Eur Arch Otorhinolaryngol (2014) 271:743–747
DOI 10.1007/s00405-013-2682-y

LARYNGOLOGY

Factors confusing the diagnosis of laryngopharyngeal reflux: the role of allergic rhinitis and inter-rater variability of laryngeal findings

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Received: 4 June 2013 / Accepted: 23 August 2013 / Published online: 3 September 2013

Abstract The objective of the study was to determine the inter-rater variability in assessment of laryngeal findings and whether diagnosing laryngopharyngeal reflux based on the laryngeal findings and history alone without considering allergic rhinitis leads to the overdiagnosis and overtreatment of laryngopharyngeal reflux. Patients with positive and negative skin prick tests were recruited from an allergy clinic in a tertiary teaching university hospital. All subjects completed the Reflux Symptom Index (RSI) and underwent laryngeal examinations by three physicians blinded to the skin prick test results and the Reflux Finding Score (RFS) was determined. RFS >7 or RSI >13 was considered reflux positive. Fleiss' kappa (κ) was used to measure inter-rater agreement. The inter-rater agreement was low for pseudosulcus vocalis ($\kappa = 0.078$), ventricular obliteration ($\kappa = 0.206$), diffuse laryngeal edema ($\kappa = 0.204$), and posterior laryngeal hypertrophy ($\kappa = 0.27$), intermediate for laryngeal erythema/hyperemia ($\kappa = 0.42$) and vocal fold edema ($\kappa = 0.42$), and high for thick endolaryngeal mucus ($\kappa = 0.61$). Although the frequency of allergy was high, there was no significant difference between allergy-positive and laryngopharyngeal reflux-positive patients. On logistic regression analysis, thick endolaryngeal mucus was a significant predictor of allergy ($p = 0.012$, odds ratio 0.264, 95 % confidence interval 0.093–0.74). The laryngeal examination for reflux is subject to marked inter-rater variability and allergic laryngitis was not misdiagnosed as laryngopharyngeal reflux. The presence of thick endolaryngeal mucus should alert physicians to the possibility of allergic rhinitis/laryngitis.

Keywords Laryngopharyngeal reflux · Allergic rhinitis · Predictor · Mucus

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Introduction

Laryngopharyngeal reflux (LPR) is a chronic disease with a laryngeal presentation that differs from that of gastroesophageal reflux. The most common clinical findings of LPR include hoarseness, chronic cough, throat clearing, postnasal drip, sore throat, and globus sensation [1]. Twenty-four hour ambulatory pH monitoring is considered the gold standard for diagnosing LPR, but double-lumen pH probes are not used routinely in daily practice because of patient discomfort and the cost [2]. In addition to pH monitoring, reflux can be diagnosed based on the response of symptoms to behavioral and empirical medical treatment and endoscopic findings of mucosal injury [3].

Belafsky et al. [4] developed a self-administered tool that can be used to evaluate the relative degree of LPR symptoms. The Reflux Symptom Index (RSI) score was significantly higher in untreated LPR patients than in controls. An RSI >13 is considered abnormal (the 95 % upper confidence limit for controls was 13.6). Belafsky et al. developed the Reflux Finding Score (RFS), a clinical severity scale for rating the laryngeal findings in LPR patients, and stated that a patient with an RFS >7 has LPR [5].

The laryngeal symptoms and signs attributed to LPR are not pathognomic. The inter-rater reliability of the laryngeal findings is low and an endoscopic diagnosis of LPR is highly subjective [6]. The laryngeal symptoms attributed to allergy and LPR are non-specific, and most of the laryngeal findings can be seen in both diseases [7]. Given the low specificity of these findings, allergic laryngitis can be misdiagnosed as LPR disease.

This study examined the inter-rater variability of assessment of laryngeal findings and whether diagnosing LPR based on the laryngeal findings and history alone without considering allergic rhinitis can lead to its over-diagnosis and overtreatment.

Materials and methods

This study was conducted between February and September 2012 in İzmir Kâtip Çelebi University Atatürk Research and Education Hospital Otolaryngology Clinic. Patients referred from the Allergy Clinic [all of the patients had skin prick test (SPT) results] were evaluated and their histories were taken. The patient group consisted of 36 males and 72 females, with a mean age of 33.8 ± 12.02 years. The İzmir Kâtip Çelebi Medical Faculty Ethics Committee approved the study.

The laryngeal examination findings (endoscopic examination was recorded by a microcamera) were evaluated independently by three physicians who were unaware of the patients' histories and SPT results. The following were excluded: patients using proton-pump inhibitors, any anti-reflux medication, or inhaled, nasal or oral steroids at least 1 month before the evaluation; those with a history of surgery for gastroesophageal reflux or laryngeal surgery; smokers; and patients with an acute upper airway infection. Each physician determined the RFS in his/her examination. The laryngeal examination for the RFS includes the presence of laryngeal erythema/hyperemia, vocal fold edema, thick endolaryngeal mucus, pseudosulcus vocalis, ventricular obliteration, diffuse laryngeal edema, posterior laryngeal hypertrophy, and granuloma/granulation tissue. An RFS >7 was accepted as being LPR positive.

A physician who was blinded to the SPT results took the patients' histories and administered the RSI questionnaire. An RSI >13 was accepted as LPR positive. The presence of dysphonia, postnasal drip, cough and throat clearing sensation was included in the patient history.

All allergen solutions were standardized ALK-Abello extracts (ALK, Denmark). We used the extract that contained the pollens (weeds, grasses) most common in İzmir. In addition, extracts of house dust mite, mold, epidermal mix (cat, dog, budgie, and chicken), cereals, grass and tree mix, and cockroach were used. The SPT results were documented as allergy being present or absent. (graded based on Patterson's system for scoring skin tests and, for the ease of statistical analysis, wheal diameter +1 and bigger was regarded as allergy-positive).

Statistical analysis was performed using SPSS version 16 and Microsoft Excel 2007 (Microsoft, Redmond, WA, USA). The level of statistical significance was established at $p < 0.05$, and the confidence intervals (CI) were 95 %. The RFS and RSI scores were assessed as LPR+ or LPR− (separately and combined) and were compared to the SPT results to evaluate the relationship between allergy and LPR using the Chi-square test. The presence of dysphonia, cough, postnasal drip, and throat clearing was compared between SPT-positive and -negative patients with the Chi-square test.

Binary logistic regression analysis was used to determine the value of each laryngeal endoscopic finding at predicting allergy.

Analysis of variance (ANOVA) with the Bonferroni correction was used to determine whether multiple allergen reactivity resulted in high RSI and RFS values.

Fleiss' kappa (κ) was used to measure the inter-rater reliability among the physicians for each laryngeal endoscopic examination finding. The resulting κ values indicate the proportion of agreement greater than that expected by chance. The range of possible values of κ is from –1 to +1, although it usually falls between 0 (agreement expected by chance) and 1 (perfect agreement). The interpretation of the κ coefficient is complex, because several factors can influence its magnitude or the interpretation of a given magnitude [8]. In the κ test, $p < 0.05$ indicated that the agreement level was not due to chance alone.

Results

Of the 108 patients, 65 (59.6 %) had a positive SPT and 43 (39.4 %) had a negative SPT. Multiple allergen sensitivity was identified in 45 (69.2 %) patients and single allergen sensitivity in 20 (30.8 %).

The inter-rater reliability of the laryngeal examination findings (i.e., for the RFS) of 108 patients was evaluated using Fleiss' κ. The inter-rater variability among the three physicians demonstrated that laryngeal erythema/hyperemia ($\kappa = 0.42$, $p < 0.001$) and vocal fold edema ($\kappa = 0.42$, $p < 0.01$) showed significant inter-rater agreement, with intermediate κ coefficients. The inter-rater variability among physicians for interpreting thick endolaryngeal mucus was significant ($p < 0.001$), with the highest κ (0.61). The inter-rater variability among the three physicians indicated that the inter-rater agreements for pseudosulcus vocalis ($\kappa = 0.078$, $p = 0.56$), ventricular obliteration ($\kappa = 0.206$, $p = 0.13$), diffuse laryngeal

Table 1 The frequencies, odds ratios, *p* values confidence intervals and Chi-square values of SPT-positive and -negative patients according to RSI and RFS

SPT	RSI ≥13	RSI <13	RFS ≥7	RFS <7
Positive	37 (34.3 %)	28 (25.9 %)	16 (14.8 %)	49 (45.4 %)
Negative	24 (22.2 %)	19 (17.6 %)	11 (10.2 %)	32 (29.6 %)
χ^2	0.013		0.013	
p	0.909		0.91	
CI	0.48–2.2		0.391–2.3	
OR	1.04		0.95	

SPT skin prick test, *RSI* Reflux symptom index, *RFS* Reflux Finding Score, *CI* confidence interval, *OR* odds ratio, χ^2 Pearson Chi-square

edema ($\kappa = 0.204$, $p = 0.13$), and posterior laryngeal hypertrophy ($\kappa = 0.27$, $p = 0.09$) were not significant, with low κ coefficients. No granuloma/granulation tissue was reported.

Given the inter-rater discrepancy regarding laryngeal symptoms, a consensus on the RFS was reached among the three physicians after a previous evaluation for inter-rater variability assessment (still blinded to patient history and SPT results) and 27 patients were considered to have LPR based on the RFS. Sixty-one patients had LPR according to the RSI. The LPR test results according to RFS and RSI were compared separately with the SPT results. In both groups, no significant difference was found. When both scales were combined to diagnose LPR, we did not find a significant difference between the SPT-positive and -negative groups (Table 1). Dysphonia, throat clearing, postnasal drip, and cough did not differ significantly between the groups (Table 2).

Binary logistic regression analysis performed to determine whether any of the laryngeal findings predicted allergic rhinitis showed that thick endolaryngeal mucus predicted allergic rhinitis ($p = 0.012$, OR 0.264, 95 % CI 0.093–074).

The effect of multiple allergen sensitivity on the RSI and RFS was investigated using ANOVA (with the Bonferroni correction) and increased allergen sensitivity did not result in a significant result ($p = 0.721$ and $p = 0.7$ respectively).

Discussion

There is growing evidence that allergic rhinitis predisposes to allergic laryngitis and cases that are diagnosed as LPR might be in fact allergic laryngitis. The laryngeal findings of LPR are non-specific, which leads to confusion in diagnosing LPR based only on laryngeal findings. This study comprised two aspects: to test the inter-rater reliability of the laryngeal findings of RFS scale and to determine whether allergic laryngitis is misdiagnosed as LPR.

The RFS and RSI are both reliable, valid tools for diagnosing LPR [4, 5]. A recent article reported that the RFS and RSI can be administered in daily practice for diagnosis LPR and both can be used to monitor the effectiveness of proton-pump inhibitor therapy [9]. Branski et al. [6] examined the reliability of the laryngeal findings associated with LPR disease; five otolaryngologists assessed the degrees of erythema and edema of the anterior commissure, a membranous vocal fold, interarytenoid pachyderma, the likelihood of LPR disease involvement, and the severity of LPR findings. They reported that an accurate clinical assessment of laryngeal involvement in LPR disease is difficult because the laryngeal physical findings differ among clinicians. They concluded that this variability makes the precise laryngoscopic diagnosis of LPR highly subjective. We found similar results. The finding with the greatest inter-rater reliability was thick endolaryngeal mucus ($\kappa = 0.61$). Pseudosulcus vocalis ($\kappa = 0.078$), ventricular obliteration ($\kappa = 0.206$), diffuse laryngeal edema ($\kappa = 0.204$), and posterior laryngeal hypertrophy ($\kappa = 0.27$) had low inter-rater agreement, and laryngeal erythema/hyperemia ($\kappa = 0.42$) and vocal fold edema ($\kappa = 0.42$) had intermediate inter-rater agreement.

Randhawa et al. [10] tested 15 patients using the RSI and RFS to diagnose LPR, and both SPT and nasal nitric

Table 2 The frequencies, odds ratios, *p* values confidence intervals and Chi-square values of SPT-positive and -negative patients according to symptoms of the patients

SPT	Cough+	Cough−	Pd+	Pd−	Dys.+	Dys.−	Th. Cl.+	Th. Cl.−
Positive	32 (29.6 %)	33 (30.6 %)	40 (37 %)	25 (23.1 %)	24 (22.1 %)	41 (38 %)	42 (38.9 %)	23 (21.3 %)
Negative	20 (18.5 %)	23 (18.5 %)	26 (24.1 %)	17 (17.5 %)	15 (13.9 %)	28 (25.9 %)	29 (26.9 %)	14 (13 %)
χ^2	0.077		0.013		0.047		0.092	
p	0.782		0.911		0.829		0.76	
OR	1.11		1.04		1.09		0.88	
CI	0.51–2.41		0.47–2.3		0.48–2.44		0.39–1.99	

SPT skin prick test, *Dys.* dysphonia, *Pd* postnasal drip, *Th. Cl.* throat clearing *CI* confidence interval, *OR* odds ratio, χ^2 Pearson Chi-square

oxide (NO) levels to diagnose the presence of allergy. In their cohort, three times as many patients had allergies compared with LPR. Although they found no significant difference or correlation between allergy and LPR, they concluded that some patients with allergic laryngitis are being misdiagnosed with LPR and thereby being over-treated with proton-pump inhibitors (PPIs). A second study investigated the relationship between the Voice Handicap Index and airborne allergen exposure [11]. It reported that patients with more airborne allergies had a higher incidence of undiagnosed vocal dysfunction, as determined by an increased Voice Handicap Index score, than those with fewer or no such allergies. Our study evaluated the effects of multiple allergen reactivity on the RFS and RSI and did not find any significant results. This might reflect the fact that we focused more on a possible relationship between LPR and allergy rather than voice quality.

In their recent review, Krouse and Altman [12] noted a frequent co-seasonal increase in dysphonia, throat clearing, globus sensation, and cough in allergic rhinitis patients. In our study, although we found that dysphonia, cough, and throat clearing were more prevalent in the allergic rhinitis group, this increased prevalence was not significant. Increased dysphonia in allergic patients raises questions about the relationship between LPR and allergic rhinitis. Turley et al. [13] investigated the possible relationship between allergy/dysphonia and LPR in 34 patients with allergic rhinitis (AR), 54 patients with non-allergic rhinitis (NAR), and 62 controls. They found that patients with a poorer rhinitis-related quality of life (QOL) according to the mini-Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) had a poorer voice-related QOL and more severe chronic laryngeal symptoms according to the RSI. They concluded that patients with rhinitis (AR or NAR) had a higher prevalence of dysphonia than controls. Patients with worse rhinitis symptoms had a poorer voice-related QOL and more severe chronic laryngeal symptoms. Our results demonstrated that although RFS- and RSI-diagnosed LPR was more prevalent in the allergic rhinitis group, this difference was not significant. This discrepancy between our results and previous studies might reflect the fact that our study focused on the difference between allergic and non-allergic rhinitis.

Pachydermia (interarytenoid cobblestoning), laryngeal pseudosulcus, laryngeal edema and erythema, granulomas, erythema, leukoplakia, nodules, edema and polyps of the vocal cords are common endoscopic laryngeal findings attributed to laryngopharyngeal reflux [7, 14]. Supraglottic edema and erythema, vocal fold edema and erythema, and abundant and viscous endolaryngeal secretions are possible signs related to allergic laryngitis [15].

The laryngeal findings of allergy and LPR might be difficult to separate. Diffuse laryngeal edema, vocal fold edema, excessive mucus, thick viscous mucus, vocal fold erythema, and arytenoid erythema are clinical signs shared by LPR and allergy, and these are the laryngeal signs described most commonly in both conditions [7]. When the RFS scores of both groups were compared, we did not find a significant difference. Direct stimulation of the larynx with dust mite antigen results in viscous endolaryngeal secretions and vocal fold edema [15]. In this study, we found that thick laryngeal mucus had the greatest inter-rater agreement and was a significant predictor of allergy, while laryngeal edema was not a predictor. Additional research is necessary to distinguish the laryngeal findings attributable to allergic stimulation due to the irritant and inflammatory effects associated with other known laryngeal pathologies.

Conclusion

There is growing evidence that allergic laryngitis might be misdiagnosed as laryngopharyngeal reflux. In our study, we did not find any evidence to support this association. However, we showed that in patients suspected of having LPR disease with thick laryngeal mucus, the allergic status of the patient must be investigated carefully.

Conflict of interest None declared.

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