



Allergy and laryngeal disorders

John H. Krouse

Purpose of review

This article reviews recent literature on the topic of allergic laryngitis. There has been sustained interest over the past 15 years and epidemiological and experimental studies have led to a clearer description of the nature of the condition and its clinical expression.

Recent findings

Recent studies have suggested an epidemiological association between the presence of allergy and concurrent laryngeal symptoms and objective signs. Both population-based studies and smaller investigations have shown a significant relationship between these two variables. In addition, recent studies have questioned the inter-rater reliability and specificity of laryngeal endoscopic examinations, which have often been used to assign a presumptive diagnosis of laryngopharyngeal reflux. The presence of sticky, viscid, thick endolaryngeal secretions, however, appears to be associated with allergic laryngitis, confirming prior observations. Experimental interventions in both laboratory animals and humans suggest that there may be a direct causal relationship for an allergic cause, at least among some individuals.

Summary

Epidemiological and experimental evidence suggests that allergy may be a valid trigger and causative mechanism in some individuals with laryngeal inflammation and symptomatology. Additional research is necessary to further characterize allergic laryngitis and to develop valid diagnostic protocols for assessment.

Keywords

allergic laryngitis, allergic rhinitis, allergy, dysphonia, hoarseness, laryngitis

INTRODUCTION

The role of allergy in the pathogenesis and symptom expression of acute and chronic laryngitis has been a topic of some controversy over the past 2 decades. Clinicians have observed inflammatory changes in the supraglottis, glottis, and subglottis and have attributed these findings to a variety of triggers, principally laryngopharyngeal reflux (LPR) [1]. Despite the widespread belief that LPR is the primary source of chronic laryngeal inflammation, a number of researchers have questioned this assumption, which can lead to overdiagnosis and misdiagnosis among patients with dysphonia, odynophagia, and other laryngeal and pharyngeal symptoms [2,3].

Krouse and others have discussed the potential role of allergic hypersensitization both in the direct inflammation of the laryngeal mucosa as well as in the increased mucus production and trafficking of mucus through the laryngeal inlet [4–6]. Symptoms that occur among these individuals are nonspecific and include hoarseness, throat clearing, cough, and globus sensation [5]. Characteristic among the signs noted on examination among individuals diagnosed with allergic laryngitis are sticky, stranding

mucus within the endolarynx and nonspecific hyperemia of the mucosa [6,7]. These findings are commonly observed in patients with allergic laryngitis and can be elicited with direct stimulation of the larynx with an antigen to which individuals have previously been sensitized [5,7].

Given that symptoms of dysphonia have been reported to have a lifetime prevalence of almost 30% [8], and that acute and chronic laryngitis are frequent causes of vocal complaints, it is important in treatment that clinicians reach an accurate diagnosis of the cause of dysphonia among these individuals. It is the purpose of this review to examine recent advances in the pathophysiology and diagnosis of allergic laryngitis.

Department of Otolaryngology – Head and Neck Surgery, Lewis Katz School of Medicine, Temple University, Philadelphia, Pennsylvania, USA

Correspondence to John H. Krouse, MD, PhD, MBA, Department of Otolaryngology – Head and Neck Surgery, Lewis Katz School of Medicine, Temple University, Philadelphia, PA 19140, USA.

Tel: +1 215 707 3665; e-mail: jkrouse@temple.edu

Curr Opin Otolaryngol Head Neck Surg 2016, 24:221–225

DOI:10.1097/MOO.0000000000000244

KEY POINTS

- There appears to be a distinct cohort of individuals who have laryngeal symptoms related to allergic mechanisms.
- There can be significant overlap in the clinical presentation and physical examination of patients with LPR and allergic laryngitis.
- The presence of sticky, viscid mucus in the endolarynx suggests a possible diagnosis of allergic laryngitis.

DIAGNOSIS

As previously noted, there is significant overlap in the symptomatic presentation of patients with LPR and allergic laryngitis, as well as considerable variability in their diagnoses. Many physicians view 24-h pH monitoring as the gold standard for diagnosing LPR, although this technique is often not used in clinical practice [9]. To assist with diagnosis, Belafsky and colleagues [10] developed a self-administered screening tool that demonstrates significant predictive ability in the clinical diagnosis of LPR. In addition, Belafsky and colleagues [11] also have developed a diagnostic tool based on laryngoscopic evaluation, although researchers have shown that the inter-rater reliability of laryngeal findings is low and the endoscopic diagnosis of LPR is highly subjective because of the lack of specificity in its diagnosis [12].

In one recent study, Eren and colleagues [13[■]] examined the variability in endoscopic assessment of laryngeal findings and whether diagnosing LPR without consideration of the patient's allergy status leads to overdiagnosis and overtreatment of LPR. The authors examined 108 patients referred for allergy testing at a university otolaryngology clinic. All patients underwent skin prick testing to common inhalant allergens and had endoscopic laryngeal examinations that were recorded and evaluated independently by three physicians who were unaware of the patients' histories and skin prick testing results. Endoscopic examinations were graded using the reflux finding scale [11] and patient symptoms of LPR were graded using the reflux symptom index [10]. Eren and colleagues [13[■]] demonstrated that while there was strong inter-rater reliability for the findings of laryngeal erythema/hyperemia, vocal fold edema, and thick endolaryngeal mucus, there was nonsignificant agreement among these evaluators for commonly accepted LPR findings such as pseudosulcus vocalis, ventricular obliteration, diffuse laryngeal edema, and posterior laryngeal hypertrophy. In addition,

there was poor agreement in the diagnosis of LPR when comparing patients judged positive for LPR using the reflux finding scale and the reflux symptom index. Finally, there was no association between allergic sensitization and the presence of LPR, nor was there any significant difference in laryngeal appearance between allergy-positive and LPR-positive individuals. The authors did note that on logistic regression analysis, thick endolaryngeal mucus was a significant predictor of allergy ($P=0.012$). They conclude that the laryngeal examination for LPR is subject to marked inter-rater variability and that 'the presence of thick endolaryngeal mucus should alert physicians to the possibility of allergic rhinitis/laryngitis'.

In a similar study, Brook and colleagues [14] examined the role of allergy testing in evaluating patients with chronic laryngeal inflammation. In their study, the authors evaluated 998 patients tested for allergy in their university otolaryngology clinic utilizing in-vitro inhalant allergy testing for symptoms of rhinitis, laryngitis, otitis media, and sinusitis. Of these 998 individuals, 27 had laryngeal symptoms as their primary complaint. On in-vitro testing, 14 of these 27 (51.9%) were positive for at least one inhalant allergen by specific IgE. The odds ratio of having a positive allergy test among patients with laryngeal complaints was noted to be similar to patients with rhinitis and sinusitis. The most common positive antigens noted to present among patients with laryngeal symptoms in this study were dust mites (63%), which was similar to findings noted by Krouse *et al.* [4]. Based on their findings, Brook and colleagues noted that the prevalence of positive allergy test results was similar for patients with laryngeal findings and those with rhinitis or sinusitis. They note that the basis for their observations remains unclear and that additional research is necessary to further characterize the nature of allergic laryngitis.

In a third study, Koc and colleagues [15] compared acoustic and stroboscopic findings and scores on the voice handicap index [16] among 30 patients with allergic rhinitis and 30 age and sex-matched control study participants without allergy. On examining their results, the authors noted that voice handicap index scores and the s/z ratio were significantly higher among patients with allergic rhinitis than in their nonallergic control study participants. They described the s/z ratio as an index of laryngeal disorder [17], and noted that as it was elevated in their patient group it suggested abnormal laryngeal function among these individuals. Based on their observations, Koc and colleagues [15] concluded that there was a 'relationship between allergy and dysphonia', and that allergy

should be considered as a potential cause of dysphonia in the diagnostic process.

The implication of these observations is that the diagnosis of allergic laryngitis can be difficult to distinguish from other causes of chronic laryngeal inflammation, such as LPR. The current diagnostic methods are accompanied with low inter-rater reliability and poor specificity to distinguish between these two conditions. Similar concerns were raised by Garrett and Cohen [18], who also questioned the specificity of diagnostic criteria for LPR and suggested that a broader view of potential causes of laryngeal inflammation, including allergy, needed to be considered to avoid misdiagnosis. Finally, voice complaints appear to be common among patients with allergic rhinitis, and laryngeal evaluations of these patients frequently demonstrate thick, viscid endolaryngeal mucus.

PATHOPHYSIOLOGY

As noted previously, voice problems have a lifetime prevalence of about 30% [8]. This rate has generally been estimated without direct visualization of the larynx and based on survey results and interviews [19]. In one recent study, Hah and colleagues [20] examined over 19 000 patients who had undergone rigid laryngeal endoscopy and who were housed in a larger Korean data registry. These examinations were carried out in a government program to collect general medical history and examination data among a random selection of households on an annual basis. In analysis of their data, the authors noted that laryngeal findings noted on endoscopic examination ranged from a prevalence of 3.5% for laryngitis and 1.5% for vocal nodules to values less than 1% for other objective laryngeal pathologies. Interestingly only about one-third of those individuals with objective findings had subjective voice complaints. Of interest is that the history of allergic rhinitis was positively associated with the presence of vocal nodules and laryngitis among this large sample. The authors note that in this large population-based study, allergic rhinitis appears to increase the risk of laryngitis, and speculate that throat clearing and chronic upper airway inflammation appear to play a role in the pathogenesis.

In another recent study, Belafsky and colleagues [21^{***}] utilized an experimental animal model to examine pathogenetic triggers for laryngeal inflammation. In this study, the authors sensitized 24 guinea pigs to the dust mite antigen *Dermatophagoides farinae*, and then subsequently exposed them to this antigen and iron soot, either alone or in combination over 4 weeks. They then sacrificed the animals and examined the laryngeal and

tracheal submucosa for eosinophilic inflammation using mean eosinophil profile. They showed that the combination of exposures to dust mite antigen and iron soot caused a significant eosinophilic infiltrate in the subglottic and tracheal submucosa of animals, supportive of their previous work [22]. Based on their findings, Belafsky and colleagues [21^{***}] conclude, 'these findings suggest that environmental pollution and allergy may work synergistically to cause laryngeal inflammation and support the notion that factors other than reflux may cause chronic laryngitis'.

Another study examined the question of whether direct stimulation of the larynx would result in changes in objective measures of vocal function using a prospective double-blinded laryngeal challenge [23]. Roth and colleagues exposed five study participants who were screened for absence of reactive airway disease using a methacholine challenge to either an inhaled saline placebo or an active allergic suspension using a randomly ordered cross-over model. They measured phonatory threshold pressure after each condition and demonstrated a significant increase in phonatory threshold pressure following antigen inhalation. Roth and associates argued that through this experiment they were able to suggest a causal relationship between allergen inhalation and worsening of objective vocal function in individuals without concurrent asthma.

An additional study examined the relationship between dysphonia and allergy among a group of patients with vocal disorders [24]. In this study, Lauriello and colleagues examined 76 patients who presented with vocal complaints who underwent endoscopic laryngeal evaluation. Using logistic regression, the authors noted that 76% of patients in their sample had a history of allergy. There was a statistically significant association of allergy and dysphonia among female patients. The authors note that there is a clinically important relationship between allergy and dysphonia, primarily noted among women in their study, and that workup of allergy is indicated in patients presenting with dysphonia.

The implication of these four studies is that there is additional support for a primary allergic causation of laryngeal dysfunction, both from epidemiological data and from direct experimental evidence. In a large population-based study, the presence of allergic rhinitis is positively associated with dysphonia and the presence of vocal nodules, suggesting that a relationship is present between these two conditions. In addition, placebo-controlled experiments in both humans and laboratory animals have shown both an increase in laryngeal eosinophilia after antigen stimulation as well as

worsening in objective assessments of laryngeal function. These recent observations continue to suggest that a subset of individuals exists that may have an allergic cause as the primary cause of their laryngeal symptoms and findings.

CONCLUSION

The concept of allergic laryngitis has commanded sustained scholarly interest among a small group of researchers and clinicians, suggesting the relevance of this line of work for physicians and their patients. Investigation into this area was rare until about 15 years ago, and during the early years of this century several groups begin to evaluate the potential role of allergy in the expression of laryngeal symptoms. The seven studies reviewed here demonstrate that interest in the topic persists and that evidence is slowly accumulating that supports an allergic cause in some patients with laryngitis and dysphonia.

There appear to be distinct cohorts of individuals who have atopic diseases such as allergic rhinitis and who also develop laryngeal symptoms. Although in many cases these symptoms have been attributed to LPR and these patients empirically treated with medications such as proton pump inhibitors, there are patients who are treated for LPR yet do not have improvement despite appropriate doses and durations of medical therapy [25]. The present studies, taken in the context of other recent literature, suggest that the primary mechanism for these symptoms may be an inflammatory response in the larynx caused by direct stimulation of the laryngeal mucosa by allergen inhalation. Although these studies do not eliminate the synergism of allergy with LPR or other laryngeal irritants, they do suggest the relevance of allergy in these individuals as well as its contributory role to laryngeal disorder.

The studies reviewed here also provide direction in the evaluation of patients suspected of having allergic laryngitis. As noted by Eren and colleagues [13], and previously reported by Garrett and Cohen [18], there is a tendency for LPR to be overdiagnosed and misdiagnosed among patients with laryngeal complaints, in part based on laryngeal findings seen on endoscopic examination that are poorly specific and have low inter-rater reliability. They did note, however, that the presence of viscid, sticky mucus stranding within the endolarynx was statistically predictive of the presence of allergy among their patient sample. This finding confirms the observations of the Krouse group [5,7], and suggests that the presence of this endolaryngeal mucus should be viewed as a sign of a potential allergic contribution

to the patient's laryngeal symptoms. Although allergy testing can be of benefit in detecting those patients that are atopic, it is not sufficient alone to diagnose the presence of allergic laryngitis. It can be useful, however, as part of the diagnostic workup, especially among patients who have failed other methods of routine management. Finally, objective measures of vocal function may be of benefit in assessing subtle changes in physiology, although would also likely be nonspecific and insufficient to diagnose allergy laryngitis without additional supportive information.

While the literature on this topic continues to expand slowly and is generally supportive of an allergic mechanism among some individuals, there is the need for additional research to both further confirm and delineate the contribution of allergy to laryngeal pathologies and to define suitable assessment methods for the detection of allergic mechanisms. Only with sufficient understanding of the role of allergy in symptomatic individuals will physicians be able to develop appropriate protocols for management and treatment.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Koufman JA, Aviv JE, Casiano RR, *et al.* Laryngopharyngeal reflux: position statement of the committee on speech, voice, and swallowing disorders of the American Academy of Otolaryngology-Head and Neck Surgery. *Otolaryngol Head Neck Surg* 2002; 127:32–35.
2. Randhaw PS, Mansuri S, Rubin JS. Is dysphonia due to allergic laryngitis being misdiagnosed as laryngopharyngeal reflux? *Logoped Phoniatr Vocol* 2010; 35:1–5.
3. Roth D, Ferguson BJ. Vocal allergy: recent advances in understanding the role of allergy in dysphonia. *Curr Opin Otolaryngol Head Neck Surg* 2010; 18:176–181.
4. Krouse JH, Dworkin JP, Carron MA, *et al.* Baseline laryngeal effects among individuals with dust mite allergy. *Otolaryngol Head Neck Surg* 2008; 139:149–151.
5. Reidy PM, Dworkin JP, Krouse JH. Laryngeal effects of antigen stimulation challenge with perennial allergen *Dermatophagoides pteronyssinus*. *Otolaryngol Head Neck Surg* 2003; 128:455–462.
6. Krouse JH, Altman KW. Rhinogenic laryngitis, cough, and the unified airway. *Otolaryngol Clin North Am* 2010; 43:111–121.
7. Dworkin JP, Reidy PM, Stachler RJ, *et al.* Effects of sequential *Dermatophagoides pteronyssinus* antigen stimulation on anatomy and physiology of the larynx. *Ear Nose Throat J* 2009; 88:793–799.
8. Bhattacharyya N. The prevalence of voice problems among adults in the United States. *Laryngoscope* 2014; 124:2359–2362.

9. Golub JS, Johns MM III, Lim JH, *et al.* Comparison of an oropharyngeal pH probe and a standard duet pH probe for the diagnosis of laryngopharyngeal reflux. *Ann Otol Rhinol Laryngol* 2009; 118:1–5.
10. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptoms index (RSI). *J Voice* 2002; 16:274–277.
11. Belafsky PC, Postma GN, Koufman JA. The validity and reliability of the reflux finding score (RFS). *Laryngoscope* 2001; 111:1313–1317.
12. Branski RC, Bhattacharya N, Shapiro J. The reliability of the assessment of endoscopic laryngeal findings associated with laryngopharyngeal reflux disease. *Laryngoscope* 2002; 112:1019–1024.
13. Eren E, Arslanoglu S, Aktas A, *et al.* Factors confusing the diagnosis of laryngopharyngeal reflux: the role of allergic rhinitis and inter-rater variability of laryngeal findings. *Eur Arch Otorhinolaryngol* 2014; 271:743–747.
Demonstrates the poor inter-rater reliability and insufficient specificity of endoscopic laryngeal evaluations, and suggests that the presence of thick, sticky endolaryngeal mucus is significantly associated with an allergic cause for the laryngitis.
14. Brook CD, Platt MP, Reese S, *et al.* Utility of allergy testing in patients with chronic laryngopharyngeal symptoms: is it allergic laryngitis? *Otolaryngol Head Neck Surg* 2016; 154:41–45.
15. Koc EAO, Koc B, Erbek S. Comparison of acoustic and stroboscopic findings and Voice Handicap Index between allergic rhinitis patients and controls. *Balkan Med J* 2014; 31:340–344.
16. Jacobson GH. The voice handicap index (VHI): development and validation. *Am J Speech Lang Pathol* 1997; 6:66–69.
17. Boone DR. The voice and voice therapy. Englewood Cliffs, NJ: Prentice-Hall; 1971.
18. Garrett CG, Cohen SM. Otolaryngological perspective on patients with throat symptoms and laryngeal irritation. *Curr Gastroenterol Rep* 2008; 10:242–246.
19. Roy N, Merrill RN, Thibeault S, *et al.* Prevalence of voice disorders in teachers and the general population. *J Speech Lang Hear Res* 2004; 47:281–293.
20. Hah JH, Sim S, An SY, *et al.* Evaluation of the prevalence of and factors associated with laryngeal diseases among the general population. *Laryngoscope* 2015; 125:2536–2542.
21. Belafsky PC, Peake J, Smiley-Jewell SM, *et al.* Soot and house dust mite allergen cause eosinophilic laryngitis in an animal model. *Laryngoscope* 2015; 126:108–112.
Outstanding experimental study demonstrating that stimulation of the larynx with dust mite antigen and soot in sensitized guinea pigs provokes an eosinophilic response in the submucosa, confirming this group's earlier work on the topic.
22. Mouadeb DA, Belafsky PC, Birchall M, *et al.* The effects of allergens and tobacco smoke on the laryngeal mucosa of guinea pigs. *Otolaryngol Head Neck Surg* 2009; 140:493–497.
23. Roth DF, Abbott KV, Carroll TL, *et al.* Evidence for primary laryngeal inhalant allergy: a randomized, double-blinded crossover study. *Int Forum Allergy Rhinol* 2013; 3:10–18.
24. Lauriello M, Angelone AM, Businco LD, *et al.* Correlation between female sex and allergy was significant in patients presenting with dysphonia. *Acta Otorhinolaryngol Ital* 2011; 3:161–166.
25. Pendleton H, Ahlner-Elmqvist M, Jannert M, *et al.* Posterior laryngitis: a study of persisting symptoms and health-related quality of life. *Eur Arch Otorhinolaryngol* 2013; 270:187–195.