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Is it Always Laryngopharyngeal Reflux? How Voice Disorders Can Manifest as LPR

¿Es siempre reflujo laríngeo-faríngeo? Cómo los trastornos de la voz pueden presentarse como LPR

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Declaration of interests

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- Pentax Medical, GSK and Merck & Co.: Consultant.
- Sofregen Medical Inc. and N-Zyme Biomedical: Scientific Advisory Board, stock options.
- Plural Publishing: Royalties from book *Chronic Cough*.

Data availability

All relevant data is in the article.
For further information, contact the corresponding author.

Abstract

Introduction. Laryngopharyngeal reflux (LPR) manifests with a constellation of common throat symptoms and inconclusive signs on laryngoscopic exam. It is a diagnosis, often made clinically, that can lead to prescriptions of proton pump inhibitors that are unnecessary and potentially harmful. Glottic insufficiency (GI) and the accompanying hyperfunctional laryngeal behaviors can also present with similar, common throat complaints that may or may not include a qualitative change to the voice.

Methods. This is a reflection article. It is written to summarize, explain, and support with evidence the opinion of the author on the topic of how symptoms of voice disorders can easily be mistaken for symptoms of LPR. The offered reflection is based on his experience, research and the available literature.

Reflection. This article intends to explore the similarities between GI and LPR, how to ultimately differentiate them and how to approach treatment with a broader differential diagnosis.

Conclusion. LPR and GI can present with identical, vague throat, and voice symptoms. Empiric medication trials, behavioral interventions and objective laryngovideoscopy, impedance-based reflux, and esophageal motility testing may all be needed, sometimes in a trial and error fashion, to correctly diagnose and treat a patient's symptoms.

Keywords

Laryngopharyngeal reflux; otolaryngology; proton pump inhibitors, alginates; vocal fold augmentation; glottic insufficiency; vocal fold injection; injection laryngoplasty; unilateral vocal fold paralysis.

Resumen

Introducción. El reflujo laríngeo-faríngeo (LPR, por sus siglas en inglés) se manifiesta con una serie de síntomas comunes en la garganta y signos no concluyentes en el examen larinoscópico. Es un diagnóstico que a menudo se realiza clínicamente y que puede llevar a la prescripción de inhibidores de la bomba de protones que son innecesarios y potencialmente perjudiciales. La insuficiencia glótica (IG) y los

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Contribution of the author

Thomas L. Carroll:

Conceptualization, supervision, writing – original draft, writing – review & editing.

comportamientos laríngeos hiperfuncionales que la acompañan también pueden presentar síntomas de garganta comunes similares, que pueden o no incluir un cambio cualitativo en la voz.

Métodos. Este es un artículo de reflexión. Está escrito para resumir, explicar y respaldar con evidencia la opinión del autor sobre cómo los síntomas de los trastornos de la voz pueden confundirse fácilmente con los síntomas del LPR. La reflexión ofrecida se basa en su experiencia, investigación y la literatura disponible.

Reflexión. Este artículo tiene la intención de explorar las similitudes entre la IG y el LPR, cómo diferenciarlos finalmente y cómo abordar el tratamiento con un diagnóstico diferencial más amplio.

Conclusión. El LPR y la IG pueden presentar síntomas idénticos y vagos en la garganta y la voz. Puede ser necesario realizar ensayos de medicación empírica, intervenciones conductuales y pruebas objetivas de laringovideostroboscopia, reflujo basado en impedancia y motilidad esofágica, a veces de manera experimental, para diagnosticar y tratar correctamente los síntomas de un paciente.

Palabras clave

Reflujo laríngeo-faríngeo; otorrinolaringología; inhibidores de la bomba de protones; alginatos; aumento de las cuerdas vocales; insuficiencia glótica; inyección en las cuerdas vocales; laringoplastia de inyección; parálisis unilateral de las cuerdas vocales.

Introduction

Dysphonia is not synonymous with the symptom of hoarseness (a rough or coarse quality of the voice), rather, dysphonia includes complaints associated with not only the glottis, but the compensation that the intrinsic and extrinsic laryngeal muscles offer to improve the best voice possible. Dysphonia is broadly defined as an alteration of voice production that impairs social and professional communication. Dysphonic complaints can be a change in the way the voice sounds, but can also include complaints of decreased vocal range, vocal fatigue, change in vocal pitch, strain, and effort.

Laryngopharyngeal Reflux (LPR), also known as atypical or extra-esophageal reflux, is the retrograde flow of stomach contents into the laryngopharynx and related structures and can (and does) cause voice and throat symptoms. LPR is a well-described etiology for dysphonic complaints in patients presenting to outpatient Otolaryngologists [1]. However, reflux may not be the cause of the patient's "classic" LPR symptoms, typically throat clearing, mucus sensation, globus sensation, throat discomfort, and dysphonia.

LPR remains primarily a diagnosis of exclusion, meaning physicians assume the symptoms and signs that the patient presents with are due to LPR, and empiric medications are prescribed to combat these complaints and physical changes. However, when a patient presents with a dysphonic complaint, offering LPR as the cause of the symptom without thorough examination of vocal fold vibration, can lead to misdiagnosis or, at a minimum, incomplete diagnosis. Over the last three decades, treating dysphonia with an acid reducing medication in the outpatient setting has remained popular [2]. Unnecessary treatment of LPR carries the additional cost of medication

side effects to the existing monetary cost of proton pump inhibitors to the health care system, among others [3]. In one study, the cost for the initial year's evaluation and treatment of LPR symptoms was quintuple that of typical GERD [4]. A total of 54% of patients' symptoms improved or resolved, while, in the same study, the remainder were stable or worsened over the 5-year time period.

The refluxate in LPR patients can be acidic ($\text{pH} < 4$), weakly acidic ($\text{pH} 4\text{--}7$) or non-acidic ($\text{pH} > 7$), and present similarly regardless of pH. As research emerges that targets pepsin and other non-acidic reflux components as primary contributors to the pathophysiology of LPR, empiric treatment with acid suppression medications alone for suspected LPR is being questioned. Acid-only treatments may be less successful in confirming reflux as the etiology of a patient's complaint by missing the non-acid and weakly acidic components of the refluxate [5]. Understanding the inflammatory role of the non-acidic components of gastric refluxate including trypsin, bile and, especially, pepsin is an ongoing target of research and has the potential for better symptom control through more targeted treatment regimens in patients with proven LPR [6,7].

Patients can present with similar, vague throat symptoms despite finally being diagnosed with a variety of glottic and other laryngopharyngeal disorders. These include throat clearing, globus sensation, mucus sensation, post-nasal drip, chronic cough, laryngeal disordered breathing complaints (i.e., inducible laryngeal obstruction, ILO), and dysphonia, none being specific to LPR [1]. LPR as a physiologic process is common. Despite LPR being implicated as the cause of a myriad of non-specific symptoms, it must be emphasized that dysphonia (and not solely a *quality* change in the voice) as a standalone complaint has many more potential, albeit likely, etiologies/pathologies than LPR; thus, an otolaryngologic exam, including stroboscopy, warrants consideration. LPR may be a contributor to a patient's symptoms. However, it cannot be blamed or concluded as the diagnosis when a white light flexible laryngoscopy does not reveal a clear reason for the patient's vague throat complaints. This dilemma is the focus of this review article.

Methods

This is a reflection article. It is written to summarize, explain and support with evidence the opinion of the author on the topic of how symptoms of voice disorders can easily be mistaken for symptoms of LPR. The offered reflection is based on his experience, research and the available literature.

Reflection

The most common reflux symptoms of heartburn, chest pressure, indigestion, acid brash and the feeling of regurgitation, do not always accompany LPR symptoms. The symptoms of gastroesophageal reflux disease (GERD) are often easier to diagnose and treat because the patient can clearly understand them, report them and are well recognized by the medical community at large as "reflux-related". It is not unusual for a patient without GERD symptoms to refute the idea that reflux is the cause of their otolaryngologic or pulmonary complaint. LPR is often called 'silent' reflux because it presents without overt GERD symptoms, but rather with vague and non-specific throat complaints.

Pepsin, a proteolytic enzyme made active in the acidic environment of the stomach is a primary mediator of the effects that reflux has on the laryngopharyngeal mucosa [7]. While the stomach and esophagus have native protection against pepsin, the upper aerodigestive tract does not [8]. Pepsin has been the primary digestive enzyme implicated in laryngopharyngeal mucosal pathology and causing LPR signs and symptoms [9]. However, the role of other digestive enzymes in the pathophysiology of LPR is also being considered [10]. Current treatment options that target pepsin with barrier agents made from sodium alginate should also relieve the aerodigestive mucosa of other non-acidic offending molecules.

In the United States, it remains common practice for primary care providers/general practitioners to prescribe acid suppressive medications like proton pump inhibitors (PPI) to their patients who present with hoarseness [11]. This is an interesting dilemma: clinicians who are not as familiar with the entity of LPR as they are with GERD think to treat voice complaints reactively with prescriptions for acid suppressive medications. More concerning is that PPIs are the chosen acid suppressive medication, often prescribed once a day for only 14 days and then stopped. As otolaryngology training typically has emphasized, longer periods of treatment, often 2 to 3 months, at higher doses of twice-daily acid suppression are often required before considering the treatment for LPR unsuccessful [12,13]. In addition to their throat complaints, patients who present with classic GERD symptoms are traditionally more likely to respond to reflux treatments including PPIs and anti-reflux surgeries [14]. This finding makes sense: the positive predictive value should, anecdotally, be higher for the clinician when the refluxate that is highly likely to be causing a patient's heartburn is also making its way into the laryngopharynx. Without the ability to evaluate the larynx on routine outpatient visits, it is understandable that the general practitioner, gastroenterologist, pulmonologist, etc., who is unable to rule out other pathology that could be causing a patient's presenting symptom, offers a treatment to appease the patient.

There are other tools available to any physician to diagnose LPR, and they are more reliable than even history and laryngoscopy. Reflux testing using Hypopharyngeal-Esophageal Multichannel intraluminal Impedance with dual pH (HEMII-pH) technology in addition to High Resolution Esophageal Manometry (HRM) is considered by many as the gold standard for diagnosing LPR [15,16]. While pH-impedance testing is more widely available, the use of the HEMII-pH catheter that can demonstrate liquid events (including pH of the liquid) traveling from the stomach to the hypopharynx (above the upper esophageal sphincter) are less widely available in the US and globally than more standard catheters that look at impedance and pH change in a more limited fashion up to 17 cm above the lower esophageal sphincter. However, for those patients evaluated with HEMII-pH testing and not pH-only testing, LPR related complaints, such as unexplained chronic cough, can be treated successfully by recognizing non-acidic reflux as the target and not the acidity of the refluxate alone [17].

Cost containment and patient safety issues surrounding PPI use are pushing otolaryngologists to diagnose and treat suspected LPR symptoms more carefully [3,4]. Due to increased concern for a variety of adverse effects, PPIs are now a medication class that physicians and their patients are less eager to use. PPI use has been linked to bone density loss, renal disease, C. difficile colitis and dementia, among others [18-21]. These issues are more associated with long-term PPI use, however the negative media attention influences patients' willingness to take PPIs, whether they remain indicated or not. Alternatives to the classic acid-suppression-only empiric trial approach is being introduced and implemented [5].

Glottic insufficiency (GI) is an often-overlooked etiology of symptoms that can easily mimic LPR. GI is the inappropriate escape of air from the glottis during normal phonation [22,23]. Common pathologies causing GI include vocal fold atrophy, immobility or paralysis, scar or sulci, and benign, premalignant and malignant lesions. Certain pathologies of the glottis are large, clear, and easy to diagnose and assign as the cause of a patient's laryngeal symptoms: a larger vocal fold polyp, a paralyzed vocal fold, a larger leukoplakic lesion, or severe vocal fold atrophy with bowing at rest. However, more subtle changes in the larynx such as a paresis, early vocal fold atrophy, a thin pseudocyst or a small scar are easily overlooked on white light exam alone (i.e., without videostroboscopy). Often accompanying subtle glottic insufficiency is supraglottic hyperfunctional behaviors, which can make diagnosing these less prominent lesions more challenging without stroboscopic evaluation. When viewed with stroboscopy under the direction of an experienced clinician who can suggest phonatory tasks to encourage unloading of the laryngeal hyperfunction, subtle abnormalities such as asymmetrical false vocal fold compression, mucosal wave and periodicity abnormalities, as well as imperfect closure patterns are revealed [24].

The symptom overlaps between GI and LPR is strong and non-specific. Hoarseness, throat clearing, a sensation of mucus in the throat, globus sensation, chronic cough, vocal fatigue/strain/effort, and difficulty swallowing are all complaints that can be caused by both LPR and GI [25-27]. LPR and GI should not be thought to exist in isolation of each other, and some discussion leans toward LPR being an initial insult that leads to hyperfunctional laryngeal behaviors and ultimately benign vocal fold lesions [28] can coexist with true glottic pathology. While laryngovideostroboscopy (LVS) hopes to identify a potential reason for the patient's symptoms beyond LPR, vocal fold inflammation and edema may be the only identifiable pathology on LVS, and it is not uncommon to see those findings in the background of other pathologies that explain a patient's voice change.

The idea of LPR and GI co-existing may be more explainable than previously emphasized. Post-viral vagal neuropathy can lead to subtle motion abnormalities from recurrent laryngeal nerve involvement while also changing the motility of the esophagus and gut [29]. It is not uncommon to see a subtle vocal fold paresis in patients with one or more of the overlapping symptoms. Esophageal motility issues can mimic LPR symptoms [30] and can lead to a higher chance of esophageal and gastric back up, and thus true LPR or LPR attributed symptoms in the esophagus, when the gut is not functioning optimally. As seen on HRM, the upper esophageal sphincter likely exhibits lower basal pressure in the setting of more typical GERD reflux patient with also higher sensations of dysphagia [31]. The proximal esophageal contractility is decreased, and lower esophageal sphincter can have variable findings in LPR patients, as seen on high resolution manometry studies [32]. Because symptoms such as hoarseness and throat clearing have been shown to improve in patients with vocal fold atrophy both when GI is improved with injection augmentation and when treated with appropriate LPR therapy, it is hard to definitively diagnose the cause of the patient's symptoms using history, patient reported outcomes (i.e., the reflux symptom index) and laryngoscopy to determine that GI, LPR or both may be the cause of the patient's presenting dysphonic or throat clearing complaint [25]. Trial and error empiric treatments or more diagnostic procedures, such as diagnostic vocal fold injection augmentation or HEMII-pH/HRM, are needed to determine the etiology of symptoms are usually necessary [33].

Globus sensation is a symptom that is often blamed on LPR. It is the feeling of a lump, fullness or foreign body in the throat. Depending on its etiology, a globus complaint may be present with dry swallows, when eating meals or at all times. Globus sensation can also be associated with laryngeal hyperfunctional behaviors secondary to GI, often seen and diagnosed in the author's practice as secondary muscle tension dysphonia (MTD). Typically, the hyperfunctional behaviors are seen on LVS during phonation and the patient exhibits tight and tender strap and base of tongue muscles with the globus sensation. These patients often complain that the lump feeling is absent upon awakening (after a night's rest) and gets worse as the day goes on, a secondary clue that using the voice is what is contributing to the compensatory muscle sensations. Interestingly, patients with globus secondary to GI and MTD do not feel the globus while talking, but rather while dry swallowing. This can easily be confused with the globus sensation from LPR, but there are subtle differences. Relying on patient reported symptoms alone is not conclusive; thus, it can be very challenging to tease the cause or causes of the globus sensation out through symptoms alone. Globus sensation associated with LPR is thought to be a result of either generalized edema of the arytenoids and post-cricoid area or compensatory cricopharyngeus muscle hyperfunction [22]. Erythema and edema seen in the laryngopharyngeal tissue in patients with LPR is thought to be due to direct inflammatory effects of the acidic and non-acid contents of the refluxate [34]. Normally, reflux is prevented from entering the laryngopharynx by tonic contraction of the UES. Over time, in the setting of a higher-than-normal reflux burden, it is theorized that the UES begins to lose its ability to relax appropriately during swallowing, and, as a patient ages, the pharyngeal constrictors also are believed to dilate and lose tone, leading to a less effective swallow [35]. Both of these issues may cause a globus sensation during meals. When the differential diagnosis includes both GI and LPR, but the patient reports their symptoms get worse as the day goes on, after significant periods of voice use or symptoms are triggered by talking or laughing, then GI may be worth addressing. Voice therapy or ultimately vocal fold augmentation may improve the presenting complaint. If voice therapy or augmentation leads to symptom improvement or resolution, GI and not their LPR was more likely to be contributing to their symptoms.

One other common symptom for otolaryngologic patient presentation is throat clearing: the sensation of needing to clear real or perceived mucus from the glottis or throat. This complaint is often blamed on LPR because it is an irritative symptom that often is the last standing possibility if allergies have been ruled out or treated. Throat clearing, however, is also a symptom of GI. Older patients with vocal fold atrophy are known to have throat clearing as a common presenting symptom of GI. A study by Patel et al. realized that throat clearing is a common symptom to both true vocal fold atrophy and LPR. Once the correct treatment was applied, throat clearing improved [25].

Chronic cough (CC), a cough lasting longer than 8 weeks, is another complaint that includes GERD in its top 3 etiologies. After asthma and sinonasal/allergy disease has been ruled out or maximally treated, the majority of patients with CC are "ruled out" for GERD as the etiology through high dose, twice daily PPI acid suppression trials [3]. It is now recognized that acid suppression as a sole treatment modality to rule out *reflux* as the cause of a CC is far from complete. An understanding of pepsin as the underlying offending LPR agent/etiology for chronic laryngopharyngeal inflammation has shifted the focus away from acid-suppressive medication trials. More comprehensive empiric reflux treatment regimens, often including barrier treatments containing sodium alginate (alginates), are on the rise. Once reflux has truly been ruled in or out using more comprehensive acid suppression plus alginate trials [17]

or with HEMII-pH and HRM testing, and if an appropriate reflux or dysmotility treatment is not successful to improve the patient's CC, the cough is now deemed "refractory" (RCC) or "unexplained" (UCC). RCC and UCC patients are one of the author's primary clinical focus and often the most challenging patients to treat. RCC and UCC patients have typically seen numerous other physicians and been told they do not have LPR based on PPI trials and a normal esophagoscopy. Educating patients about LPR and non-acid reflux takes energy, time, and patience as well as requiring physicians who are willing to think outside the box and look at other potential stimuli for the etiology of the UCC.

One stimulus for CC that is becoming more recognized is GI [26]. If a patient has GI from paresis, atrophy or scar and voice therapy has not improved the patient's symptoms, diagnostic vocal fold injection augmentation (VFIA) can be performed to give the patient a chance to see what improved glottic competence does for their cough symptom [33]. During the first 2 weeks after the VFIA, if the patient's symptoms improve/resolve for even a day or two during the first few weeks after the temporary substance (often a carboxymethylcellulose or hyaluronic acid product) is placed and closure pattern improves on LVS, then a more durable procedure or surgery can be performed [36]. Anecdotally, in patients with GI and UCC, who did not improve with behavioral management (cough suppression therapy) alone, will often find the behavioral interventions for cough more effective after VFIA.

The reflux symptom index (RSI) and reflux finding score (RFS) have been part of the otolaryngologic LPR vernacular for more than two decades. The 9-item reflux symptom index (RSI) was developed by Belafsky and colleagues [37]. It was not created using impedance technology, but rather using pH-only detection technology to determine if LPR was present. The RSI was never intended to be a diagnostic tool for LPR, but it is often used that way. Anecdotally, the RSI seems less useful for diagnosing LPR but more so a good tool for following vague throat symptoms, regardless of etiology, over time [38]. Small studies have connected LPR-attributed symptoms and GI; and at least one study has demonstrated that with concomitant allergic disease, the optimal RSI cutoff may be different than in those with LPR alone [25,26,38]. A recent study by Devore et al. revealed that the RSI did not correlate with impedance results [39]. The RSI is helpful for following any and all throat complaints but is not LPR specific.

The 8-item reflux finding score (RFS) is a rating scale derived by Belafsky and colleagues to facilitate a standardized approach to assessing LPR using laryngeal findings on flexible laryngoscopy [40]. The RFS was also developed in patients with pH-only technology and before HEMII-pH testing and HRM became readily available to truly identify patients with LPR. The ability of laryngoscopy to diagnose or even suggest LPR has been contested and remains a controversial topic. Laryngeal findings attributed to reflux may also be seen in healthy volunteers [41,42]. More recent data cast a shadow on the reliability of the RFS [43-45].

Modern answers to the RSI and RFS have been developed. With a sensitivity of 94.5% and a specificity of 81% in its ability to predict true impedance LPR in subjects, the Reflux Symptom Score (RSS), although somewhat cumbersome for patients due to its length, was developed using HEMII-pH technology and is proving a more reliable clinical and research tool [15]. The Reflux Sign Assessment (RSA) was similarly developed and validated using patients diagnosed with LPR based on HEMII-pH testing. The RSA reports a sensitivity of 89.1% and specificity of 95.2% when suspecting the presence of LPR by rating physical signs in the larynx, oropharynx, and laryngopharynx. Although somewhat cumbersome for the

clinician due to the number of subsites that must be scored, it is a much more reliable way to suspect LPR based on exam findings alone [46].

There is a paucity of research that objectively evaluates the overlap of common symptoms of LPR and GI. The author's reflection is primarily based on experience and patient outcomes. Hopefully, this article will stimulate more concrete research on the topic.

Conclusions

Laryngopharyngeal reflux and glottic insufficiency can present with highly similar, yet vague throat and voice symptoms. The etiology of a patient's symptoms can often be determined by a dedicated clinician. Laryngovideostroboscopy should be considered in any patient where the flexible laryngoscopic exam does not reveal a clear reason for a patient's presenting laryngeal complaint. Both diagnostic vocal fold augmentation and behavioral therapy can evaluate the role glottic insufficiency may play while objective HEMII-pH and HRM LPR testing and/or empiric trials that treat both acid and non-acid LPR components are often needed to find the treatable causes of non-specific throat and voice complaints.

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