Typical and atypical symptoms of laryngopharyngeal reflux disease

Rūta Pribuišienė, Virgilijus Uloza, Laimas Jonaitis

Clinic of Otorhinolaringology, Clinic of Gastroenterology, Kaunas University of Medicine, Lithuania

Key words: laryngopharyngeal reflux disease, typical, atypical symptoms.

Summary. The aim of the study was to evaluate and compare intensity and incidence of both, typical (heartburn, acid regurgitation) and atypical (hoarseness, throat clearing, globus pharyngeus) symptoms of laryngopharyngeal reflux disease among 72 patients and 123 healthy persons. Diagnosis of laryngopharyngeal reflux disease in 58 cases (80.6%) was confirmed by endoscopic and histological findings of esophagitis and in 14 cases (19.4%) by Omeprasol test. The intensity of the symptom was calculated by multiplication of the intensity and frequency of the symptom. According to the data obtained laryngopharyngeal reflux disease manifested more frequently with atypical symptoms. In the patients’ group mean intensity of hoarseness was 5.29±0.74 points, mean index of hoarseness 7.06±1.35 points. Typical symptoms were found only in 14–22% of patients. The mean intensity of heartburn was 2.6±0.66 points, mean index of heartburn was 4.73±1.02 points. The incidence of atypical symptoms was three times higher than the incidence of typical symptoms (p<0.05).

According to the multinomial logistic regression analysis the combination of three atypical symptoms (hoarseness, throat clearing and globus pharyngeus) separated groups of the patients and healthy persons. The combination of these symptoms increases the odds ratio for laryngopharyngeal reflux disease 59.7 times. Idiopathic hoarseness as a single symptom increases the odds ratio for laryngopharyngeal reflux disease 85 times.

Introduction

Laryngopharyngeal reflux disease (LPRD) is the retrograde extraesophageal reflux of gastric contents into the larynx, pharynx, trachea and bronchus. Clinical manifestation and symptoms of LPRD distinctly differ from the pattern of typical gastroesophageal reflux disease (GERD) followed with esophagitis (1). LPRD represents itself as atypical form of GERD. Typical GERD manifests with typical symptoms (TS): heartburn, acid regurgitation and endoscopically proved esophagitis. The most frequent and specific typical symptom is heartburn (2). According to the literature LPRD often manifests with atypical symptoms (AS): hoarseness, globus pharyngeus, throat itching, throat clearing, “too much throat mucous”, cough, asthma, dysphagia or/and odynophagia (1, 3-6).

The diagnostics of GERD is based on detection of combination of TS, reveal of pathological reflux monitored by esophageal pH-metry and endoscopically proved esophagitis. However, these pathological changes are not frequent in LPRD patients: proximal pathological reflux was found by pH-metry only in 1/3 of patients, erosive esophagitis endoscopically was diagnosed only in 1/4 of patients (3, 7). Furthermore, it is known about existence of non-erosive form of esophagitis with increased sensitivity and good regeneration of esophageal mucousa (9).

As the specificity and sensitivity of the conventional diagnostic methods of GERD is rather low, diagnostics of LPRD often is based on analysis and monitoring of changes of specific symptoms in response to antireflux treatment (Omeprasol test) (1, 2, 10). For the diagnostics and treatment of LPRD it is necessary to evaluate both, typical and atypical groups of the symptoms, because they reflect pathological changes in different organs or systems caused by pathological reflux. Detection of the severity and frequency (for example, times per week) of the symptoms is also of great importance (6). Various questioners and scales for the evaluation of the intensity of the symptoms filled in by the patient have been...
used in several studies (6, 11, 12). Comprehensive analysis of typical and atypical symptoms of LPRD is very important for the diagnostics of the disease, comparison of different methods of treatment and evaluation of treatment efficacy.

The goal of the study was to evaluate and compare intensity and prevalence of typical and atypical symptoms of GERD among LPRD patients and healthy persons, to define the most important symptoms for the diagnostics of LPRD.

Material and methods

The patients’ group consisted of 72 outpatients of the Department of Otalaryngology of Kaunas University of Medicine (KMU) who during the period of 2001-2002 years due to idiopathic hoarseness, throat clearing, throat itching, globus pharyngeus and characteristic laryngeal findings were suspected for LPRD. There were 27 males (mean age 43.9±12.7 years) and 45 females (mean age 40.0±13.1 years). The age of the patients was from 17 to 64 years (mean 40.1±12.7). There was no gender related age difference (p=0.22). Diagnosis of LPRD was confirmed by: 1) endoscopically or/historologically proved esophagitis, 2), improvement of characteristic laryngoscopic and voice changes after 4 weeks Omeprsol 20 mg b.i.d treatment (1, 2, 10) in cases when esophagitis was not diagnosed. Persons with infections of the upper respiratory tract, mass lesions of the vocal cords (nodules, polyps, cysts, Reinke-Hajek disease), mechanical or chemical injures of the larynx and who used antireflux medical therapy for two months were not included into the study.

Control group consisted of 123 healthy persons (employers and students of KMU). The possible symptoms of GERD have never disturbed working capacity and night sleep of these persons and they never consulted a doctor due to possible GERD symptoms. There were 55 males (mean age 38.4±13.8 years) and 68 females (mean age 35.9±13.4 years). The age range in the control group was from 22 to 72 years (mean 36.9±13.6 years). There was no gender related age difference (p=0.31).

A special questionnaire was designed to evaluate two most specific typical (heartburn and regurgitation) and three atypical (hoarseness, throat clearing, globus pharyngeus) symptoms of GERD. A 10 cm long visual analogue scale (VAS) was used for the evaluation of the intensity of the symptom (11). The patients were asked to rate their symptoms on the scale, ranging from the absence of the symptom to the most severe intensity of the symptom, by marking a slash mark where they felt it was appropriate. A score of 0 indicated absence of the symptom; a score of 10 indicated the most severe intensity of the symptom.

The frequency of the typical symptoms (heartburn and regurgitation) of GERD was rated from 0 to 2 points: 0 – absent, 1 – one-three times per week, 2 – more then three times per week. A heartburn index (Hbi) and regurgitation index (RI) were calculated by multiplication of the intensity and frequency of the each symptom. The range of the possible values of the indexes was from 0 to 20 points. The sum of Hbi and RI was considered as the typical symptoms index (TSI). The possible range of TSI was from 0 to 40 points.

The intensity of atypical symptoms (hoarseness, throat clearing, globus pharyngeus) of GERD was evaluated according to the VAS scale from 0 to 10 points. Frequency of these symptoms was evaluated from 0 to 2 points: 0 – absent, 1 – recurrent, 2 – permanent. A hoarseness index (HoI), throat clearing index (TCI) and globus pharyngeus index (GPI) were calculated by multiplication of the intensity and frequency the each symptom. Intensity of throat clearing and globus pharyngeus was evaluated according to the VAS scale from 0 to 10 points. However, frequency of these symptoms was evaluated only as “recurrent” (1 point). Therefore, the possible values of TCI and GPI ranged from 0 to 10 points. The values of HoI ranged from 0 to 20 points in relation to recurrent hoarseness (1 point) or permanent hoarseness (2 points). The sum of HoI, TCI and GPI was considered as the atypical symptoms index (ASI). The possible range of ASI was also from 0 to 40 points.

Evaluation of the other six more rare atypical symptoms of GERD (inspiration dyspnea, throat itching, chronic and night cough, dysphagia and odynophagia) was performed as well. Frequency and correlation of both, typical and atypical symptoms were calculated in control and patients’ groups. According to the multinomial logistic regression analysis the combination of atypical symptoms separating LPRD patients and healthy persons was detected.

Statistical analysis was performed using SPSS 10.0 (Statistical Package for Social Sciences) for Windows. The confidence interval was 0.95. The power of the tests was not less then 0.95. Student’s t test was used for the comparison of the groups’ means. Spearman’s correlation coefficient r was used for the detection of correlation (weak correlation r<0.3, middle correlation 0.3<r<0.8, strong correlation 0.8<|r|<1) (14).
The study was approved by the Independent Ethical Commission of Kaunas University of Medicine.

**Results**

*Diagnostics of LPRD.* In 58 cases (80.6%) LPRD diagnosis was confirmed by esophagitis proved endoscopically or/histologically. In 14 cases (19.4%) diagnosis was confirmed by Omeprosol test.

*Comparison of the intensity of TS and AS.* The mean values both, of intensity and indexes of TS and AS of control group differed significantly from the respective values LPRD patients’ group (Table). There was no significant difference between the mean values of the intensity and indexes of the symptoms in male and female subgroups ($p>0.05$). The mean of TSI in control group was $0.78\pm0.05$ points, the mean of ASI was $2.5\pm1.05$ points; in the patients’ group $5.13\pm1.6$ and $15.76\pm2.3$, respectively.

Heartburn was the most frequent and more intensive typical symptom in the patients’ group: mean intensity was $2.6\pm0.66$ points, mean HbI was $4.73\pm1.82$ points. These values were statistically significantly lower to compare with the mean values of hoarseness (the most frequent atypical symptom): mean intensity $5.29\pm0.74$, mean HoI $7.06\pm1.35$ points, respectively.

*Prevalence of TS and AS.* The most prevalent symptoms of LPRD patients were as follows: hoarseness, throat clearing, throat itching, and globus pharyngeus (Fig.1). These symptoms were found in 74–90% of LPRD patients. However, typical symptoms of GERD (heartburn and regurgitation) were found only in 14–22% of patients. In 41% of persons of control group mean intensity of heartburn was 1.02 points. Thirty-seven percent of persons in control group suffered from throat clearing. However, the persons have never consulted a doctor due to symptoms mentioned above. The prevalence of other symptoms in the control group was significantly lower to compare with heartburn and throat clearing. There was no significant difference among intensity and frequency of hoarseness, throat clearing, and globus pharyngeus. There was a significant difference in prevalence of all symptoms of LPRD (except regurgitation) between patients’ and control groups.

Each LPRD patient indicated more atypical symptoms to compare with the persons of control group. From total number of nine atypical symptoms 18% of patients indicated three symptoms, 33% - four symptoms, 25% - five symptoms, respectively. Persons of control group more frequently indicated 1 – 2 atypical symptoms: 24% of persons – one symptom, 21% - two symptoms (Fig.2).

*Correlation and regression analysis of the symptoms.* A strong correlation was found only among TSI and heartburn ($r=0.87$), TSI and HbI ($r=0.91$), hoarseness and HoI ($r=0.91$), heartburn and HbI ($r=0.98$), regurgitation and RI ($r=0.98$). Moderate

<table>
<thead>
<tr>
<th>Table 1. Means of intensity of typical and atypical symptoms and indexes of the symptoms in control and LPRD patients groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>mean ± CI</strong></td>
</tr>
<tr>
<td>Heartburn (points)</td>
</tr>
<tr>
<td>HbI</td>
</tr>
<tr>
<td>Regurgitation (points)</td>
</tr>
<tr>
<td>RI</td>
</tr>
<tr>
<td><strong>TSI</strong></td>
</tr>
<tr>
<td>Hoarseness (points)</td>
</tr>
<tr>
<td>Hol</td>
</tr>
<tr>
<td>Throat clearing (points)</td>
</tr>
<tr>
<td>Globus pharyngeus (points)</td>
</tr>
<tr>
<td><strong>ASI</strong></td>
</tr>
</tbody>
</table>

HbI – heartburn index, RI – regurgitation index, TSI – typical symptom index,
HoI – hoarseness index, ASI – atypical symptom index, CI – 95% confidence interval.

* significant difference.
correlation was found among ASI and TSI ($r=0.43$), ASI and hoarseness ($r=0.74$), ASI and HoI ($r=0.75$), ASI and throat clearing ($r=0.73$), ASI and globus pharyngeus ($r=0.75$). There was moderate correlation between hoarseness and throat clearing ($r=0.36$), hoarseness and globus pharyngeus ($r=0.33$). A moderate correlation was detected between throat itching and throat clearing ($r=0.39$) and between dysphagia and inspiration dyspnea. Correlation among other symptoms was weak. According to the multinomial logistic regression analysis the combination of three atypical symptoms (hoarseness (Ho), globus pharyngeus (GP) and throat itching (TI) separated LPRD patients and healthy persons. It was found that in the case of this combination of the symptoms, the symptom of hoarseness increases the odds ratio (OR) for LPRD 59.7 times (OR=$59.7$, $p=0.000$; 95% CI – 17.6-203.2), globus pharyngeus – 5.1 times (OR=$5.1$, $p=0.005$; 95% CI – 1.6-16.0), throat itching – 11.6
times (OR=11.6, p=0.000; 95% CI – 3.4-39.1). In case of the presence of these symptoms the patient could be assigned to the LPRD group with the accuracy of 89.7%. The probability of LPRD in accordance with the various combinations of the symptoms was as follows: p (Ho, GP, TI) – 0.98; p (Ho, TI) – 0.89; p (Ho, GP) – 0.78; p (Ho) – 0.42; p (GP, TI) – 0.41; p (TI) – 0.12; p (GP) – 0.06, respectively. (Fig. 3).

It was found that idiopathic hoarseness (without any mass, physical, chemical or thermal lesions or innervation disturbances of the vocal cords) as single symptom increases the odds ratio for LPRD 85.1 times (OR=85.1, p=0.000; 95% CI – 31.9-226.9). In the presence of idiopathic hoarseness the patient could be assigned to the LPRD group in 90.2% of cases.

Discussion
Since the year 2000 several papers related to the various aspects of GERD and laryngology appeared in Lithuanian medical literature (16, 17). However, in these studies only patients with suspected GERD or LPRD were analyzed; the diagnosis was not proved endoscopically and histologically. In the present study LPRD diagnosis in 80.6% of cases was confirmed after endoscopic and histological examination. Only in 19.1% of cases LPRD diagnosis was confirmed by Omeprsol test. This test could be recommended for the safe diagnostics of LPRD in cases when endoscopic examination does not prove esophagitis. However, an endoscopic examination of the digestive tract is necessary in relation to increasing morbidity of esophageal and gastric carcinoma (15). This examination is obligatory in cases of threatening symptoms of digestive tract: bleeding, weight loss (≥3 kg), progressing dysphagia or odynophagia (2).

Despite the fact that GERD symptoms are considered as the most prevalent complains in the population of the developed countries, there are few data about the prevalence of these symptoms among people who consider themselves as healthy and do not consult a doctor. However, some prevalence of typical and atypical symptoms of GERD among healthy persons (which were not considered by these persons as the symptoms of the disease) was found in the present study. Some persons of the control group showed slight intensity heartburn and throat clearing (in average 1.02 points). However, all mean values of the intensity and indexes of typical and atypical symptoms were significantly lower to compare with the mean values of LPRD group patients. There were significantly more (p<0.05) AS in the LPRD patients’ group to compare with the control. The patients most frequently manifested with 3–5 symptoms, the persons from control group – with 1–2 symptoms.

Analysis of the etiology of the most frequent LPRD symptoms was presented in several papers (1, 6, 7, 14, 16). However, there are fewer studies related to the analysis of the intensity and frequency of the symptoms (6). After all, appearance of the symptom of the same intensity once per month or every day can cause pathological changes of different severity in the esophagus, pharynx and larynx. In
this study a modified D.Jaspersen’s (1996) and W.Haberman’s evaluation of the intensity and frequency of the symptoms was used and indexes of the symptoms and TSI and ASI were calculated. According to the data obtained, the mean ASI of the LPRD group was three times higher then the mean TSI (p<0.05). These findings confirm an existing opinion about the prevalence of atypical symptoms among the laryngological patients (1, 3, 7). In our study the LPRD patients also more frequently (74–90% of cases) showed following AS: hoarseness, throat clearing, throat itching, and globus pharyngeus. However, multinomial logistic regression analysis revealed that only combination of three following symptoms – hoarseness, throat itching and globus pharyngeus – significantly separated LPRD patients from healthy persons (Fig.3). This is important for LPRD diagnostics. However, throat clearing was also mentioned relatively often (37% of cases) by persons of the control group, therefore this symptom was not included into the list of the most specific LPRD symptoms.

Only less then quarter of LPRD patients (14–22% of cases) indicated typical symptoms of disturbance of the digestive tract. These findings point out an importance of evaluation of atypical symptoms in the diagnostics of LPRD.

In the LPRD patients’ group both, the mean intensity of hoarseness (the most prevalent atypical GERD symptom (1, 6) and HoI were significantly (p<0.05) two times higher to compare with mean values of heartburn (the most prevalent typical symptom). In the study of 29 patients A.Habermann et all. (1999) found that index of hoarseness was two and half times higher to compare with the indexes of other typical and atypical GERD symptoms (6). In our study the importance of idiopathic hoarseness in the diagnostics of LPRD was proved out. It was determined that idiopathic hoarseness as a single symptom increases the odds ratio for LPRD 85 times. In the case when characteristic laryngoscopic findings were found and LPRD was suspected, the symptom of idiopathic hoarseness in 90.2% of cases allowed to determine patient to the LPRD patients’ group.

Conclusions
1. Atypical symptoms of GERD (hoarseness, globus pharyngeus, throat itching, throat clearing) dominate in the group of LPRD patients – the mean indexes of atypical symptoms are significantly higher to compare with the mean indexes of typical symptoms.
2. In the LPRD patients’ group the mean indexes of atypical symptoms are significantly higher to compare with the mean indexes of atypical symptoms of control group.
3. Combination of three atypical symptoms (hoarseness, throat itching, globus pharyngeus) separates significantly LPRD patients and healthy persons.
4. In the case when characteristic laryngoscopic findings are found and LPRD is suspected, the symptom of idiopathic hoarseness in 90.2% of cases allows to determine the patient to the LPRD patients’ group.

Gerklū ir ryklės reflukso ligos būdingi ir nebūdingi simptomai

Rūta Pribušienė, Virgilijus Uloza, Laimas Jonaitis

Kauno medicinos universiteto Ausų, nosies, gerklės ligų klinika ir ‘Gastroenterologijos klinika’

Raktąžodžiai: gerklė ir ryklės reflukuos ligos, būdingi ir nebūdingi simptomai, simptomų indeksai.

Santrauka. Straipsnio tikslius – įvertinti ir palyginti dažniausią būdingų (rėmuo, atypimas) ir nebūdingų (užkimimas, krenkstimas ir “kašnis” ryklėje) gerklų ir ryklės reflukuos ligos (nebūdingos gastroezofagino reflukuo ligos) simptomų pasireiškimo intensyvumą ir dažnį tarp 72 sergančiųjų ir 123 sveikų asmenų. Dėl nebūdingų simptomų ir pokyčių gerklose įtarus gerklų ir ryklės reflukuos ligą, 58 pacientams (80,6 proc.) diagnozė patvirtinta endoskopinė ar histologinė stabausius ezofagą, likusiems 14 (19,4 proc.) – omeprazolio testu. Specialiame klausymine vertinti du būdingi ir trys nebūdingi simtomės. Padaugius simptomų pasireiškimą intensyvumą ir dažnį, gautas atskirų simptomų indeksas, išvesti bendrieji būdingų simptomų ir nebūdingų simptomų indeksai. Indeksaus lyginti tarpusavyje ir tarp grupių.

Gautais duomenimis, pacientų nurodomi gerklų ir ryklės reflukuos ligos simptomai yra reikšmingai intensyvesni ir dažnesni už sveikų asmenų. Gerklėi ir ryklės reflukuos liga dažnai pasireiškia nebūdingais simptomais. Iš
Typical and atypical symptoms of laryngopharyngeal reflux disease

nebūdingų simptomų grupės pacientų intensyviausias ir dažniausias buvo užkimimas; vidutinis užkimimo intensyvumas 5,29±0,74, užkimimo indekso vidurkis – 7,06±1,35 balo. Būdingus simptomus nurodė tik 14–22 proc. pacientų. Rėmens intensyvumo vidurkis 2,6±0,66, rėmens indekso – 4,73±1,82 balo. Gerklų ir ryklės refluiko liga sergančių pacientų grupėje nebūdingų simptomų indeksas viršijo būdingų simptomų indeksą tris kartus (p<0,05). Gerklų ir ryklės refluiko liga sergančius pacientus nuo sėkmingų atskyrė trijų nebūdingų simptomų; užkimimui, „kąsnio“ ryklėse, ryklės perštėjimo derinys. Didžiausia diagnostinė reikšmė tenka tarp kitų gerklų ir ryklės refluiko ligos požymių nustatytam neišskios kilmės (idiopatinių) užkimimui, kuris šansų santykį sigrįti gerklų ir ryklės refluiko liga didina 85 kartus. Dėl būdingų laringoskopinių požymių šimtus gerklų ir ryklės refluiko liga ir nustačius idioptinių užkimimų, 90,2 proc. atvejų asmenį jau galima priskirti gerklų ir ryklės refluiko liga sergančių pacientų grupėi.

Adresas susirašinėjimu: R.Pribišienė, KMUANG ligų klinika, Eivenių 2, 3007 Kaunas
El. paštas: ruta-prib@takas.lt

References


Received 21 February 2002, accepted 27 May 2002