nine-item scoring system including the most common laryngeal lesions has great reproducibility and is useful to evaluate the effectiveness of therapy in patients with LPR. Thus, the laryngeal lesions have low specificity for LPR and that is the reason why patients initially diagnosed with reflux laryngitis do not respond to antireflux treatment. However, Park et al. showed a high specificity of the laryngeal findings for LPR (91%) (15). Rafii et al. demonstrated that LPR may be over diagnosed, all the 21 patients included in the study, had already been diagnosed with laryngopharyngeal reflux disease (16). In fact, all suffered from other laryngeal pathologies, different from LPR, as the cause for their chief complaint of dysphonia. The most common findings were vocal fold paresis (29%) and muscle tension dysphonia (14%). Therefore, the recommendation is for a diagnosis of reflux-induced laryngitis to not be made based on laryngoscopy findings alone.

Upper digestive endoscopy (UDE). UDE has excellent specificity for the diagnosis of GERD in the presence of erosive esophagitis, but only one third of patients with GERD symptoms and even fewer after treatment with PPIs have ero-
sive esophagitis (17). However, erosive esophagitis could be generate also by other pathologies (e.g. Candida esophagitis, varices) that were found in 25% of LPR patients (18). It is important to notice that, although upper endoscopy is necessary to rule out esophageal cancer, it is not a specific diagnostic test for LPR. Indeed, it has been reported that up to 80% of LPR patients have normal UDE. Red flags that necessitate early endoscopy include dysphagia, bleeding, chest pain, weight loss or dyspnea.

**Ambulatory pH monitoring/ impedance-pH monitoring.** Ambulatory reflux monitoring is a diagnosis method which can demonstrate the presence of GERD by documenting an abnormal esophageal acid exposure. A 24-hour-double-probe (simultaneous pharyngeal and esophageal) pH monitoring has been the gold-standard for LPR diagnostic in last twenty-five years (19).

The sensitivity and specificity of ambulatory pH monitoring as a means for diagnosing GERD in patients with extraesophageal reflux symptoms have been challenged (6). Koufman showed a sensitivity of 24-h dual-probe pH monitoring ranging from 50% to 80% (8). In the presence of esophagitis, the sensitivity and specificity of this method is higher (up to 100%), but in patient without esophagitis, the sensitivity is dropped to about 70% (20). Also, it has been determined that pH monitoring cannot predict the severity of patient’s reflux laryngitis symptoms or signs and only the heartburn correlates with LPR. There is great variability in the reported prevalence of abnormal pH monitoring in patients with laryngitis. A pathological reflux detected during a pH measurement does not confirm GERD as the cause of the laryngitis as well as a negative pH monitoring test can direct the diagnostic toward non-GERD etiologies. However, ambulatory reflux monitoring may be used to determine whether the patients’ symptoms are related to reflux or not. The temporal association between reflux episodes and ENT symptoms may be evaluated by two methods: the symptom index (SI) and the symptom association probability (SAP) (21). For these methods to yield results, the patient has to keep a log and use a detection device accurately and timely.

The availability of multichannel intraluminal impedance and pH monitoring (MII-pH) seems to perform better in the diagnosis and management of extraesophageal manifestations of GERD than pH-testing alone (22). It is currently emerging as the new “gold standard” for clarifying differences in PPI refractory symptoms. Esophageal pH-impedance monitoring is a method that detects both the antegrade and retrograde movements of the refluxate and evaluates the physical (liquid, gaseous or mixed) and chemical (acid or non-acid) nature of the refluxate. According to the American College Guideline published in 2013, impedance-pH is used to establish the diagnosis of GERD when: the diagnosis is uncertain, or before consideration of endoscopic or surgical therapy in patients without esophagitis, or in the evaluation of patients refractory to PPI therapy.

A very recent study (23) comparing MII-pH and Bravo® capsule in patients with LPR symptoms found high prevalence of discordant esophageal pH results, most commonly a negative MII-pH testing, but positive Bravo testing. The researchers considered that the Bravo test results were more likely to be true, as the patients included in the study presented characteristics consistent with GERD (heartburn, defective LES, hia-
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tal hernia). They concluded that MII-pH catheter study may be inadequate to diagnose GERD in the patients with both typical and atypical symptoms.

A new technology able to detect aerosols of acid and gaseous clouds of acid tends to be more used in patients with LPR. The Dx-pH measurement system® (Respiratory Technology Corp., San Diego, CA) is a highly sensitive and minimally invasive device for the detection of acid reflux in the posterior oropharynx. It uses a nasopharyngeal catheter with the pH probe placed in the oropharynx instead of hypopharynx and it measures the pH in either liquid or aerosol droplets (24). The advantages of this method are that it does not require manometry or endoscopy and the catheter is better tolerated as it does not traverse the upper esophageal sphincter. However, it is limited because it cannot confirm if a reflux event originates in the stomach, since it does not entail simultaneously probing the esophagus.

Empirical PPI treatment. The therapeutic test with PPIs is considered by many clinicians as a reasonable approach to the diagnosis of LPR, in which a favorable response is defined as diagnostic confirmation (18). Most published researchers consider a favorable response when there is a resolution of LPR symptoms after 3 months of double dose PPI trial. But the role of PPI trial is still controversial. A meta-analysis of randomized studies has demonstrated no benefit of PPIs vs. placebo in diagnosing GERD-related laryngitis (25). A placebo-controlled study including patients with LPR showed an improvement in 50% of patients when using placebo compared with 53% of patients who received PPIs (26). Due to this seemingly strong placebo effect, patients who have some response to an empiric PPI trial may be incorrectly diagnosed with reflux disease. Nowadays, the current recommendation for the empirical trial is to include patients with concomitant typical symptoms of GERD (1). The advantage of this diagnostic tool is the cost-effectiveness, the ease of use and its sensitivity, but it lacks specificity.

Pepsin testing. The use of the pepsin test to diagnose GERD is justified, because pepsin is produced exclusively by the stomach. The pepsin test (Peptest) is a non-invasive, quick and inexpensive tool for the diagnosis of LPR. It consists of a lateral flow device that uses 2 monoclonal antibodies to human pepsin to detect the presence of pepsin in saliva. Its results can be read very easily in 5-15 minutes. Because of the benefits and ease of application, a positive salivary pepsin test in a patient suspected of having LPR can be a cost effective, accurate and alternative diagnostic method. Yuksel et al. (27) found sensitivity and specificity of 87%, a positive predictive value of 85% and a negative predictive value of 68% for the pepsin test in the diagnosis of LPR. In a very recent cross-sectional study, in vitro pepsin detection tests were compared to the 24-hour double probe pH monitoring results for patients with suspected LPR (28). The authors found a sensitivity and specificity of the pepsin detection test of 33% and 100%, respectively. A positive predictive value of 100% was recorded.

Current diagnostic tests for GERD and LPR are suboptimal and do not accurately and reliably measure chronicity of reflux. New methods to diagnose LPR are needed. Recently, a minimally invasive device has been developed to assess esophageal mucosal impedance (MI) as a marker of chronic reflux. Ates et al. conducted a prospective
longitudinal study using a prototype device to investigate MI patterns in patients with GERD and common non-reflux conditions, to assess MI patterns before and after treatment with PPI and to compare the performance of MI and wireless pH tests (29). They discovered that measurements of MI detect GERD with higher levels of specificity and positive predictive values than wireless pH monitoring. They are hopeful that this device may be employed in the future also in patients with LPR.

Another diagnostic method that offers an objective and quantitative alternative is computer-based analysis of laryngeal image color and texture features. The study of Witt et al. suggested that a combination of laryngeal hue and texture features could be used to diagnose LPR (30).

CONCLUSION

Laryngopharyngeal reflux is being diagnosed increasingly frequently in recent years, especially by ENT surgeons and gastroenterologists. It has become one of the most common reasons why patients see otolaryngologists. LPR is considered to be a different clinical entity than GERD as it features different symptoms, clinical manifestations and treatment objectives. The controversy about its pathophysiology and diagnosis continues still, despite the numerous studies that have been published in the last 5-10 years. We consider that upon initial consultation, the ENT specialist should be able to recognize reflux laryngitis signs and symptoms and refer the patient to a gastroenterologist, thus acknowledging the importance of interdisciplinary collaboration in such cases. Given that LPR diagnosis and treatment have not been standardized, we emphasize that further large randomized-controlled trials are needed for more accurate diagnosis.

REFERENCES

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