Correlation between female sex and allergy was significant in patients presenting with dysphonia

Associazione tra sesso ed allergia in pazienti affetti da disfonia

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SUMMARY
Aim of the present study was to investigate the prevalence of allergy in patients affected by both organic and/or functional vocal fold disorders. The secondary aim was to assess the correlation between sex and allergy in dysphonic patients. A retrospective chart review was performed on dysphonic patients. A total of 76 patients underwent fiberoptic endoscopy to assess the objective picture. Logistic regression analyses have been conducted to assess the association between sex and the outcome variables. The laryngoscopic examination revealed the presence of poor glottic closure in 32.9%, hyperkinesias in 11.8%, redness in 11.84%, polyps in 5.3%, oedema in 3.95%, vocal fold hypertrophy in 5.3%, nodules in 42.1%, cordectomy in 2.6%. Allergic rhinitis was present in 56.6%, milk intolerance in 13.2%, asthma in 9.2%, atopic dermatitis in 3.9%, drugs intolerance in 11.8%. A total of 76.32% patients presenting with dysphonia were allergic. A statistically significant association was found between female sex and presence of allergy. In conclusion, allergy testing should be performed routinely on female professional voice users. Mild respiratory disorders must be taken into serious consideration in female professional voice users, who may primarily complain of vocal dysfunction rather than upper and lower respiratory diseases.

KEY WORDS: Allergy • Dysphonia

Introduction
The troubles caused by allergies are often compounded by the multiplicity of complaints involved 1. Among common symptoms, such as rhinitis, middle ear effusion, asthma, vocal quality disorders had been found frequently in association with respiratory allergy 2. In a population of 80 allergic children and young adults (age range 8 to 23 years), Baker et al. 1 found vocal quality disorders (hoarseness, breathiness, low vocal intensity) in 44.75% of the cases. This percentage was about eight times greater than that (6%) found in mass screening in the same metropolitan area. The Authors suggested that chronic allergic rhinosinusitis may predispose a child to recurrent hoarseness and eventual development of a benign lesion in the true vocal folds. Occasionally, patients report that they became dysphonic when they were exposed to various external irritants or pollutants in the air: generally the complaints are dryness, harshness, tickling and hoarseness 3.
A medical approach for functional voice disorders had been proposed in a recent prospective randomised pilot
study. A very detailed anamnesis and systematic objective routine analyses led to the discovery of “micro-organic disorders” caused by reflux, infection, allergy or environmental irritants. The medical treatment of these pathological conditions resolved also the functional voice disorders. According to the Authors the reason was that the mucosal swelling/dysfunction of the vocal folds was secondary.

The aim of the present study was to establish whether a correlation exists between the sex and the presence of allergy in dysphonic patients.

Methods
A retrospective chart review was performed of all patients seen in the Voice Centre of the ENT Department ASL RM C and in the ENT Clinic, University of Siena, between September 2006 and September 2007.

The patients (a total of 90) came to the centres for vocal training because of symptoms including hoarseness, vocal fatigue, pitch break, and loss of vocal range.

The retrospective study was carried out excluding not only those cases for whom the anamnesis was positive for smoking habits, but also women already in menopause.

A total of 76 patients (13 male, 63 female) were included in the study. Age range 14-80 years (mean 34.3 years).

The patients underwent fiberoptic endoscopy, aimed at assessing the exact state of the larynx. Acoustic analysis of the voice was performed in 9% of the patients enrolled, albeit the results are not reported in this study as they were not statistically significant.

Statistics
The data collected have been very carefully assessed and then recorded on a magnetic support at the Department of Internal Medicine and Public Health of the University of L’Aquila, and elaborated using the STATA 8 programme. Therefore, logistic regression analyses have been carried out to assess the association between sex and the outcome variables after adjusting for age, these being considered potential confounders.

The associations have been expressed as Odds Ratio (OR) with a confidence interval (CI) reaching 95%.

Results
The laryngoscopic examination revealed the presence of muscle tension dysphonia in 25 patients (32.9%), hyperkinesia in 9 (11.8%), redness in 9 (11.84%), polyps in 4 (53%), oedema in 3 (3.95%), vocal fold hypertrophy in 4 (5.3%), nodules in 32 (42.1%), cordecomy in 2 (2.6%) (Table I). Otorhinolaryngologic evaluation is summarized in Table II together with other disorders. A pale nasal mucosa was observed in 2 subjects (2.6%), nasal secretion in 6 (7.9%), turbinates hypertrophy in 24 (31.6%), pharyngitis in 2 (2.6%), gastro-oesophageal reflux in 15 (19.7%), as assessed by 24hr intraluminal oesophageal pH monitoring; furthermore mood disorders were reported in 4 cases (5.3%), other diseases in 4 (5.3%).

Pertinent medical history is summarized in Table III: allergic rhinitis was present in 43 patients (56.6%), milk intolerance in 10 (13.2%), asthma in 7 (9.2%), atopic dermatitis in 3 (3.9%), drugs (aspirin/FANS and penicillin/derivatives) allergy in 9 (11.8%).

The percentages of allergic and not allergic subjects are shown in Figure 1.

Subjects suffering from one, two or three kinds of allergy were, respectively, 44 (57.89%), 13 (17.11%), and 1

<table>
<thead>
<tr>
<th>Table I. Laryngological assessment (the total percentage is higher than 100 because some subjects are suffering from more than one disease).</th>
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<tbody>
<tr>
<td>%</td>
</tr>
<tr>
<td>Poor glottic closure</td>
</tr>
<tr>
<td>Hyperkinesia</td>
</tr>
<tr>
<td>Vocal fold redness</td>
</tr>
<tr>
<td>Polyps</td>
</tr>
<tr>
<td>Vocal fold oedema</td>
</tr>
<tr>
<td>Vocal fold hypertrophy</td>
</tr>
<tr>
<td>Nodules</td>
</tr>
<tr>
<td>Cordectomy</td>
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<tr>
<th>Table II. Otolaryngologic assessment.</th>
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<tbody>
<tr>
<td>%</td>
</tr>
<tr>
<td>Pale nasal mucosa</td>
</tr>
<tr>
<td>Nasal secretion</td>
</tr>
<tr>
<td>Hypertrophy of turbinates</td>
</tr>
<tr>
<td>Pharyngitis</td>
</tr>
<tr>
<td>Gastro-oesophageal reflux</td>
</tr>
<tr>
<td>Mood disorders</td>
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<tr>
<td>Others</td>
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Fig. 1. Percentages of allergic and non allergic subjects.
Correlation between allergy and dysphonia

A total of 58 patients (76.32%) affected by dysphonia were allergic. As far as concerns the correlation between sex and allergy, manifestations of allergic disorders have been found in 6 males and 52 females. The application of Pearson’s chi square revealed a significant association between female sex and presence of allergy in patients suffering from dysphonia (Pearson’s chi square = 7.89, p = 0.005).

 Furthermore, sex was considered a “risk factor” and was associated with each pathological condition detected. A statistically significant association has been pointed out between female sex and presence of allergy (OR 5.51; CI: 1.55 - 19.63). In the same subjects female sex status resulted a “protective factor” against gastro-oesophageal reflux (OR 0.12; CI: 0.03 - 0.46) (Table IV).

The same statistical analysis had been carried out referring to each above-mentioned disease. The results were not shown in the Tables because the respective associations were not significant.

Discussion

Together with other organs of the supraglottic vocal tract, the nose is responsible for vocal quality, timbre and the perceived character of all speech sounds. A recent study focusing on acoustic estimation of the voice when incorrect resonance function of the nose takes place, showed that in patients (aged from 5 to 15 years) with seasonal allergic rhinitis, presenting also bronchial asthma, the mean Jitter and Shimmer values were higher than in the control group, but the values did not show a statistically significant difference.

The most common acute vocal fold injuries are submucosal haemorrhage and mucosal tears.

Our laryngoscopic examination revealed the presence of muscle tension dysphonia in 25 patients (32.9%), hypertrophy in 9 (11.8%), redness in 9 (11.84%), polyps in 4 (5.3%), oedema in 3 (3.95%), vocal fold hypertrophy in 4 (5.3%), nodules in 32 (42.1%), cordectomy in 2 (2.6%).

Most patients suffering from vocal fold haemorrhages have concurrent reflux, asthma or allergy. Chronic laryngeal disorders include vocal nodules, polyps and vocal fold oedema. The latter can result from chronic inflammation, environmental allergy, inhaled irritants, poor vocal technique, or any combination of these factors.

In our study, a pale nasal mucosa was observed in 2 subjects (2.6%), nasal secretion in 6 (7.9%), hypertrophy of the turbinates in 24 (31.6%), pharyngitis in 2 (2.6%), gastro-oesophageal reflux in 15 (19.7%), as assessed by 24-hour intra-luminal oesophageal pH monitoring.

The larynx is seldom mentioned in the reports on allergy of the upper and lower respiratory system. In spite of this lack of information, allergic reactions of the larynx exist, but they are not usually diagnosed or are misdiagnosed: only in the case of anaphylactic reaction does the severe impairment of the airways draw the attention to the relationship between allergy and larynx. The existence of a direct allergic response in the larynx has meaningful implications for the diagnosis and treatment of dysphonia.

A direct demonstration of laryngeal allergy has been obtained by applying drops of an antigen solution to the arytenoid mucosa and then carrying out a cytodiagnostic study of the site. The latter demonstrated the degranulation of the plasma cells.

The presence of mast cells in the larynx had been demonstrated in the human embryo, although the mast cell count in the larynx was lower than in the trachea and bronchi.

In the study carried out by Haapanen, the provocation of voice disorders had been performed by spraying the allergen onto the posterior wall of the pharynx in order not to elicit the laryngeal protective reflex: the hypersensitivity to house dust proved to induce laryngeal dysfunction. The latter had been demonstrated by indirect laryngoscopy and by voice recordings, analyzed with a Sonagraph or with a real-time spectrograph.

Immediate allergic laryngitis by pollen and mites had been reported by Buczylko et al.: 34 allergic patients, revealed by positive skin prick tests, confirmed a change in vocal cord status after natural provocation.

Takeda et al. proposed five features as diagnostic criteria for laryngeal allergy:

- History: past or family history of allergic disease.
- Symptoms: cough, foreign body sensation in the throat and sputum.
- Local findings: oedema and pale arytenoid mucosa.

### Table III. Pertinent medical history of allergy.

<table>
<thead>
<tr>
<th>Allergy</th>
<th>%</th>
<th>N</th>
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<tbody>
<tr>
<td>Allergic rhinitis</td>
<td>56.6</td>
<td>43</td>
</tr>
<tr>
<td>Milk intolerance</td>
<td>13.2</td>
<td>10</td>
</tr>
<tr>
<td>Asthma</td>
<td>9.2</td>
<td>7</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>3.9</td>
<td>3</td>
</tr>
<tr>
<td>Intolerance to drugs</td>
<td>11.8</td>
<td>9</td>
</tr>
</tbody>
</table>

### Table IV. Associations (Odds Ratio - OR confidence interval up to 95%) between some diseases and sex (* Statistically significant differences OR adjusted for age).

<table>
<thead>
<tr>
<th>Sex</th>
<th>OR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>5.51</td>
<td>(1.55-19.63)*</td>
</tr>
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<table>
<thead>
<tr>
<th>Reflux</th>
<th>OR</th>
<th>(95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Male</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.12</td>
<td>(0.03-0.46)*</td>
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</tbody>
</table>
Laboratory data: eosinophilia in the peripheral blood, positive intradermal reactions.

Treatment: efficacy of anti-allergic and antihistamine agents.

Foods, bee sting, drugs, and inhalants had already been mentioned since the first decades of the past century as factors involved in the pathogenesis of chronic laryngitis and oedema of the vocal folds 13-17.

According to Williams 18, the mechanism of allergic laryngitis is primarily oedema formation in the entire larynx or in specific portions such as arytenoids or vocal folds. The oedema of the contact surface of the true vocal cords produces hoarseness, which is a quality of the voice that is harsh, discordant and of low pitch. In fact, the oedema changes the size and the rigidity of the vibrating mass, interfering with the pitch and the proprioceptive sensations through which the voice is controlled during speaking and, more important, during singing.

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The main aetiological factors are inhalants (house dust, moulds, animal danders, feathers) and pollens. Williams 18 mentioned three basic types of food allergens as being responsible for mild to severe oedema of the laryngeal structures:

- **Fixed food allergy** will still produce symptoms on each ingestion, regardless of the time when it was eliminated from the diet or the amount ingested.
- **Cyclic food allergy**, which can be controlled by elimination or rotation of a food in the diet, while continuative usage is responsible for sensitization and symptoms.
- **Thermal food allergy**, which is triggered by the exposure to a low temperature “critical for the patient”.

Particles of dietary antigens may adhere to the mucosa of the arytenoid region and consequently may cause direct oedema in this region 12.

In our study, we have reported milk intolerance in 10 patients (13.2%). On the other hand, inhaled antigens may enter the postnasal drip and may reach the arytenoid region by mucociliary transport 12.

Laryngeal oedema may be the only symptom of hypersensitivity to salicylic acid or other substances which affect the biosynthesis of prostaglandins, such as other analgesics or certain colour additives and preservatives in food 19. We have found allergy to drugs in 9 cases (11.8%): 3 were allergic to salicylic acid and FANS, 6 were allergic to penicillin and derivates.

In the event of allergic rhinitis, the hypersecretion of the nasal glands is responsible for a postnasal drainage onto oropharyngeal and laryngeal tissue: the consequences are throat clearing, irritating cough, and dysphonia 20. According to our study, allergic rhinitis was present in 43 patients (56.6%).

Another mechanism hypothesised to explain cases of dysphonia secondary to allergic rhinitis is based on the presence of rhino-laryngeal reflexes: the presence of vasomotor and secretomotor fibres of sympathetic and parasympathetic origin have been demonstrated in the mucosa and in the musculus vocalis, particularly in the posterior third of the vocal cords 21-22.

Specific receptors in the laryngeal mucosa are sensitive to negative pressure in the nasal cavity and in the rhinopharynx 23. A negative nasal pressure due to allergic rhinitis is responsible for a reflex increase of the muscular activity of the posterior crico-arytenoid, as recorded by electromyography 24.

Another correlation between allergic rhinitis and vocal disorders may be mediated by the diminished hearing. In fact, it has been estimated that serious otitis occurs in about 66% of children affected by allergic rhinitis 1. The consequent conductive hearing loss may induce vocal abuse.

Gastro-oesophageal reflux is not a rare finding in laryngeal disorders 25. Professional voice users, whose performances need an increase of abdominal pressure are at high risk of gastro-oesophageal reflux disease (GERD). We have found gastro-esophageal reflux in 15 patients (19.7%).

Both allergic reactions and autonomic imbalance may result in the respiratory mucosa becoming hyper-reactive to unspecific irritants 26.

The methacholine challenge may show a non-specific bronchial reactivity in professional voice users presenting with voice complaints and responding to bronchodilators and to allergy-directed therapy. In other words, in these patients, the hyperventilation associated with performing is responsible for an exercise-induced asthma-like condition, related to voice dysfunction: resolution of the vocal complaints has been recorded in conjunction with a decrease in methacholine reactivity 27.

A history of seasonal/perennial allergy symptoms was reported in 37% of 150 patients seen by Altman et al. 28. The total prevalence of allergic rhinitis was 87% in the group of singers studied by Hamdan et al. 29. Both figures exceeded the average prevalence of 25% observed in the general population 30.

In our study, muscle tension dysphonia and nodules were present, respectively, in 32.9 and in 42.1% of the subjects. As 76.3% of patients presenting with dysphonia were also allergic, it may be concluded that this result is higher than the well-known average prevalence of 25%.

With regard to the association between female sex and presence of allergy in patients suffering from dysphonia, the application of Pearson’s chi square revealed a significant association between female sex and presence of allergy in dysphonic patients (Pearson’s chi square = 7.89, P = 0.005). Furthermore, sex was considered as a “risk factor” and was associated with each disease detected. A statistically significant association had been revealed between female sex and presence of allergy in patients suffering from dysphonia (OR 5.51; CI: 1.55-19.63). In the same subjects being female was shown to be a “pro-
tective factor” against gastro-oesophageal reflux (OR: 0.12; CI: 0.03-0.46) (Table IV). This same statistical analysis was shown to be not significant for the other above-mentioned diseases.

Conclusions
According to our study, allergy testing should be performed routinely on female professional voice users. Singers, actors, teachers, physicians, politicians, secretaries, call-centre operators, football quarterbacks are the best known people whose voice troubles impair job performances 30. Dust and mold found in curtains and trappings, chemical fumes, smoke, animal exposure, costumes, perfumes, cosmetics are only a few examples of the several common and less common antigens, that can be responsible for allergic problems. Mild respiratory disorders, that may not be particularly relevant in the general population, must be taken into serious consideration in female professional voice users, who may primarily complain of vocal dysfunction rather than upper and lower respiratory diseases 20. Twenty-four-hour intraluminal oesophageal pH monitoring should be included in the diagnostic examinations, particularly in the case of males. If chronic vocal disorders are the reason for therapy, the possibility of allergy as the cause should be carefully evaluated 31 and skin prick testing is mandatory. We agree with Pedersen et al. 4 that the doctors should examine any other diagnosis besides “dysphonia” and “dig down to” any of the medical reasons of the “non-organic disorders”. Therefore, we can conclude with the recommendation made by Moore 32 to remember that “the remediation of voice disorders encompasses more than voice assessment and voice exercises”.

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