Gastroesophageal reflux disease correlation with posterior laryngitis

Povezanost gastrointestinalne reluksne bolesti sa posteriornim laringitisom

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Abstract

Background/Aim. Over the last years numerous studies have been performed dealing with mutual relations among gastroesophageal reflux disease (GERD) and numerous diseases of the upper airways. The aim of the present study was to establish possible causal relationship between GERD and posterior laryngitis (PL). Methods. The study included 103 patients with gastrointestinal complaints. Diagnostic procedure included a medical history, gastroscopy and laryngeal directoscopy. The obtained data processed using classic methods of the descriptive statistics, as well as Pearson's chi-square test, Student's t test, rank sum test and Fisher's parametric analysis of variance. Results. Out of the total number of 103 examined patients, 33 (32%) were diagnosed with PL, while GERD was diagnosed in five of the examined patients all belonging to the PL group (15% of the patients with PL). In the remaining patients, PL was caused by other factors. All the patients with GERD had PL and globus sensation while 80% of GERD patients had prominent symptom of pain. Conclusion. The results of the study are indicative of the causal relationship between GERD and PL.

Key words: gastroesophageal reflux; laryngitis; diagnosis; gastroscopy; laryngoscopy; diagnosis, differential.

Introduction

Over the last several years numerous studies on association and/or causal relationship among gastroesophageal reflux disease (GERD) and numerous other diseases (e.g. laryngeal malignancy, otitis, cricoarytenoid joint fixation, posterior laryngitis, pachyderma, granulomatous laryngitis, asthma, rhinosinusitis, subglottic stenosis, contact ulcer, Rainker's edema) affecting airways, accompanied by diverse symptoms, have been performed. This study was conducted to identify inflammation of the back portions of the larynx – posterior laryngitis (PL) and its association with the GERD.

The lack of evidence or insufficient evidence on association between GERD and PL are not indicative of the lack of the association, while a confirmed association is not the evidence on the causal relation.

In-between two extreme claims – the first stating that reflux laryngitis is not a separate clinical entity and the second one stating the reflux laryngitis is a real clinical entity, there have been numerous studies controversially presenting association or causative relations between the diseases.
The most ardent opponents of the causative relationship between GERD and PL argue that no direct evidence on laryngeal defects induced by gastric reflux is available, and in spite of availability of the indirect evidences, they consider the association between laryngitis and GERD to be unspecific, since the diagnosis of one of the diseases does not necessarily mean the other disease is present. Only 10–20% of PL patients are diagnosed with GERD 3,4.

Posterior laryngitis is considered to be the entity characterized by edema and hyperemia of the interarytenoid region and arytenoids, with mucous bridge (assuming the accumulation of mucus which extends, in the form of bridge, between arytenoids), in-between and different extent of prominence, enabling the classification in three types depending on the prominence of the above-mentioned characteristics. Posterior laryngitis was defined by Hanson score dated from 1988, and currently it is applicable for PL diagnosis.

In addition to GERD, PL also associated with smoking, alcoholism, antibiotics, corticosteroid inhalation, persistent cough, changed esophageal motility caused by different factors.

Pathohistological PL substrate is a loss of the cilia on the cells of the cylindric laryngeal epithelium 5,6.

The symptoms are diverse, ranging from occasional hoarseness to the loss of voice, cough, globus sensation, enhanced salivation and pain 2,5,7.

Red score was established in patients with PL, using quantitative color analysis of erythema developing in this disease 5. Moreover, the conclusion was drawn based on the studies that symptoms and signs of the PL were improved after administration of omeprazole – proton pump inhibitor (PPI), to be relapsed subsequent discontinuation of the therapy. It was concluded at the same time that numerous patients with PL do not have esophagitis, and thus it is possible that they have non erosive GERD (NGERD) 3,4.

Proton pump inhibitors are indispensable in the therapy lasting 3–6 months, twice a day, although the issue of PPI therapy lasted at least three months. The Fisher's exact probability test was applied in numerical characteristics for one or two characteristics. The rank sum test as a nonparametric test for comparison of difference between frequencies of PL and GERD relations.

Methods

The study included 103 patients with gastrointestinal complaints. All of the patients were examined at the polyclinics of otorhinolaryngology and gastroenterology. The examinations were performed over the period January–June 2005.

The study was prospective, randomized (patients were admitted from the general practitioner to the otorhinolaryngologists, and were selected with symptoms listed in the text), unicentric.

The following parameters were defined for the purpose of the present study:

- PL: hyperemia, edema of arytenoids and interarytenoidal regions with mucous bridge involving 0.5 cm around the arytenoids;
- GERD: Endoscopic evidence on esophageal inflammation in patients with complaints.

Diagnostic procedure was performed in all the patients including: medical history, indirect laryngoscopy, laryngeal directoscopy and gastroscopy. The patients were examined by a flexible endoscope, and the results were simultaneously recorded by VHS system. The material was examined by the same device and on the same monitor by two gastroenterologists and otorhinolaryngologists, respectively.

The medical history included provision of information on certain symptoms or habits: pharyngeal pain, hypersalivation (symptom defined on the basis of medical history), cough, hoarseness, globus sensation (defined by patients as a sensation of a ball in the throat, or something present in the throat, constant irritation provoking cough or swallowing), nocturnal dyspnea, snoring, asthma, rhinosinusitis, alcoholism, heartburn and smoking.

We have compared the presence or absence of certain symptoms with respect to PL or GERD, patient’s sex and age and mutual PL and GERD relations.

Description of the numeric characteristics was performed in our study using classic methods of the descriptive statistics, ie, arithmetic mean and mean value median, as well as using standard deviation, variation coefficient and standard error as measures of variability, including minimal and maximal values. Relative numbers are used in all tables.

Depending on the nature of the variables themselves, analysis of the results was carried out using the Pearson’s \( \chi^2 \) statistic, in the form of congruence tests and contingency tables, for comparison of difference between frequencies of nonparametric characteristics for one or two characteristics. The Fisher's exact probability test was applied in numerical limitations of the table two-by-two.

Comparison of the average values of the parametric characteristics was performed using the Student’s \( t \) test for the two groups of data. The rank sum test as a nonparametric supplement was applied in independent samples, while the equivalent paired test was applied in the dependent samples.

For comparison of three or more groups of data, the Fisher's parametric analysis of variance (ANOVA) was used for parametric data while nonparametric analysis of variance was used for nonparametric data.
The methods of single correlation and regression were used in analysis of association.

In all the applied analytical methods the level of significance was 0.05.

Logistic regression was used in the analysis of influence of symptoms on the outcome, i.e., type of the disease.

The ANOVA with proportions was used in analysis of the mutual relationship between PL and GERD.

Database and data processing were performed using the Institute program developed by the Institut of Medical Statistics and Informatics, Faculty of Medicine, Belgrade.

Results

The total of 103 patients were examined at the poly clinics of otolaryngology and gastroenterology, out of whom 53 were males, mean age 58 years, and 50 females, mean age 60 years. The youngest patient was aged 23 and the oldest one was 80 years.

An increased salivation, cough, globus and smoking were all individually related to PL and documented in the presented results.

The analysis of habits and symptoms of the examined patients according to their sex revealed statistically significant distribution of nocturnal dyspnea in females ($p < 0.05$), while rhinosinusitis ($p < 0.01$), alcohol use ($p < 0.01$) and cigarette smoking ($p < 0.01$) were evidenced in males. As for the distribution of PL and GERD according to sex, no statistically significant differences were evidenced.

The presence of enhanced salivation in the patients with PL was evidenced in almost one half of the patients with PL (Table 1). Analysis of the relation between PL and enhanced salivation evidenced statistically significant difference between the studied groups ($\chi^2 = 8.826; df = 1; p < 0.05$). It may be explained by more frequent presence of the enhanced salivation the symptom in patients with PL (45.4%) in comparison to those without this finding (17.1%) (Table 1).

The incidence of cough symptom in PL patients was high, since it was evidenced in 20 out of the total of 33 patients. Analysis of the relation between PL and onset of cough evidenced the presence of statistically significant difference between the observed groups ($\chi^2 = 9.129; df = 3; p < 0.05$). The difference may be explained by greater presence of cough symptoms in patients with PL (60.6%) in comparison to those free of this finding (37.1%) (Table 1).

The share of smokers in the PL group of patients was statistically significant ($p < 0.05$) (Table 2). Analysis of relation between PL and cigarette smoking evidenced statistically significant difference between the observed groups ($\chi^2 = 10.074; df = 3; p < 0.05$). The difference is explained by higher incidence of the habit among the patients with PL (48.5%) when compared to those free of PL finding (21.4%).

The analysis evidenced statistically significant correlation between PL and enhanced salivation, cough, globus phenomenon and smoking ($\rho$ correlation coefficient is (in the same order) 0.277; 0.268; 0.298 and 0.310 while in all cases $p < 0.05$). Smoking was the factor most frequently associated with PL.

Heartburn was present in 23 patients in the PL group (33 patients) ($p < 0.05$) and in three patients in the group with GERD.

Pain as a symptom was present in the majority of the GERD patients. Analysis of the relation between the presence of GERD and onset of pain evidenced the presence of statistically significant difference between the observed groups ($\chi^2 = 6.945; df = 1; p < 0.05$). It may be explained by higher incidence of the symptoms among the patients with GERD (80.0%) in comparison with those free of such finding (20.4%) (Table 2).

Globus sensation was present in all the patients with GERD. Analysis of the relation between GERD finding and globus phenomenon evidenced the presence of statistically significant difference ($\chi^2 = 7.844; df = 1; p < 0.01$). The difference is explained by the presence of the symptom in all the patients with GERD (100%) in comparison with those free of this finding (33.7%) (Table 2).

The patients with GERD were eight years older (67.5) at the average from the group without the finding (59) and the obtained difference was statistically significant ($t$ test; $t = 4.138, p < 0.05$).

The analysis evidenced statistically significant association of GERD with pain, and globus phenomenon (correlation of coefficient was 0.246 and 0.263, respectively with $p < 0.05$ in both cases). The relation of smoking and GERD was analyzed, and 60% of GERD patients were smokers.

### Table 1

<table>
<thead>
<tr>
<th>Patients</th>
<th>Enhanced salivation</th>
<th>Cough symptom</th>
<th>Globus sensation</th>
<th>Smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>Total</td>
<td>No</td>
</tr>
<tr>
<td>Without laringitis posterior</td>
<td>58</td>
<td>12</td>
<td>70</td>
<td>44</td>
</tr>
<tr>
<td>With laringitis posterior</td>
<td>18</td>
<td>15</td>
<td>33</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>76</td>
<td>27</td>
<td>103</td>
<td>57</td>
</tr>
</tbody>
</table>

Globus sensations were present in more than a half of PL patients (56.0%) (Table 1). Analysis of the relation between PL and globus phenomenon evidenced the presence of statistically significant difference among the observed groups ($\chi^2 = 10.129; df = 3; p < 0.05$). The difference is explained by higher frequency of the symptom in patients with PL (57.6%) in comparison to the patients free of this finding (27.1%) (Table 1).

Out of 33 patients with PL, five (15%) had GERD in our study, and all the patients with GERD were in the group of patients with PL.

Analysis of the relation between GERD and the presence of the PL evidenced the presence of a statistically significant difference ($\chi^2 = 8.058; df = 1; p < 0.01$). The difference may be explained by greater frequency of the disease among the patients with GERD (100%) in comparison with those free of the finding (28.5%) (Table 3). The result evidenced that patients with GERD by far more frequently also have PL (the odds for one with GERD to develop the PL is 4:1 in comparison to those without GERD).

The analysis evidenced that the onset of enhanced salivation, globus phenomenon and smoking were the most frequent in patients with PL while the most frequent complaints of GERD patients include pain, and globus sensations, and all of them had PL.

Our study did not review the relation of laryngeal cancer and chronic laryngitis with GERD and PL.

### Discussion

The epithelium covering laryngeal mucosa is dual: pseudostratified, cylindric, ciliated covering most of the larynx and stratified squamous epithelium without keratinization, covering vocal cords and upper epiglottic surface.

Stratified squamous epithelium of the esophageal mucosa has a function of defense against reflux attack acidity, while supraesophageal structures do not have such functions, and thus clinical diagnosis of GERD may be impossible due to the absence of the evident epithelial metaplasia, while, as opposed to this, clinical manifestation of PL induced by reflux is present

The reflux attack with its acidity, ie, pepsin, causes mucosal ulcerations and submucosal hemorrhages, while trypsin causes submucosal edema; however the cause of chronic inflammation in otorhinolaryngology region caused by GERD is still doubtful.

The results of our study are similar to those reported in most of the analyzed studies: out of 103 examined patients, 33 (32%) had PL, out of whom five also had GERD, which makes 15%, while the incidence of PL was reported in 35%, while GERD incidence ranged between 10 and 20%.

Out of 33 patients with PL, GERD was evidenced in five (15%) while the remaining had PL caused by other factors. The patients with GERD were in the group with PL. The onset of PL in the remaining 28 patients with no GERD could be explained by insufficiently long episodes of the gastric reflux (number of attacks and their duration), to produce epithelial metaplasia on the resistant esophageal mucosa, necessary for diagnosis of GERD. The presence of NGERD associated with PL is possible. A patient may still have PL in spite of the lack of any changes on the esophageal mucosa or significant changes of pH environment.

It has been observed that GERD is present in 60% of patients with chronic laryngitis, as well as in 71% of patients with laryngeal carcinomas. The studies have evidenced that the onset of the reflux laryngitis is in the function of time of exposure to the reflux. The duration of exposure and number of attacks are in the close positive correlation with GERD. It has been evidenced that the treatment of PL patients with PPI leads to favorable response – their complaints are ameliorated and clinical findings are improved. Six out of twelve PL patients responded to PPI therapy in comparison to only one positive response among 10 patients who received placebo.

Regular monitoring of patients with gastroesophageal reflux is recommended using videostroboscopy, occasional biopsies and PPI treatment lasting for at least three weeks. Although other authors report different duration of PPI therapy, our approach is three months minimum. In patients with continual difficulties and clinical findings, the therapy was continued even after three months. The therapy was corrected/discontinued on regular controls if a patient changed his/her lifestyle and type of nutrition, which, in synergism with therapy, contributed to the treatment of disease.

### Table 2

| Onset of pain and globus sensations in patients with gastroesophageal reflux disease (GERD) |
|---|---|---|---|---|---|---|---|---|---|
| Patients | Pain | | | Globus sensation | | | | | |
| | No | % | | Yes | % | Total | No | % | Yes | % | Total |
| Without GERD | 78 | 75.7 | 28 | 91.4 | 106 | 62.1 | 33 | 32 | 95.1 |
| With GERD | 4 | 3.8 | 5 | 4.8 | 9 | 0 | 5 | 4.8 | 5 | 4.8 |
| Total | 82 | 76.7 | 33 | 23.3 | 115 | 100 | 38 | 36.9 | 103 | 100 |

### Table 3

| Mutual relation between posterior laryngitis (PL) and gastroesophageal reflux disease (GERD) |
|---|---|---|---|---|---|---|---|
| Diagnosis | PL [n (%)] | | | | Total | |
| | Absent | Present | | | | |
| GERD | n | % | n | % | n | % | n | % |
| Absent | 70 | 67.9 | 28 | 27.2 | 98 | 95.1 |
| Present | 0 | 0 | 5 | 4.9 | 5 | 4.8 |
| Total | 70 | 67.9 | 33 | 32.1 | 103 | 100 |
In case of suspected PL, omeprazole test may be performed in order to verify or rule out the diagnosis \textsuperscript{11}. The effects of omeprazole treatment of GERD were evidenced by videostroboscopic monitoring of the changes and vocal correlated improvements were observed \textsuperscript{5}. The patients with PL without GERD underwent omeprazole treatment and after improvement of the local findings in PL patients, indirect correlation of the two diseases is evidenced. The former justified treatment of PL patients with PPI \textsuperscript{3, 10}. Successful PPI therapy of patients with established PL not diagnosed with GERD is indirect evidence on the presence of NGERD disease. The patients with diagnosed PL were administered PPI although GERD was not confirmed by gastroscopy. Their being cured is indirect evidence of NGERD.

Six out of twelve patients with PL had the abnormal hypopharyngeal pH values, but also two out of 10 healthy individuals had abnormal pH value, which may lead to conclusion that pH value is not significantly correlated with the diseases of the posterior portions of the larynx \textsuperscript{9, 10}.

The studies on patients with globus phenomenon mostly evidenced the diagnosis of achalasia and disturbed motility of the esophagus, while GERD and PL were rare \textsuperscript{12}.

The results of our study indicate that GERD is not correlated with sex, smoking and heartburn, which is consistent with the results of other authors obtained on patients with globus phenomenon \textsuperscript{13}.

In our study, cough and globus sensation were evidenced in 38% and 27% of PL patients, respectively as opposed to 51% of patients with cough and 47% of those with globus sensation evidenced also in patients with PL \textsuperscript{14}. The highest statistical significance of the disturbed pH finding is observed in patients with laryngeal carcinomas (71%) and patients with stenosis (78%) followed by patients with globus sensation (58%) and those with PL (60\%) \textsuperscript{15}.

Neither edema nor erythema are specific sign and erythema is not necessarily associated with the reflux. Nevertheless, it is expected from further studies to elucidate the problem \textsuperscript{2}.

**Conclusion**

The study confirmed an association between GERD and PL, although a significant number of PL patients were free of GERD. The most frequent common symptom for both PL and GERD is globus phenomenon.

Despite the association between GERD and PL was confirmed it is necessary to provide more evidence in order to prove that GERD causes this pathological condition. The presence is not as equal as causality.

In the meantime, treatment of PL using PPI has been of most importance in patients with no other possible causes. Therapeutic procedure is determined by clinical examination, laboratory analysis and endoscopic examinations, however, clinical judgment is necessary and it leads to final decision when the available evidence provides no clear answer.

**References**


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