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Should the Reflex Be Reflux? Throat Symptoms and Alternative Explanations

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Although laryngopharyngeal reflux, also known as extraesophageal reflux (EER), was codified more than 25 years ago, it has not been characterized fully. There is no sensitive and specific diagnostic test, and its symptoms often are nonspecific and overlap with those of other conditions commonly seen in primary care and specialist practices. Otolaryngologists have an important role in the evaluation and management of these patients—they must investigate persistent reflux-attributed symptoms by direct visualization of the upper airway and larynx, and, in some circumstances, the esophagus. It is of utmost importance to rule out the possibility of malignancy, which often presents with symptoms similar to those of EER. Once cancer is excluded, many benign upper airway conditions also can masquerade as, and often incorrectly are attributed to, EER. Although reflux is a potential etiologic factor for upper-airway symptoms, it is important not to reflexively blame reflux. We discuss other etiologies that should be considered carefully for persistent symptoms.

Keywords: LPR; GERD; Treatment; Therapy.

Gastroesophageal reflux disease (GERD) affects an estimated 40% of the US population.[1] It therefore is no surprise that GERD medications are among the highest-selling pharmaceutical classes; totaling more than 127 million US prescriptions and $9.5 billion for proton pump inhibitor (PPI) sales alone in 2012.[2] Increased attention to GERD has shifted focus to whether it affects other physiologic processes beyond the esophagus into the upper and lower respiratory tracts. Anecdotes dating back to the 1960s hypothesized a connection between reflux and hoarseness,[3,4] cancer,[5] and upper-airway pathology.[6,7] These propositions were based largely on the proximity of the upper-esophageal sphincter and laryngeal inlet and the inherent potential for extraesophageal refluxate spillage onto laryngeal and hypopharyngeal mucosa. In 1991, Koufman[8] operationalized and codified laryngopharyngeal reflux (LPR), finding that it did have a greater affect on laryngeal function than previously considered. Furthermore, a distinction was made and perpetuated that LPR patients do not necessarily have classic GERD symptoms (eg, heartburn, regurgitation); rather, a large proportion have asymptomatic reflux, which manifests in sundry vague upper-airway symptoms.[9] Although these symptoms initially were limited to the proximate upper airway (ie, pharynx and larynx), over the past 20 years, LPR has been implicated in everything from otitis media[10,11] to asthma,[12] with variable degrees of scientific rigor.

Laryngopharyngeal or, perhaps more appropriately termed, *extraesophageal reflux* (EER), exists; however, a sensitive and specific gold standard method to identify these patients consistently remains elusive despite exponentially growing literature (Figure 1), rapid technological advancements, and vast expenditure on the subject.[13] Many investigators have tried to correlate specific endoscopic findings and the presence of reflux with little success.[14–16] This limitation has been recognized by the American College of Gastroenterologists, who in their most recent GERD guidelines specifically state that GERD cannot be diagnosed based solely on laryngoscopy.[17] Despite the lack of pathognomonic symptoms or signs, EER has become a primary diagnosis offered by otolaryngologists, allergists, gastroenterologists, and primary care physicians, and has resulted in many patients given a barrage of medications, undergoing diagnostic tests, and even undergoing surgeries.[13]

Role of the Otolaryngologist

EER has been associated with many symptoms including hoarseness, cough, dyspnea, globus, post-nasal drainage, and dysphagia. These otolaryngologic symptoms are some of the most common seen in the primary care setting,[18] where most are treated appropriately. However, when refractory, voice, swallowing, and breathing complaints often are referred to specialists for further symptom-based assessment. Thus, pulmonologists,

Abbreviations used in this paper: EER, extraesophageal reflux; GERD, gastroesophageal reflux disease; LPR, laryngopharyngeal reflux; MTD, muscle tension dysphonia; PPI, proton pump inhibitor.

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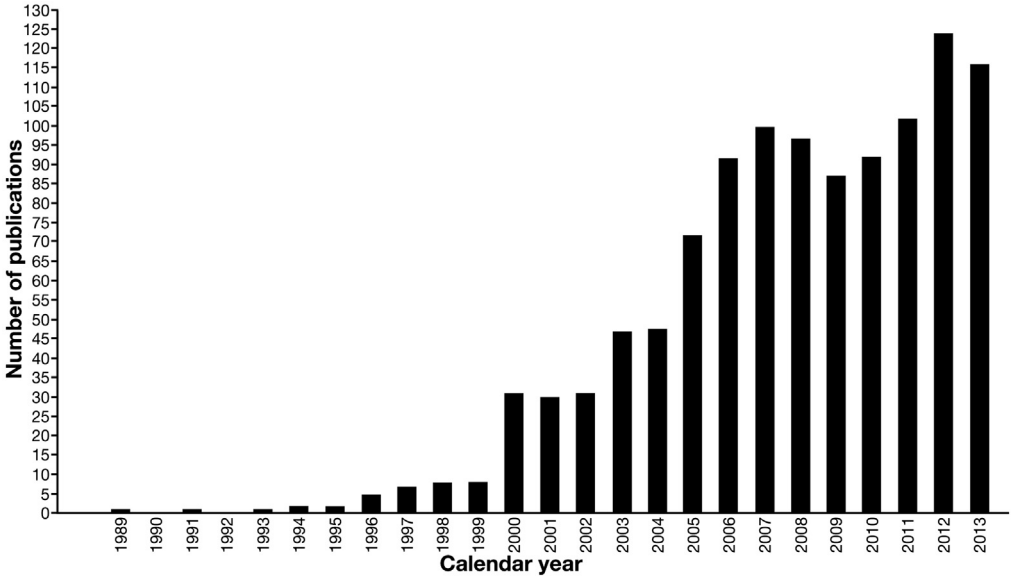

Figure 1. Publications on Laryngopharyngeal Reflux or Extraesophageal Reflux Over Time (Source: Web of Science)

Table 1. Alternative Laryngopharyngeal Pathologies With Symptoms Overlapping With Those Attributed to Extraesophageal Reflux and Their Laryngoscopic Findings

Pathology	EER-associated symptoms	Typical laryngoscopy findings
Muscle tension dysphonia	Hoarseness, globus, throat pain, dysphagia	No vocal fold lesions Supraglottic hyperfunction
Vocal fold paralysis/paresis	Hoarseness, cough, dysphagia, dyspnea Globus	Immobile or hypomobile vocal fold Glottic insufficiency Ipsilateral vocal fold atrophy ± bowing Supraglottic hyperfunction[a]
Presbylaryngis	Hoarseness, cough, globus	Bilateral vocal fold bowing Glottic insufficiency Supraglottic hyperfunction[a]
Irritable larynx syndrome	Cough, globus, hoarseness	Normal laryngoscopy (typical) Vocal fold erythema/edema
Cancer	Throat pain, hoarseness, cough, dysphagia Dyspnea, globus, ear pain	Mass in pharynx or larynx ± superficial ulceration Vocal fold leukoplakia Vocal fold hypomobility (if joint involved)
Recurrent respiratory papillomatosis	Hoarseness, cough, dyspnea, globus	Sessile or pedunculated fungiform mass in larynx/trachea Red stippling or vascular stalks within lesion
Laryngotracheal stenosis	Hoarseness, dyspnea	Narrowing at supraglottis, glottis, subglottis, or trachea Scarring at site of stenosis ± erythema
Phonotraumatic lesion	Hoarseness	Nodule, polyp, cyst, fibrous mass on vibratory edge Glottic insufficiency Supraglottic hyperfunction[a]
Vocal fold hemorrhage	Hoarseness	Submucosal hemorrhage Ipsilateral vocal fold edema/erythema
Polypoid corditis	Hoarseness, cough, globus, ± dyspnea	Polypoid changes of entire vocal fold epithelium Hyperdynamic mucosa
Vocal fold scarring	Hoarseness	Vocal fold sulcus Supraglottic hyperfunction
Vocal process granuloma	Throat pain (often ipsilateral), hoarseness Cough, globus	Lesion or ulceration at arytenoid vocal process Glottic insufficiency (depending on size) Supraglottic hyperfunction[a]
Laryngeal candidiasis	Throat pain, hoarseness, cough, dysphagia Globus	White speckling of fungus in pharynx and larynx Laryngeal erythema ± ulcerations
Zenker's diverticulum	Regurgitation, hoarseness, dysphagia Globus	Normal laryngoscopy (typical) Food debris in left pyriform sinus
Paradoxic vocal fold motion	Dyspnea	Normal laryngoscopy at rest Laryngospasm with triggers (eg, scents, exercise)

[a]Compensatory muscle tension dysphonia.

allergists, gastroenterologists, and otolaryngologists variably are consulted. Of these subspecialties, otolaryngologists have a unique role and advantage because of their ability to routinely perform awake, nonsedated, rigid and/or flexible endoscopic assessments of the upper airway from the nose to the trachea and, in some cases, the esophagus.

Malignancy

The first step in any evaluation is to perform a focused history and physical examination. The biggest concern when evaluating often nonspecific upper-airway concerns is to rule out malignancy. Laryngeal and pharyngeal malignancies can be insidious, presenting only with vague complaints such as sore throat, hoarseness, globus, and even referred ear pain. Overlap between symptoms of EER and early laryngeal cancer (Table 1) have led many to suggest EER as a cancer risk factor.[19–22] However, establishing temporality to avoid reverse causality (ie, effect preceding purported cause) must be considered carefully to prevent perpetuation of a potentially false association.[23] Further study is important to characterize this relationship.

It is necessary to perform a careful history considering known risk factors, which includes inquiry into smoking, alcohol use, occupational exposures, and other behavioral and lifestyle choices. Furthermore, any warning symptoms of unexplained weight loss, night sweats, and others should be gleaned. All physicians must be aware that persistent and refractory symptoms often casually attributed to EER can, in rare circumstances, be harbingers for malignancy. Concern for malignancy is heightened further and earlier referral to otolaryngology is indicated in patients with persistent EER-associated symptoms and known risk factors for head and neck cancer (eg, tobacco, alcohol use). Referral to otolaryngology allows for a focused examination of the nasal vault, oral cavity, nasopharynx, oropharynx, and should include noninvasive visualization of the pharynx and larynx via fiberoptic laryngoscopy and/or stroboscopy. If concern for malignancy is confirmed, then further work-up and biopsy are indicated.

Benign Conditions

Most upper-airway complaints such as hoarseness, cough, and globus have nonmalignant etiologies. Once malignancy is excluded by careful examination, endoscopic visualization and, potentially, ancillary testing (eg, computed tomography); it is necessary to investigate alternative explanations. A comprehensive discussion is beyond the scope of this commentary; however, an abbreviated list of potential pathologies with symptoms that overlap with EER is provided in Table 1. A brief review of standard work-up and management considerations for some of the more common EER-associated conditions is discussed in the following sections.

Gastroesophageal Reflux Disease

In all circumstances, the presence or absence of classic gastroesophageal reflux symptoms (ie, heartburn, regurgitation) are reviewed. Patients presenting to the otolaryngologist may have concomitant GERD symptoms with their upper-airway symptoms of hoarseness, cough, globus, and others. If so, this should raise suspicion that EER may be a contributor to their upper-airway complaints. These patients may require antireflux treatment and/or referral to a gastroenterologist for appropriate testing.[24] However, many, or arguably most, patients with EER will have silent reflux devoid of classic GERD symptoms,[9] thereby requiring more thoughtful and subtle questioning, examination, and, when necessary, testing. In every patient it is important to parse out the onset, duration, relieving factors, and exacerbating factors for their chief complaint. For example, coughing or laryngospasm that wakes a patient from sleep has been associated with nocturnal GERD, but also can be a symptom of obstructive sleep apnea.[25–27]

Moreover, any medical interventions directed at alleviating symptoms should be discussed. A large portion of patients presenting to the otolaryngologist for presumed EER have been started on empiric PPI therapy.[28] If so, inquiry into the duration of treatment, dose, dosing schedule (eg, once or twice daily), and timing (eg, before meals) is compulsory. It is particularly important to ask about compliance with antireflux medication. Lack of compliance can result in false-negative treatment failures and also, in the case of PPIs, cause breakthrough reflux events.[29] Breakthrough or rebound events can confound patients' perception of the identity and severity of their underlying condition. Perhaps most critical, however, is to determine whether medication has reduced their symptoms.

Nonetheless, symptom response is complicated because the act of giving a diagnosis and providing medical treatment can engender a placebo effect and/or may influence patients to alter their diet, and improve their vocal hygiene (eg, hydration). Thus, accurately measuring treatment response is difficult. Caution also must be exercised to establish a cause and effect between reflux and presenting EER-attributable symptoms. Nearly all people experience postprandial physiologic reflux and this must be differentiated from pathologic reflux, which by its nature has symptomatic ramifications. Thus, normal patients theoretically will test positive for reflux if they are tested frequently enough or with tests that have very high sensitivities (and thus low specificity). Moreover, it is important that alternative explanations be considered if increasingly more sensitive tests have to be used to prove causation between reflux and vague upper-aerodigestive symptoms.

Cough and Globus

Cough is one of the most common conditions seen worldwide by primary care physicians and exists at a

watershed of several specialties, which is testament to the complexity of its mechanism. Afferent triggers are mediated by chemoreceptors, and nocireceptors within the respiratory system (ie, nose to alveoli) provide feedback to the cough center within the medulla, which, in turn, activates an efferent cascade and reflex that involves instantaneous vocal fold closure. Tight and complete laryngeal closure permits creation of a transglottic pressure gradient that translates into aggressive expulsion of noxious material from the respiratory tract when the subglottic pressure threshold is exceeded. Illustrating the vocal folds' importance is the recognition that patients with vocal fold paresis or paralysis who are unable to achieve vocal fold closure have frequent complaints of inefficient cough, inability to clear pharyngeal secretions, and globus sensation.[30,31] Thus, the vocal folds play a central effector role in cough. This often is overlooked in the initial work-up, which typically focuses on nasal or pulmonary-related cough etiologies (eg, rhinitis, infection, asthma, allergies). Moreover, there is a misconception in the public and among some physicians that bronchitis and cough are synonymous. Assessing whether someone truly has swelling of the bronchi is rare. Instead, bronchitis in this setting more appropriately may describe laryngitis that occurs as a result of repeated vocal fold trauma from coughing. It follows that patients who have chronic cough often have concomitant hoarseness, globus, and pharyngitis from irritation.

Chronic cough frequently is accompanied by globus sensation and or postnasal drainage symptoms. Obtaining a careful history of the present illness in addition to reviewing previous and current medical treatments is critical because many are being treated aggressively with various regimens that can, in certain circumstances, be counterproductive. Rarely on flexible laryngoscopy do these symptoms correlate with an actual foreign body, throat lesion, or excessive running postnasal drainage; rather, what is seen on examination is thickening of upper airway secretions (ie, mucus and saliva). The human body makes between 0.75 and 1.5 L of secretions from the upper airway daily,[32] which is all sluiced into the esophagus. Thus, postnasal drainage is not a syndrome,[33] but rather a normal physiologic process. Experience is that patients describing postnasal drainage symptoms often have significantly thickened secretions (ie, decreased water leading to increased protein concentration), which the body recognizes as abnormal, thus manifesting in throat clearing and cough.

Patients with globus or postnasal drainage and cough traditionally are thought to have allergies and are placed on antihistamines, decongestants, and often self-medicate with metholated cough drops. All of these interventions act to increase the viscosity of these secretions and can, in some circumstances, exacerbate symptoms. Furthermore, it is critical that patient history should focus on other drying medications that they may be taking because these can exacerbate the situation further. Caffeine also can act as a diuretic and can thicken secretions in the upper airway and worsen cough, throat irritation, and globus. Therefore, hydration and avoidance of excessive drying medications, although seemingly simplistic, can reverse some symptoms often attributable to reflux (eg, hoarseness, globus). Such behavioral throat hygiene education and interventions should be considered as first-line therapy before entertaining a diagnosis of EER.

Another important component in the assessment of chronic cough is to determine the triggers. Classic triggers for cough are irritants/allergies, postnasal drainage (as discussed), infection, asthma, and reactive airway disease. There is also mounting evidence that reflux may play a role and be a prevalent cause of chronic cough.[34] Determining this relationship is complicated and often is presumed based on response to empiric treatment with PPI therapy. If the cough subsides after therapy then reflux is the assumed culprit. Other patients with chronic cough undergo esophagoduodenoscopy or transnasal esophagoscopy with or without pH and impedance testing. Abnormal testing in the presence of chronic cough strengthens the potential association. For example, a recent study showed that those patients with concomitant heartburn and/or regurgitation and esophageal pH less than 4 more than 12% of the time over a 24-hour period were significantly more likely to have resolution of their EER symptoms after Nissen fundoplication.[35]

However, voice behavior is a less-discussed and perhaps more common trigger in this population.[36] Phonation requires vocal fold vibration, which causes vocal fold perturbation. If the larynx has been sensitized by chronic cough then this can decrease the cough threshold. Irritable larynx syndrome is a term used to describe chronic cough and throat irritation that results from repeated vocal fold trauma and manifests in the form of a sensory neuropathy.[37,38] Highlighting the trauma's intensity is the recognition that the sound of cough derives from violent vocal fold adductory contact and release. If someone has chronic cough, they are necessarily causing repeated trauma to their vocal folds, which causes irritation, swelling, and a foreign body sensation. The body's reflex to such irritation/foreign body sensation at the glottis is to throat clear or cough, which perpetuates the process in a positive feedback loop. Thus, cough begets cough. Beyond improving vocal hygiene as described earlier, the goal of treatment is to desensitize the laryngeal mechanism. Often, this requires trying to change a person's reaction to this sensation. For example, rather than quenching the urge by coughing, instead the sensation can be used as a cue to take a hard swallow of water, which, over time, can help to break this cycle.

Several other medical and behavioral treatment options have been proposed.[39] In particular, this condition is one that can benefit from speech language pathology intervention. There is a growing body of literature regarding therapy techniques for cough that specially

trained speech language pathologists can use to help this patient population.[40,41] Finally, those patients with chronic cough secondary to irritable larynx syndrome or neuropathic cough refractory to vocal hygiene and desensitization therapy may require pharmacologic interventions. In these situations, appropriately dosed medications used for peripheral sensory neuropathies (eg, gabapentin, tricyclic antidepressants) can be helpful.[42] For example, these patients are often treated with an escalating dose of gabapentin, amitriptyline, or baclofen. There is growing data that these may be helpful in a select group of patients.[42]

Hoarseness

Extraesophageal reflux also commonly is implicated in unexplained hoarseness. Although there is evidence to suggest that it does and can play a role, there are many other possible explanations for this symptom and, therefore, a careful otolaryngologic history and examination can be enlightening. History should include onset (eg, upper-respiratory infection, surgery, intubation, allergy), duration, relieving/exacerbating factors, presence or recent history of cough, and consistency of hoarseness symptoms (eg, constant, variable, fatiguing). It also is critical to determine whether any interventions—medical, surgical, or behavioral—have been exercised to treat the condition. An examination of the larynx with laryngoscopy is standard of care for a patient with persistent dysphonia to rule out malignancy, mass lesions, or neurologic deficits (Table 1). Most isolated vocal fold lesions are considered phonotraumatic in origin secondary to voice overuse, misuse, or abuse. Their presence can result in glottic insufficiency and mediate an inefficient cough, and thereby interfere with clearance of secretions from the laryngeal inlet. It is not uncommon for patients with glottic insufficiency to have symptoms that overlap with those attributed to EER. In fact, studies have shown that cough can be eliminated and the reflux symptom index[43] normalized when patients' glottic insufficiency was corrected.[31,44] This highlights the relative insensitivity of using symptoms in general, and this measure specifically, to identify those with LPR/EER. Instead, these symptoms seem to be a more generalized measure of vague and nonspecific throat symptoms.

One lesion identifiable on laryngeal examination that has been linked to reflux is vocal process ulceration or granuloma,[45] which tend to present with asymmetric discomfort in the throat with or without hoarseness and globus.[46] Several etiologies have been proposed including trauma from intubation or instrumentation,[47,48] phonotrauma,[48,49] glottic insufficiency,[50] and EER.[45] Granulomas typically occur secondary to mucosal disruption over the vocal process of the arytenoid cartilage with subsequent development of perichondritis.[51,52] These lesions can be difficult to manage depending on their etiology and, therefore, treatment is directed based on the presumed cause. There is a tendency to treat all vocal process granulomas as if they were related to reflux, but a more pragmatic approach is to carefully consider other possible etiologies. For example, prognosis for spontaneous recovery is best when symptoms start in close proximity to intubation-related trauma.[53] In this same study, Wang et al[53] found that 82% of 53 patients with granulomas achieved spontaneous remission between 13 and 70 weeks (mean, 30.6 wk) without any treatment. Determining whether the relationship between reflux and granulomas represent an association, causation, or co-factor has proven difficult because of their relative rarity and an inability to perform rigorous large-scale epidemiologic or interventional studies.

In situations in which no identifiable mass lesion or neurologic deficit is present, there is a reflex to attribute hoarseness to reflux. Many argue that it is easier and potentially more cost effective to treat patients empirically with a PPI than to spend additional time and effort investigating other explanations. However, all nonorganic persistent dysphonia is not reflux. Large epidemiologic studies have found that the most common diagnoses made in dysphonic patients are "non-specific dysphonia" and "acute laryngitis."[54] The nonspecific dysphonia International Classification of Disease, Ninth Revision, Clinical Modification code is the code typically used by otolaryngologists for muscle tension dysphonia (MTD), a muscular dyscoordination and inefficiency in the voicing mechanism or for other functional dysphonia conditions. Based on experience, MTD is one of the most common diagnoses made in patients presenting with chronic dysphonia. Moreover, MTD can occur as a primary diagnosis, but it also exists as a compensatory or secondary phenomenon in patients with laryngeal lesions, neurologic deficits, or inflammation (Table 1). Differentiating the cause of nonorganic dysphonia can be complex and often requires the expertise of specialists in voice (ie, laryngologists, speech language pathologists) who have expertise in evaluating the voicing mechanism perceptually and laryngoscopically.

Studies have highlighted that the symptoms of MTD and LPR/EER significantly overlap,[28,55] thus further muddying the distinction. This conundrum breeds different approaches. Some clinicians empirically treat with PPIs, with the expectation that if no improvement is achieved then perhaps the diagnosis is MTD instead. Others approach this problem from the opposite direction, opting for voice therapy as the primary modality. Effective treatment with this modality requires the treating speech language pathologist to have experience, knowledge, and the skill set to treat voice disorders. The Cochrane Collaboration has found that voice therapy is an effective treatment for muscle tension or functional dysphonia,[56] and it is appropriately recognized as the standard of care for this disorder. Reinforcing the overlap between MTD and LPR is a study by Park et al,[57] who randomized patients with presumed LPR to treatment with either PPI alone or PPI combined with voice

therapy. Interestingly, patients randomized to combination treatment had significantly greater improvement in subjective and perceptual voice measures compared with those receiving PPI alone. This finding has been interpreted variably, but does imply that voice therapy is an effective treatment for LPR, which physiologically is difficult to reconcile. Instead, their results seem to provide evidence that some proportion of their patients had MTD in addition to, or in lieu of, LPR. In summary, symptoms attributed to LPR overlap substantially with MTD, making some question whether a trend toward misdiagnosis of MTD has increased the relative prevalence of LPR.

Conclusions

Despite its codification more than 25 years ago,[8] laryngopharyngeal reflux or extraesophageal reflux is a condition yet to be fully characterized. In a recent editorial, EER management has been described as "furor medicus"[58]: the unbridled frenzy of doctors to do something, especially when the clinical situation is confusing. In general, this situation is promulgated by the uncertainty of the doctor, and the insistence of the patient to get something done. It behooves the broad medical community that treats these patients to do a better job at defining, diagnosing, and treating this disorder. The otolaryngologist plays an important role because most EER-associated symptoms fall within our purview. Many upper-airway conditions can masquerade as, and easily incorrectly be attributed to, EER. It is easy to reflexively blame reflux. However, a more thoughtful approach that heeds my medical school neurology professor's advice, "don't just do something, stand there," is advocated when considering the differential diagnosis. In the context of EER, careful consideration is encouraged instead of chalking up vague symptoms to reflux. Accurately diagnosing EER requires thoughtful clinical judgment when taking the history, choosing diagnostic testing, and in the treatment approach. In this field, clinical practice still relies heavily on anecdote and dogma. It is important that we strive toward clinical practice based on well-designed studies so we can direct care of this patient population more effectively and efficiently.

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Conflicts of interest
The authors disclose no conflicts.