PREVALENCE OF ALLERGY IN PATIENTS WITH BENIGN LESIONS OF THE VOCAL FOLDS

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ABSTRACT

Objective*:Allergy commonly affects the upper and lower airways concurrently. Although allergic inflammations effects on nasal and pulmonary diseases have been well described, allergic inflammations effects on the larynx are not compietely well understood. We investigated the prevalence of allergy in patients with benign lesions of the vocal folds and types of allergens causing these reactions.*

Materials and methods*: Laryngeal examination was done by rigid laryngoscope and lesions of each patients were recorded. All patients underwent skin prick tests on the forearm with a full set of 35 common allergens.*

Results*: Forty patients(15 male and 25 female)with vocal fold pathology were included. Twenty two(55%) subject swere affected by vocal polyps, 12(27.5%) by nodules, 7 (17.5%) by Reinke's edema. Skin prick tests resulted positive in 60% of the patients.The most common allergen found was mite mixture(47,5%) and weed mixture (42.5%).*

Conclusion*: Skin prick tests were found to be highy positive in patients with benign lesions of vocal folds compared to normal population. Further research is needed to identify the underlying pathways mediating the laryngeal response to allergy to develop better diagnostic and therapeutic techniques.*

Key words*: Allergy, skin prick test, Reinke's edema, vocal nodule, vocal polyp, laryngopharyngeal reflux, dysphonia, IgE, SFAR, ISAAC.*

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Introduction

Dysphonia is one of the most frequently encountered symptoms in the daily practice of Ear-Nose and Throat (ENT) specialists. Dysphonia is frequently associated to respiratory tract infections, even if neoplasms, trauma, neuromuscular diseases, drug use, metabolic disorders, vocal fold edema, polyps or nodules can be the cause. Vocal fold edema and dysphonia might emerge due to laryngopharyngeal reflux (LPR)[(1)]. However laryngeal manifestations of allergy might be confused with findings of LPR leading to unnecessary treatment[(1)]. Allergic inflammation affects upper and lower respiratory tract, while their effects on laryngeal abnormalities have not been fully elucidated yet[(2,3)].

The prevalence and etiology of allergic rhinitis vary among regions, and it is estimated to affect 10-20% of the population. Its prevalence increases especially in industrialized western countries as is the case in other allergic diseases[(4-6)]. Antalya region has a flora including various kinds of grass, plants, and trees which are known to cause allergic diseases. Warm and humid climate constitutes an ideal environment for the sustenance of mites, and cockroaches. Respiratory and food allergens are thought to be among prevalent, but latent causes of chronic laryngitis which has not been clearly revealed yet.1 These allergens can induce thickening, edema, and hypertrophy of laryngeal mucosa, leading to vocal fold polyp, nodule or Reinke's edema(RE). The etiology of vocal fold nodule, polyp or Reinke's

edema progressing with benign epithelial swelling of the vocal folds are multifactorial, and personal characteristics, reflux, respiratory and/or food allergies are most frequently implicated abnormalities[1,7]. Recent laboratory analyses have detected vocal edema after exposure to inhaler antigens[8].

In this study we intended to investigate type of allergens and the prevalence of allergy positivity in benign lesions of the vocal fold.

Materials and methods

Study design

The study was approved by the local ethic committee and written informed consent was obtained from patients and from patient's parents who are under 18 years old. Patients over 15 years of age complaining of dysphonia at least for the last 4 weeks were evaluated. Patients with vocal fold polyp, Reinke's edema or nodule revealed as a result of detailed ENT examination who consented for laboratory and skin prick tests (SPT) were included in the study. All patients had examination of the larynx with a rigid laryngoscope with angle optics of 90° (Karl Storz, Gottingen, Germany). Endoscopic examinations of all patients were performed, and recorded by the same physician (Figures 1 A, B, C).

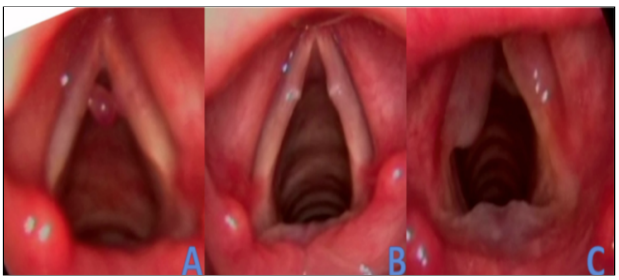

Figure 1: Stroscopic examination findings related to vocal fold polyp (1A) nodule (1B), and Reinke's edema (1C).

Outcome analysis

Questionnaire forms prepared by the researchers after review of the relevant literature were used by the investigators in order to identify etiology of allergy. Questions included in the questionnaire forms were directed to determine patients' age, gender, levels of education, living place, social security status, previous diseases, onset of the diseases, duration of symptoms, irritants, allergens aggravating symptoms, smoking status and socioeconomic characteristics. Score For Allergic Rhinitis (SFAR) and International Study of Asthma and Allergies in Childhood (ISAAC) survey tests were performed in all patients[9]. LPR was diagnosed when the patient stated typical anamnesis problems and had typical signs of allergic inflammation in the larynx10 (Figure 2).

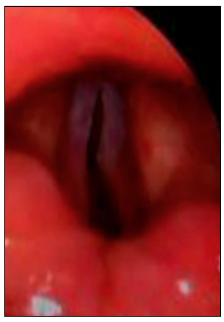

Figure 2: Endoscopic examination findings related to LPR.

Laboratuary tests

The total IgE levels were determined by fluoroenzyme immunoassay (ImmunoCAP-FEIA) method via use of ImmunoCAP (Phar-macia, Uppsala, Sweden) kit. The values above 100 kU/L for the total IgE levels were considered high.In patients with Reinke's edema serum thyroid stimulation hormone (TSH) levels were determined. The complete blood count test was performed to estimate the number of eosinophils per mm3 and values over 500 were accepted as high.

Skin prick tests

Alyostal ST-IR (Stallergenes S.A. - France) standard allergen extracts were used for SPT. The anti-histaminic drugs were stopped 5 days before, the H2 receptor blocker drugs were stopped 24 hours before and the antidepressants were stopped 20 days before the prick test. The cleansed volar aspect of the forearm and the standard concentrations of allergen solutions were applied dermally with sterile lancets for penetration to the epidermis. Then, 20 minutes later the dermal reaction was evaluated. Histamine hydrochloride was used as positive and the isotonic NaCl solution was used as negative control.

The criteria for prick tests were defined as follows

Erythema and edema in the positive control site but none in the test region: negative (-),

Erythema and edema area is less than half of the positive control site: positive (+),

Erythema and edema area is >½ and <1 of the positive control site: (+ +),

Erythema and edema area is equal to the positive control site: (+ + +),

Erythema and edema area is larger than the positive control site: (+ + + +).

The prick tests is considered positive if the erythema and edema area was equal or larger than the positive control site (+ + + or higher).

Statistical analysis

All data were analyzed using the SPSS (Statistical Package for Social Sciences) 11.0 package program. Medcalc statistical program was used for chi-square tests. Statistical significance was set at $P<0.05$.

Results

A total of 40 patients with established benign vocal fold pathologies referred to our clinics were included in the study. Only 14 subjects had professions requiring frequent and intensive use of voice (teachers, peddlers, public relations specialist). Study population consisted of 15 (37.5%) males and 25 females (62.5%). There was no statistically significant difference of benign vocal fold pathologies between males and females (χ=5.534, p=0.06). Patients ranged between 15-74 (39.8±13.40 yrs) years of age. Based on the mean age of 39.8 years, patients were divided into 2 groups of 20 patients each as <40 or ≥ 41 years of age. Reinke's edema was significantly more frequent in patients aged <40 years (χ=4.32, P=0.03). However, in patients aged ≥ 40 years, vocal nodules were significantly more common (χ=6.14, P=0.01). No statistically significant difference was found for polyps between these groups (χ=0.404, p=0.52).

Benign vocal fold lesions consisted of 22 (55%) polyps, 11 (27.5%) nodules, 7 (17.5%) Reinke's edema. Lesions were localized in the left (47.5%), right (30%) vocal cords or bilaterally (22.5 %). In the 37.5% of cases patients were complaining of dysphonia for more than 6 months. Five (12.5%) patients were affected by asthma, and they were receiving inhaler steroid therapy. Mean total IgE level and eosinophil count were found to be 116.9 units/ml, and 10757.6 /μL, respectively (Table 1).

Based on SFAR, and ISAAC screening scores applied before the skin prick test, allergic rhinitis (22.5%), asthma (18%), and allergic conjunctivitis (32 %) were found in our patients with indicated percentages. Twenty-one (52.5%) patients were smokers. However correlation between smoking status and vocal cord lesions was not statistically significant (χ=4.30, p=0.11). LPR was found in only 10 (25%) patients and correlation between vocal fold lesions and LPR was not statistically significant either (χ=1.351, p=0.50) (Table 2).

No	Patient	Gender	Age	Vocal fold pathology	Total IgE (*units*/ml)
1	ZA	F	23	Nodule	35
2	EK	F	29	Nodule	49
3	BG	F	52	Polyp	153
4	OK	F	25	Nodule	52
5	FB	M	48	Polyp	322
6	SY	M	31	Polyp	15
7	AK	M	58	Reinke's edema	976
8	SY	F	41	Polyp	15
9	NA	F	57	Polyp	267
10	NK	F	40	Nodule	15
11	ED	F	32	Reinke's edema	340
12	MO	F	42	Polyp	52
13	DO	F	37	Nodule	96
14	MD	F	32	Nodule	21
15	MH	M	22	Polyp	43
16	EA	F	50	Reinke's edema	976
17	ED	F	36	Polyp	15
18	NK	M	37	Nodule	86
19	AO	M	35	Polyp	70
20	YC	F	42	Polyp	15
21	SE	F	48	Polyp	167
22	VG	F	43	Polyp	75
23	ZK	F	15	Polyp	73
24	HB	M	46	Reinke's edema	230

Table 1: Clinical characteristics of the patients with skin prick test positivity.

Pathology	SPT(+)	SFAR(+)	ISAAC(+)	Age 40>	Smoking	LPR	Voice abuse	Total
Reinke's edema	85.7%	14.3%	14.3%	85.7%	85.7%	28.6%	14.3%	100%
Nodule	54.5%	27.3%	27.3%	18.2%	54.5%	36.4%	72.7%	100%
Polyp	40.9%	22.7%	18.2%	54.5%	40.9%	18.2%	22.7%	100%

Table 2: Prevalence of some risk factors for occurrence of benign pathology on vocal folds.

SPT positivity was detected in 60 % of 40 patients in all. SPT positivity was mostly observed for allergens in mixtures prepared from mites (47.5 %), weeds (42.5%), and grasses (35%) (Table 3, Figure 3). No statistically significant correlation was found between benign vocal fold lesions and SPT positivity. (χ=0.09, p=0.95). From the comparison between SFAR, ISAAC scores, Total Ig E levels, eosinophil counts andbenign vocal pathology groups, a statistically significant relationship was

found only between total IgE levels of vocal nodule group and Reinke's edema group (Table 4).

No	Patients	Grasses mixture	Barley mixture	Weed mixture	Tree mixture	Epithelium (Dog and cat)	Molds	Mites mixture	Cockroach	Oleaauropeae
1	ZA	-	-	+1	+1	-	-	-	-	-
2	EK	-	+2	+2	-	-	-	+2	-	+3
3	BG	+1	+1	+1	+1	-	-	+1	-	+1
4	OK	+1	+1	+1	-	-	-	-	-	-
5	FB	-	-	-	-	-	-	+1	-	+4
6	SY	-	-	-	+2	-	-	-	-	+2
7	AK	+1	+2	+1	-	+1	-	+2	-	-
8	SY	+1	-	-	-	-	-	+2	-	-
9	NA	+1	+1	+1	+1	-	-	+3	-	+2
10	NK	+1	+1	+1	+1	+4	+1	+2	-	-
11	ED	-	+	+	+	+	+	+	-	-
12	MO	+1	+1	+2	-	+1	+1	+1	-	+2
13	DO	-	-	+2	-	-	-	+4	-	-
14	MD	-	+1	+1	+1	-	-	+1	-	+1
15	MH	-	+1	+1	-	-	-	+1	-	+1
16	EA	+1	+1	+1	+1	-	-	+1	-	+1
17	ED	+1	+1	+2	+1	-	-	+2	-	+2
18	NK	+1	+1	+2	+1	-	+1	+1	+2	+1
19	AO	+1	+1	+3	-	-	-	-	-	-
20	YC	+1	1+	+1	-	+1	-	-	-	-
21	SE	+2	-	-	-	-	-	+4	-	-
22	VG	-	-	-	-	-	-	+2	-	-
23	ZK	+1	-	-	+1	-	-	+1	+2	-
24	HB	+1	-	-	-	-	-	+4	-	-

Table 3: Allergy test panel for the patients with skin prick test positivity.

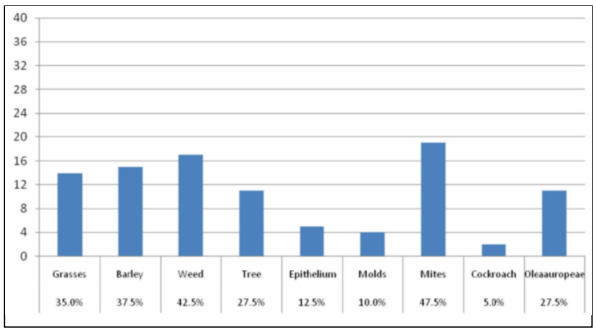

Figure 3: Distribution of positive allergy tests for various allergens.

	Polyp(p=)	Nodule(p=)	Reinke's(p=)
SFAR	0,970	0,656	0,567
ISAAC	0,751	0,479	0,677
Total IgE	0,970	***0,036***	***0,016***
Eosinophil	0,348	0,221	0,457

Table 4: Statistical relationship between benign vocal fold lesion groups and SFAR and ISAAC scores, Total Ig E and Eosinophil count.

Discussion

The prevalence and etiology of allergic rhinitis varies from region to region and affectapproximately10-20 % of the population[11,12].

In a study conducted in Antalya, on the south coast of Turkey, prevalence of asthma, allergic rhinitis and allergic eye disease were detected as 8.2%, 10.8% and 7.5% respectively. Etiologic factors for allergies detected in these patients were house dust mites (51.8%), pollens (42.3%), and both mites, and pollens (5.9%)[5]. However in our study group,prevalence ofallergic rhinitis (22.5%), asthma (18%), and allergic conjunctivitis (32 %) were found to be higherthan the general population.SPT positivity was detected in 60 % of 40 patients. SPT positivity was mostly observed for allergens in mixtures prepared from mites (47.5 %), weeds (42.5%), and grasses (35%).

Vocal fold nodules are bilateral epithelial swelling of the anterior third of the true vocal fold and can be found in children, adolescent, and adults working in jobs with high voice demands, predominantly females[13]. The evidence linking allergy to vocal fold nodule is weak. It is thought to be a synergistic effect of inhalational and/or nutritional allergens with other factors such as reflux, smoking, and voice abuse[2]. Several factors can be responsible for the development of the vocal polyp, such as vocal abuse or overuse, chronic infections of the upper airways, allergy, smoking, and gastroesophageal reflux. Its physiopathology involves vascular trauma, secondary to acute or chronic vocal trauma, followed by bleeding, fibrin exudation, thrombosis, and capillary proliferation. Fibrosis and basophilic or hyaline degeneration are also frequently observed[14]. Reinke's edema is a hyperplastic epithelial lesion on the vocal folds. The etiology of Reinke's edema remains unclear.15 A retrospective study by Hocevar-Boltezar et al. showed that allergy can be an important factor in the etiopathogenesis of lesions on the laryngeal mucosa, since it makes the mucosa more sensitive to other unfavorable factors.16 We detected SPT positivity in 60% of our patients without any statistically significant intergroup differences between benign vocal fold lesions, and SPT positivity (p=0,955).

However, larger scale investigations conducted with increased number of study groups are needed. The mechanism is most probably induced by inflammatory allergic changes in the mucosa, which make it more sensitive to damage by other risk factors for occurrence of Reinke's edema.

In a study investigating the role of allergy in the etiology of Reinke's edema, Krovas et al. detected SPT positivity in the 20% and the 23.8% of patients with and without Reinke's edema with-

out any statistically significant difference between groups[10].

All of 16 patients with Reinke's edema who resulted positive in allergy screening tests were sensitive to inhalatory allergens, while in only 3 patients food allergies (against flour, eggs, some fruits) were detected. In our study, patients affected by Reinke's edema resulted often positive to allergens found in grasses mixture, barley mixture and mites in accordance with literature findings. Dzulet al.investigated etiologic factors for focal edema, and reported house dust allergens as one of the most important and frequently encountered causes of recurrent laryngitis[17]. In our study, in accordance with the above-mentioned prevalence study, the main detected allergen (47.5 %) was mite mixture.

In allergic diseases allergens may have regional variations. That's why the allergen profiles of the regions must be determined and the SPT must be prepared accordingly. Mostly mite mixtures, weed and grass mixture are responsible from the allergy cases due to our observations in our clinic. The other important allergens that are linked to the flora and climate of the region are oleaauropeae (olive tree) and the cockroaches. Cockroaches live in places at the temperature of 20-25 °C with a relative humidity of 60-70%, especially in kitchens and bathrooms. It is hard for them to survive in less humid places and places with scarce amount of food residues[18]. Likewise, to fight to eradicate the cockroaches; the hygiene conditions must be improved and insecticides must be used regularly. Mediterranean region has ideal environmental conditions for cockroaches to live. In this region it is possible to have higher allergy prevalence for both mites and cockroaches[5]. The other studies conducted in allergic rhinitis patients' sensitivity for cockroaches are reported to be 14.7-26.1%[19]. In 8.3% of our SPT positive cases with benign vocal fold lesions cockroaches were the culprit agents.

Respiratory allergies can also cause decreased pulmonary function, excessive secretions in the lower airway, trachea, bronchi or in the upper airway of the pharynx, edema of the vocal folds themselves and unusual resonance characteristics of the pharynx or nasal cavity due to congestion of the membrane in those areas[1]. Cohn et al. determined that allergic diseases of the respiratory system have significant influence on voice production[20]. Krouse et al. examined the baseline laryngeal effects among individuals with dust mite (Dermatophagoidespteronyssinus) allergy.

These pilot data suggest that at baseline, allergic individuals perceive greater vocal handicap than their nonallergiccounterparts, even in the absence of current allergy symptoms or observable physical or functional abnormalities[3].

One of the causes of dysphonia is the chemical injury to the larynx, especially in asthmatic patients who are being treated with inhaled corticosteroids. Dysphonia is considered to be caused by dyskinesia of the muscles that provides vocal cord tension, and steroid myopathy of the laryngeal muscles has also been implicated in laryngopharyngitis. However Del Gaudio mentioned that inhaled corticosteroid-induced laryngitis is a form of chemical irritation that have laryngeal findings ranging from mucosal edema, erythema and thickening to leukoplakia, granulation, and candidiasis[21]. Asthmatic patients having new-onset dysphonia who are being treated with inhaled corticosteroid should be referred to an otorhinolaryngologist to detect laryngeal mucosal changes and myopathies[22]. Only in 12.5% of our patients who had been using inhaled corticosteroids for more than one year for their asthma had vocal cord polyps which explained dysphonic complaints of all these patients.

Chronic laryngeal signs and symptoms associated with gastroesophageal reflux disease (GERD) are frequently referred to as reflux laryngitis or LPR[23]. Despite the remark that 24-h double probe pH monitoring is considered the gold standard for the diagnosis of LPR, the technique and the interpretation of pharyngeal probe pH monitoring recordings are still somewhat controversial[24]. In addition, LPR diagnosis based on laryngoscopic finding is highly subjective, thereby leading to overdiagnosis[25]. Few previous studies have reported on the prevalence of LPR and GERD in true vocal fold lesions such as nodules, polyps and RE in particular[26,27]. Vocal fold edema and voice dysfunction can also be caused by LPR, which is the backflow of food or stomach acid into the larynx or pharynx[1]. Beltsiset al.reported that acidic gastric fluid affected vocal folds of their patients as revealed by double probe pH-monitoring findings[23]. GERD causes inflammation of laryngeal mucosa, so that the vessels become more fragile. Thick mucus accumulating in the posterior part of the larynx forced the patients to clear their throats. Coughing represent a huge mechanical strain of vocal folds and results in their damage[10]. Randhawa et al. investigated the relation between allergy test results and LPR symptom index in 15

patients with primary voice disorders using LPR symptom index and GERD scores; in 5 patientsallergy tests resulted negative, while the remaining 10 resulted positive[28]. Because of limited technical possibilities, we determined LPR on the basis of history and estimated typical changes in the larynx and pharynx by the rigid laryngoscope. We detected LPR in 25% of the patients based on medical history, and endoscopic examination findings, while SPT positivity was found in 5 of 10 patients with LPR positivity.

Epidemiological studies have indicated a link with smoking, since the majority of patients are smokers[29]. Kravos et al reported a significantly higher percentage of smokers in the Reinke's group than in the control group.10As revealed by medical histories, the 52.5% of our patients were smokers, and SPT positivity was detected in 62.5% of them. Correlation between smoking status and benign vocal cord lesions was not statistically significant.

Conclusion

Skin prick tests were found to be highly positive in patients with bening lesions of vocal folds compared to normal population. Thus we can speculate that allergy may play a role in pathopysiology of these lesions. Further research is needed to identify the underlying pathways mediating the laryngeal response to allergy to develop better diagnostic and therapeutic techniques.

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