The Laryngoscope

Incidence of Underlying Laryngeal Pathology in Patients Initially Diagnosed With Laryngopharyngeal Reflux

Benjamin Rafii, MD; Salvatore Taliercio, MD; Stratos Achlatis, MD;
Ryan Ruiz, BA; Milan R. Amin, MD; Ryan C. Branski, PhD

Objectives/Hypothesis: To characterize the videoendoscopic laryngeal findings in patients with a prior established diagnosis of laryngopharyngeal reflux disease (LPR) as the sole etiology for their chief complaint of hoarseness. We hypothesized that many, if not all, of these patients would present with discrete laryngeal pathology, divergent from LPR.

Study Design: Prospective, nonintervention.

Methods: Patients presenting to a tertiary laryngology practice with an established diagnosis of LPR as the sole etiology of their hoarseness were included. All subjects completed the Voice Handicap Index and Reflux Symptom Index, in addition to a questionnaire regarding their reflux diagnosis and prior treatment. Laryngoscopic examinations were reviewed by the laryngologist caring for the patients. Reliability of findings was assessed by interpretation of videoendoscopic findings by three outside laryngologists not involved in the care of the patients.

Results: Laryngeal pathology distinct from LPR was identified in all 21 patients felt to be causative of the chief complaint of dysphonia. Specifically, the most common findings were benign mucosal lesions and vocal fold paresis (29% each), followed by muscle tension dysphonia (14%). Two patients were found to have vocal fold leukoplakia, of which one was confirmed to be a microinvasive carcinoma upon removal.

Conclusion: LPR may be overdiagnosed; other etiologies must be considered for patients with hoarseness who fail empiric LPR treatment.

Key Words: Voice, voice disorder, laryngopharyngeal reflux disease.

Level of Evidence: 4.

***Laryngoscope*, 124:1420–1424, 2014**

INTRODUCTION

Laryngopharyngeal reflux (LPR) is increasingly cited as a primary underlying etiology of hoarseness in adults.[1,2] Support for this trend is rooted in previous studies suggesting that a significant number of patients presenting with voice complaints are found to have a detectable reflux of gastric contents into the laryngopharynx by pharyngeal pH probe.[3] Accordingly, many patients who present with the constellation of symptoms and laryngoscopic findings commonly attributed to LPR hoarseness, throat clearing, cough, globus, and posterior laryngeal erythema/edema[4–7] are often empirically treated prior to objective confirmation of reflux.[8,9]

However, studies evaluating the efficacy of proton pump inhibitors (PPIs) specifically for LPR symptoms demonstrate mixed outcomes, even with high PPI doses for prolonged periods.[10,11] A number of explanations have been proposed for the frequent failure of PPI therapy in select patient cohorts. Some contend that breakthrough reflux may occur despite aggressive pharmacological management, while others hypothesize other mechanisms as the source of symptoms.[12,13] Some patients presenting with symptoms commonly attributed to LPR may, in fact, harbor other laryngeal pathology requiring completely divergent treatment. Neoplasms, benign mucosal lesions, postviral vocal fold paresis, and other disorders of the larynx are known to present with heterogeneous symptoms that can often include the "classic" LPR complaints.[14,15] Therefore, we sought to determine the incidence of laryngeal pathology in dysphonic patients previously diagnosed with LPR as the etiology of their hoarseness. We hypothesize that LPR may be over-diagnosed, potentially leading to excessive and unnecessary pharmacological treatment and also delaying the identification of distinct disorders that require alternate management.

MATERIALS AND METHODS

The current study was approved by the institutional review board at the New York University School of Medicine. Data were prospectively collected from consecutive patients seeking consultation at a tertiary laryngology practice between March and December 2012. Inclusion criteria were 1) chief

From the New York University Voice Center, Department of Otolaryngology–Head and Neck Surgery, New York University School of Medicine, New York, New York, U.S.A.

Editor's Note: This Manuscript was accepted for publication October 18, 2013.

Portions of data contained in the current manuscript were accepted for a poster presentation at the American Laryngological Association Annual Meeting at the Combined Otolaryngologic Spring Meetings, Orlando, Florida, U.S.A., April 10–11, 2013.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Send correspondence to Ryan C. Branski, PhD, New York University Voice Center, Department of Otolaryngology–Head and Neck Surgery, 345 East 37th Street, Suite 306, New York, NY 10016. E-mail: ryan.branski@nyumc.org

DOI: 10.1002/lary.24483

complaint of hoarseness warranting previous consultation from another provider (primary care physician or otolaryngologist), 2) presumptive diagnosis based on the findings of the referring physician of LPRD as the sole etiology of this hoarseness, and 3) previously prescribed treatment for LPR. Prior workup including pH testing, fiberoptic laryngoscopy and stroboscopy, contrast esophageal studies, was not standardized among the included patients. Patients with a known concurrent diagnosis of any other laryngeal disorder or additional lesion were excluded.

Data collection occurred at the time of each subject's initial visit. Each patient completed the Voice Handicap Index (VHI-10) and Reflux Symptom Index (RSI) as a component of standard care. In addition, each patient completed an intake form regarding their chief complaint, associated symptoms, duration of symptoms, previously attempted therapies, and duration of therapy. Flexible transnasal videolaryngoscopy and stroboscopy were then performed with a Pentax VNL-1170 endoscope (Pentax Imaging, USA; Ricoh Imaging, Denver, CO) following topical, aerated 0.05% oxymetazoline and 4% lidocaine spray to decongest and desensitize the nasal airway. Patient history and examination findings were reviewed by the senior laryngologist (M.R.A.) and the suspected diagnosis was selected as either: 1) benign vocal fold lesions (cysts, nodules, polyps, etc); 2) neoplastic lesions (leukoplakia, cancerous lesion, papillomas); 3) glottal incompetence (defined for the purposes of this study as incomplete glottal closure that is not secondary to an obstructive mass lesion or a deficiency in vocal fold motion, i.e., presbylaryngis); 4) vocal fold paresis or paralysis; 5) vocal fold scar or sulcus; 6) functional disorders/muscle tension dysphonia (MTD); 7) miscellaneous neurologic disorders (spasmodic dysphonia, tremor); or 8) LPR.

Deidentified videos containing the complete endoscopic examination were then created for each patient. Three separate fellowship-trained laryngologists not involved in the care of the patients reviewed each video. Each laryngologist was asked, in multiple-choice format, to identify the most likely primary cause of each patient's dysphonia using the aforementioned diagnostic categories. These laryngologists were blinded to the purpose of the study as well as patient history. Diagnosis was made based only on a single video examination (audio was included) for each patient. Reviewers were not asked to provide any quantifiable metrics based on laryngoscopic exam, so no intrarater or interrater reliability analysis was performed. The authors responsible for data collection and analysis were not directly involved in any aspect of patient care.

RESULTS

Twenty-one patients met inclusion criteria during the study period. The mean age was 48 years, with a range of 20 to 76 years. Fifteen of 21 were female (71%). Seventeen of 21 were referred from an otolaryngologist (81%); the remaining four patients were referred from other practitioners (two primary care physicians, one cardiothoracic surgeon, one speech language pathologist). The average duration of hoarseness at the time of presentation was 10 months, with a range of 1 to 36 months. Nineteen of 21 patients had symptoms for at least 3 months. The average VHI-10 score for the cohort was 20.1 (range 4–40) and the average RSI score was 16.3 (range 7–31). Eleven of 21 patients (52%) had an RSI score greater than 13 (Table I).

The majority of patients received a trial of PPI therapy prior to referral (18 of 21; 86%). One patient received prednisone in addition to PPIs; one patient received H2-blockers in addition to PPIs; one patient underwent voice therapy with no reflux management; and two patients were prescribed treatment but had yet to undergo any intervention at the time of presentation (Table I). The most common concurrent symptoms were throat clearing (71%), excess mucus (62%), globus (38%), and coughing (33%). Three of 21 (14%) reported at least occasional heartburn (Table I).

TABLE I.
Patient Demographics.

Total patients	21
Mean age/range (years)	48 (20–76)
Female sex (%)	15 (71)
VHI-10 (mean/range)	20.1 (4–40)
RSI (mean/range)	16.3 (7–31)
RSI > 13	11 (52%)
Duration of symptoms (months)	10 (1–36)
	No. of subjects (%)
Symptoms	
hoarseness	21 (100)
throat clearing	15 (71)
mucus	13 (62)
globus	8 (38)
cough	7 (33)
heartburn	3 (14)
Referral source	
otolaryngologist	17 (81)
PCP	1 (4.7)
SLP	1 (4.7)
CT surgeon	1 (4.7)
Intervention	
Proton-pump inhibitor	18 (86)
H2-blocker	1 (4.7)
Voice therapy	1 (4.7)
Prednisone	1 (4.7)
No intervention	2 (9.5)

PCP = primary care physician; RSI = Reflux Symptom Index; SLP = speech language pathologist; VHI = Voice Handicap Index.

The diagnoses determined by the senior laryngologist (M.R.A.) based on a review of the history and videoendoscopic and stroboscopic findings are summarized in Table II. The most common findings were benign mucosal lesions (6/21 or 29%), paresis/paralysis (5/21 or 24%), and neoplastic lesions (3/21 or 14%). Together, these represented two-thirds of all findings. The remaining seven patients had identifiable vocal pathology, yet none of the patients were identified as having videoendoscopic findings consistent primarily with LPR. Of the three patients identified as having a neoplastic lesion, one patient was found to have a microinvasive carcinoma following biopsy (Fig. 1).

Three laryngologists not involved in the care of the patients were asked to provide a diagnosis based on review of laryngostroboscopic video recordings. Benign lesions, paresis/paralysis, and neoplasms were again the

TABLE II.
Laryngoscopic/Stroboscopic Findings for Both the Study Laryngologist and Blinded Reviewers.

	No. of Subjects (%)			
	Study Laryngologist	Reviewer 1	Reviewer 2	Reviewer 3
Benign Lesions	6 (29)	6 (29)	7 (33)	6 (29)
Paresis/Paralysis	5 (24)	4 (19)	7 (33)	4 (19)
Neoplastic Lesions	3 (14)	4 (19)	4 (19)	4 (19)
Glottal Incompetence	2 (9.5)	1 (4.7)	1 (4.7)	4 (19)
Vocal Fold Scar/Sulcus	2 (9.5)	3 (14)	1 (4.7)	2 (9.5)
Functional Disorders/MTD	3 (14)	1 (4.7)	0	1 (4.7)
Other Neurological Disorders	0	1 (4.7)	0	0
Laryngopharyngeal Reflux	0	1 (4.7)	1 (4.7)	0

MTD = muscle tension dysphonia.

most commonly cited findings. Two of the three laryngologists selected a primary diagnosis of LPR in one patient out of 21 patients, whereas the third laryngologist identified none (Table III). Comparison of the nonblinded author's diagnostic assessments to those of the three blinded laryngologists revealed a generally high level of concordance, with an agreement of 75% or better (at least 3 of 4 selected the same diagnosis) in 15 patients out of 21 patients (71%). At least two laryngologists out of three blinded laryngologists agreed with the author's diagnosis in 14 cases (67%). In two cases, none of the blinded laryngologists agreed with the initial diagnosis of the author (Table III).

DISCUSSION

In the two decades following Koufman's report on the diverse otolaryngologic manifestations of laryngopharyngeal reflux disease,[7] LPR has been increasingly implicated as a cause of hoarseness. However, symptoms of LPR can closely mimic those of other laryngeal disorders, and laryngostroboscopic findings of LPR are notoriously nonspecific.[4,16,17] The failure of PPI therapy to alleviate symptoms in a significant proportion of patients diagnosed with LPR may be an indication that a laryngeal abnormality distinct from reflux may instead be the true underlying cause of the patient's dysphonia. Despite these shortcomings in the diagnosis and treatment of LPR, the *2009 Clinical Practice Guideline: Hoarseness (Dysphonia)* supported the empiric use of antireflux medication in patients with hoarseness and laryngoscopic signs of laryngeal irritation.[18]

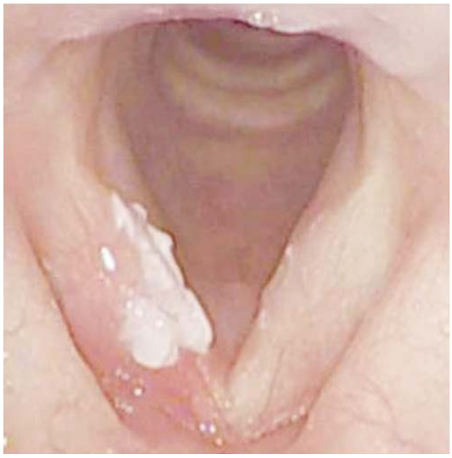

Fig. 1. Clinical image of the three patients identified as having a neoplastic lesion. On biopsy, this lesion was determined to be microinvasive carcinoma. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The present study details the laryngoscopic findings of a cohort of patients presenting to a tertiary care laryngology practice with a working diagnosis of LPR, who have failed to respond to first-line treatment. In 18 of 21 patients, this initial therapy consisted of a PPI; and in all but one patient, symptoms had been present for at least 3 months without improvement. Seventeen of 21 patients had received prior consultation with an otolaryngologist. Although documentation of prior laryngeal examination was not available, it is reasonable to postulate that the larynx was visualized in most, if not all, of these patients at the time of their outside consultation.[19] However, the senior author's (M.R.A.) laryngoscopic examination revealed a specific functional, neurological, or mucosal abnormality distinct from LPR in all 21 patients. Outside review of the laryngoscopic examinations by blinded clinicians revealed a similar pattern, with no more than one patient identified as having LPR as the primary diagnosis.

A recent retrospective chart review by Thomas and Zubiaur[20] reported comparable findings. The authors identified 105 patients in their practice with a previous diagnosis of LPR as the sole cause of their hoarseness, and they reviewed their final diagnoses following office evaluation. Impressively, all were found to have a functional or organic voice disorder distinct from LPR. Almost 90% of patients had received the prior diagnosis of LPR by an otolaryngologist, and 78% had undergone prior PPI treatment. Laryngeal findings were diverse, but patients were most commonly found to have mucosal disease or disorders related to increased muscle tension

TABLE III.
Summary of Findings for Both the Study Laryngologist and Blinded Reviewers.

	Number of Subjects (%)			
	Study Laryngologist	Reviewer 1	Reviewer 2	Reviewer 3
All Other Disorders	21	20	20	21
Laryngopharyngeal Reflux	0	1	1	0

during phonation. In a similar study, Cohen and Garret[21] examined the prevalence of PPI use and the final laryngoscopic findings in patients referred to a tertiary laryngology practice for the management of hoarseness. Of 264 patients, 56% had previously tried PPIs, with an average duration of treatment of 5.6 months. Although the study's main purpose was to describe patterns of PPI use, it is notable that up to one-third of patients were found to have a mucosal lesion and another one-third were found to have muscle tension dysphonia. Our study is distinguished from these by its prospective nature, as well as its use of multiple blinded reviewers to account for expected variability in interpretation of laryngoscopic findings.[16] It is notable that a significant number of patients in both studies were diagnosed with MTD. In the current study, in comparison, over one-third of patients were found to have a benign or neoplastic mucosal lesion, whereas no more than 15% of patients were diagnosed with primary MTD by any of the reviewers.

In many cases, MTD is believed to be a compensatory manifestation of an underlying disturbance in laryngeal architecture or function, such as a mucosal lesion, neurologic disorder, or laryngitis—including that due to LPR (so-called secondary MTD).[22] However, the diagnostic category of MTD in our study specifically referred only to primary MTD; that is, the presence of laryngeal muscle tension in the absence of any other detectable disturbance in laryngeal function. When an underlying disturbance was detected, it was designated as the primary diagnosis. This level of detail may account for the low frequency of primary MTD in our population.

In a 2005 open-label prospective cohort study of symptomatic response to various PPI regimens for LPR, Park et al.[23] evaluated the efficacy of twice daily PPI use versus once daily PPI use in patients diagnosed with LPR based on symptoms, laryngoscopic examination, and esophageal manometry with pH monitoring. Twice daily PPIs resulted in symptomatic improvement in 50% of patients compared to 28% in once daily users; 50% of nonresponders in the once daily group had subsequent improvement after being changed to 2 months of twice daily PPI therapy. The presence of alternate laryngeal pathology was offered as a possible explanation for the overall modest response rate to PPI therapy, but ultimately the authors concluded that a 4-month course of twice daily PPI therapy was a reasonable approach for patients with symptoms, signs, and confirmatory testing suggestive of LPR. The evident downside of this approach is that 50% of patients falling into such a management algorithm may undergo treatment for up to 6 months before being considered nonresponders, only then prompting further consideration of alternate laryngeal pathology. Instead, our findings suggest that more aggressive attempts at identification of an underlying laryngeal disorder at the time of initial presentation may identify those patients with an alternate diagnosis upfront, and thus avoid both unnecessary treatment as well as a delay in initiation of appropriate treatment.

The handful of prospective, blinded studies evaluating the efficacy of PPI therapy for LPR have had similarly modest results compared to Park et al.,[23] with some showing no improvement in laryngeal symptoms over placebo.[10] Additionally, pH probe findings in patients without gastroesophageal reflux disease (GERD) symptoms have repeatedly been shown to have poor correlation with both the presence of laryngeal symptoms, as well as subjective improvement in symptoms following treatment.[24] Given the difficulty in definitive identification of LPR as the causative factor in a patient's vocal symptoms, it becomes imperative to rule out other laryngeal disorders in patients with hoarseness. The high prevalence of distinct laryngeal pathology, found in both our study and Thomas and Zubiaur's study,[20] is especially compelling given the significant proportion of patients who had undergone prior evaluation by an otolaryngologist. Although laryngoscopic findings can be subjective and interpretations can vary from one practitioner to the other,[16] a poor response to empiric medical treatment should, at the very least, stimulate strong suspicion regarding a non-LPR etiology for patient complaints and garner consideration for repeat laryngoscopic examination or outside consultation.

Limitations of the current study include its small size and the single time-point of data collection. Furthermore, it is unknown what, if any, specific methods were utilized for laryngeal visualization in the patients who had previously been evaluated by an otolaryngologist. Compliance with prescribed therapy prior to referral was also not objectively quantified. Finally, VHI and RSI scores following treatment of the underlying laryngeal disorders were not included as they were not available at the time of data collection. Therefore, it is unknown if identification of additional laryngeal pathology led to an improvement in treatment outcome in this patient cohort. Nevertheless, the prevalence of distinct laryngeal disorders identified in this small population of patients suggests that hoarseness may be frequently misattributed to LPR, and that alternate diagnoses should be strongly considered before beginning lengthy trials of medical therapy.

CONCLUSION

Hoarseness is a nonspecific symptom with many underlying causes. Careful laryngoscopic examination, with particular attention to functional and organic laryngeal disorders that can cause hoarseness, is prudent in patients without an early response to PPI therapy in the setting of presumed LPR. Referral to the otolaryngologist should be strongly considered to avoid a delay in a diagnosis of treatable laryngeal pathology.

BIBLIOGRAPHY

1. Van Houtte E, Van Lierde K, D'Haeseleer E, Claeys S. The prevalence of laryngeal pathology in a treatment-seeking population with dysphonia. *Laryngoscope* 2010;120:306–312. doi:10.1002/lary.20696.
2. Franco R A, Andrus JG. Common diagnoses and treatments in professional voice users. *Otolaryngol Clin North Am* 2007;40:1025–1061, vii. doi: 10.1016/j.otc.2007.05.008.
3. Koufman JA, Amin MR, Panetti M. Prevalence of reflux in 113 consecutive patients with laryngeal and voice disorders. *Otolaryngol Head Neck Surg* 2000;123:385–388, doi:10.1067/mhn.2000.109935.
4. Bove MJ, Rosen C. Diagnosis and management of laryngopharyngeal reflux disease. *Curr Opin Otolaryngol Head Neck Surg* 2006;14:116 – 123. doi:10.1097/01.moo.0000193177.62074.fd.
5. Book DT, Rhee JS, Toohill RJ, Smith TL. Perspectives in laryngopharyngeal reflux: an international survey. *Laryngoscope* 2002;112:1399–1406. doi:10.1097/00005537–200208000-00014.
6. Vaezi MF, Hicks DM, Abelson TI, Richter JE. Laryngeal signs and symptoms and gastroesophageal reflux disease (GERD): a critical assessment of cause and effect association. *Clin Gastroenterol Hepatol* 2003;1:333–344.
7. Koufman JA. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24-hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. *Laryngoscope* 1991;101:1–78.
8. Bilgen C, Ogut F, Kesimli-Dinc H, Kirazli T, Bor S. The comparison of an empiric proton pump inhibitor trial vs 24-hour double-probe Ph monitoring in laryngopharyngeal reflux. *J Laryngol Otol* 2003;117:386–390. doi: 10.1258/002221503321626438.
9. Karkos PD, Wilson JA. Empiric treatment of laryngopharyngeal reflux with proton pump inhibitors: a systematic review. *Laryngoscope* 2006; 116:144–148. doi:10.1097/01.mlg.0000191463.67692.36.
10. Noordzij JP, et al. Evaluation of omeprazole in the treatment of reflux laryngitis: a prospective, placebo-controlled, randomized, double-blind study. *Laryngoscope* 2001;111:2147–2151. doi:10.1097/00005537–200112000-00013.
11. Sen P, Georgalas C, Bhattacharyya AK. A systematic review of the role of proton pump inhibitors for symptoms of laryngopharyngeal reflux. *Clin Otolaryngol* 2006;31:20–24, discussion 24. doi:10.1111/j.1749–4486.2006.01134.x.
12. Tutuian R, Mainie I, Agrawal A, Adams D, Castell DO. Nonacid reflux in patients with chronic cough on acid-suppressive therapy. *Chest* 2006; 130:386–391. doi:10.1378/chest.130.2.386.
13. Wong RK, Hanson DG, Waring PJ, Shaw G. ENT manifestations of gastroesophageal reflux. *Am J Gastroenterol* 2000;95:S15–22.
14. Chung JH, et al. The significance of laryngopharyngeal reflux in benign vocal mucosal lesions. *Otolaryngol Head Neck Surg* 2009;141:369–373. doi:10.1016/j.otohns.2009.05.033.
15. Amin MR, Koufman JA. Vagal neuropathy after upper respiratory infection: a viral etiology? *Am J Otolaryngol* 2001;22:251–256. doi:10.1053/ajot.2001.24823.
16. Branski RC, Bhattacharyya N, Shapiro J. The reliability of the assessment of endoscopic laryngeal findings associated with laryngopharyngeal reflux disease. *Laryngoscope* 2002;112:1019–1024. doi:10.1097/00005537–200206000-00016.
17. Kelchner LN, et al. Reliability of speech-language pathologist and otolaryngologist ratings of laryngeal signs of reflux in an asymptomatic population using the reflux finding score. *J Voice* 2007;21:92–100. doi: 10.1016/j.jvoice.2005.09.004.
18. Schwartz SR. et al. Clinical practice guideline: hoarseness (dysphonia). *Otolaryngol Head Neck Surg* 2009;141:S1–S31. doi:10.1016/j.otohns.2009.06.744.
19. Chang JI, Bevans SE, Schwartz SR. Otolaryngology clinic of North America: evidence-based practice: management of hoarseness/dysphonia. *Otolaryngol Clin North Am* 2012;45:1109–1126. doi:10.1016/j.otc.2012.06.012.
20. Thomas JP, Zubiaur FM. Over-diagnosis of laryngopharyngeal reflux as the cause of hoarseness. *Eur Arch Otorhinolaryngol* 2013;270:995–999. doi:10.1007/s00405-012-2244-8.
21. Cohen SM, Garrett CG. Hoarseness: is it really laryngopharyngeal reflux? *Laryngoscope* 2008;118:363–366. doi:10.1097/MLG.0b013e318158f72d.
22. Van Houtte E, Van Lierde K, Claeys S. Pathophysiology and treatment of muscle tension dysphonia: a review of the current knowledge. *J Voice* 2011;25:202–207. doi:10.1016/j.jvoice.2009.10.009.
23. Park W, et al. Laryngopharyngeal reflux: prospective cohort study evaluating optimal dose of proton-pump inhibitor therapy and pretherapy predictors of response. *Laryngoscope* 2005;115:1230–1238. doi:10.1097/01.MLG.0000163746.81766.45.
24. Friedman M, et al. The value of routine pH monitoring in the diagnosis and treatment of laryngopharyngeal reflux. *Otolaryngol Head Neck Surg* 2012;146, 952–958. doi:10.1177/0194599812436952.