EXTRADIGESTIVE MANIFESTATIONS OF GASTROESOPHAGEAL REFLUX DISEASE: DEMOGRAPHIC, CLINICAL, BIOLOGICAL AND ENDOSCOPIC FEATURES

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EXTRADIGESTIVE MANIFESTATIONS OF GASTROESOPHAGEAL REFLUX DISEASE: DEMOGRAPHIC, CLINICAL, BIOLOGICAL AND ENDOSCOPIC FEATURES (Abstract): Gastroesophageal reflux disease (GERD) with extradigestive manifestations is a disorder increasingly recognized both by gastroenterologists, pneumologists, otolaryngologists and cardiologists. Aim: To evaluate the demographical, clinical, biological and endoscopic features of the patients with gastroesophageal reflux disease and extradigestive manifestations (chronic laryngitis, asthma, pseudoangina). Material and methods: Prospective case-control study, including 137 patients selected from patients referred to the Iași Institute of Gastroenterology and Hepatology between July 2014 - September 2015. In the presence of typical GERD symptoms (heartburn or regurgitation), the patients were assessed by upper digestive endoscopy for the detection or exclusion of esophagitis. Despite the absence of esophageal lesions, the patients were further assessed by impedance-pHmetry. Results: Depending on the dominant extradigestive manifestation, the patients were assigned into 3 groups: 94 chronic laryngitis patients, 24 asthma patients and 19 pseudoangina patients. Females were more frequent among pseudoangina patients (68.4%). Mean age of the male patients with dysphonia or asthma was lower (p=0.002), the majority (78.1%) living in urban areas. Obesity was predominant in pseudoangina group (52.6%), as compared to dysphonia group (16%) the differences being statistically significant (p=0.002). A share of 57.9% of pseudoangina patients were dyslipidemic, in contrast to dysphonia (24.5%) or asthma group (37.5%) (p=0.013). Esophagitis was also more frequent at pseudoangina group (84.2%), but with no significant statistical difference between the study groups (79.8% and 75%, respectively) (p=0.115). It seems that Helicobacter pylori infection tends to be protective in patients with GERD and pseudoangina (RR=0.61), but it can not be extrapolated to the general population (p=0.459). Conclusion: GERD with extradigestive manifestations is a prevalent and heterogeneous disease. There are demographic, clinical, biological and endoscopic differences between patients with extradigestive GERD. Keywords: GASTROESOPHAGEAL REFLUX DISEASE, EXTRADIGESTIVE MANIFESTATIONS.

Gastroesophageal reflux disease (GERD) with extradigestive manifestations is a topic debated in literature in the last decades. It became an important diagnostic issue for both gastroenterologists and specialists in other medical fields, like otolar-
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Yngology, cardiology, pneumology and dentistry, as demonstrated by the increasing number of patients suspected of GERD which are referred to gastroenterologists from these services. Apparently a banal disease, GERD has a significant morbidity, consuming human and material resources and burdening health system budget. So far, in Romanian literature there are limited data on extradigestive GERD.

The aim of this study was to evaluate extradigestive GERD patients in terms of demographic, clinical, biological and endoscopic features.

MATERIAL AND METHODS

A prospective case-control study including 137 patients referred to the Iasi Institute of Gastroenterology and Hepatology Iasi from otolaryngology, cardiology and pneumology services in the interval July 2014-September 2015 was performed. Included in the study were adult patients previously diagnosed with asthma, non-cardiac chest pain or chronic laryngitis in whom GERD was suspected. Written informed consent for the participation in the study was obtained. Excluded from the study were the patients with prior gastric or esophageal surgery, malignant tumors, esophageal motility disorders (achalasia, scleroderma, myopathies), alarm signs (hematemesis, jaundice, unexplained weight loss), psychiatric disorders, pregnant women, peptic ulcer, active tuberculosis or other acute lower respiratory tract infections, unstable arrhythmias or myocardial infarction in the last 6 months.

Demographic data, personal history of diseases and smoking and anamnesis were recorded in individual files. All patients were tested for *Helicobacter pylori* antibodies by ELISA. As it is known that dyslipidemia and obesity are risk factors for GERD, the cholesterol and triglycerides serum levels were analyzed and body mass index (BMI) was calculated in all patients. Obesity was considered if BMI was greater than 30 kg/m².

Depending on the presence/absence of typical symptomatology (heartburn or regurgitation), the patients were differently investigated in order to diagnose or exclude GERD. The patients presenting typical manifestations underwent a therapeutic test with double-dose PPI (Pantoprazole 40 mg BID), while the patients not presenting the classical symptoms were assessed by upper digestive endoscopy (UDE) for the detection of the lesions of esophagitis or hiatus hernia. In some cases, biopsies were taken and submitted to anatomo-pathological exam for diagnosing or excluding a Barrett's esophagus. Patients without esophageal lesions were further assessed by impedance-pH metry in order to make a certain diagnosis of GERD.

The data were statistically analyzed using SPSS 18.0. The used parametric tests were: student's t-test for comparing the means, $\chi^2$-test for comparing frequency distribution and Pearson's test correlation coefficient. A $p$ value < 0.05 was regarded as statistically significant.

RESULTS

According to the predominant extradigestive manifestation, the patients were assigned into 3 groups: group I included 94 patients with chronic laryngitis, group II-24 patients with asthma and group III-19 patients with non-cardiac chest pain.

**Demographic features.** Both non-cardiac chest pain group and chronic laryngitis group showed a slightly tendency towards females (68.4% and 52.1%, respectively), while asthma patients were more likely to be men (58.3%), the majority (78.1%) living in urban areas. The study patients were homogenous in terms of gender ($p=0.218$): 47.4% were males and 52.6% were females (fig. 1).
The age of reflux laryngitis patients ranged from 20 to 83 years, with a mean of 50.33±15.10 years and a median of 50 years. In the asthma group the mean age was slightly lower than in group I (50.25±14.14 years) and the median was also 50 years. The age of non-cardiac chest pain patients ranged between 44 and 74 years, with a median of 59 years and a mean age of 58.84±8.33 years, which is significant higher compared to the other two groups (p=0.05) (tab. I). The age > 50 years introduced an estimated risk of GERD four times higher in the pseudoangina group (p=0.012).

Mean age was lower in males presenting asthma and laryngitis (p=0.002).

Of the 137 patients enrolled, 1 was under 20 (0.7%) and 3 (2.2%) were over 80 years of age. In group I the pick frequency was between 40-49 years (26.6%), in group II-between 50-59 years (33.3%) and in group III-between 60-69 years (47.4%) (p=0.026) (fig. 2).

TABLE I.

Descriptive statistical indicators of age (years) by study groups

<table>
<thead>
<tr>
<th>Study group (Lots)</th>
<th>N</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>Std. error</th>
<th>Confidence interval</th>
<th>Min</th>
<th>Max</th>
<th>P FANOVA test</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>94</td>
<td>50.33</td>
<td>15.10</td>
<td>1.56</td>
<td>47.24</td>
<td>53.42</td>
<td>20</td>
<td>83</td>
</tr>
<tr>
<td>II</td>
<td>24</td>
<td>50.25</td>
<td>14.14</td>
<td>2.89</td>
<td>44.28</td>
<td>56.22</td>
<td>18</td>
<td>77</td>
</tr>
<tr>
<td>III</td>
<td>19</td>
<td>58.84</td>
<td>8.33</td>
<td>1.91</td>
<td>54.83</td>
<td>62.86</td>
<td>44</td>
<td>74</td>
</tr>
<tr>
<td>Total</td>
<td>137</td>
<td>51.50</td>
<td>14.41</td>
<td>1.23</td>
<td>49.06</td>
<td>53.93</td>
<td>18</td>
<td>83</td>
</tr>
</tbody>
</table>

Fig. 1. Gender distribution

Fig. 2. Percent distribution of events by age
Clinical features. Typical reflux symptoms were more frequent in asthma subjects (54.2%), but there were no significant statistical differences between this group and laryngitis (39.4%) and non-cardiac chest pain patients (36.8%) (p=0.384) (fig. 3).

Fig. 3. Distribution of typical symptoms by study groups

The highest frequency of obese patients was found in the pseudoangina group (52.6%) and the lower in the laryngitis group (16%), with significant statistical differences (p=0.002); the overall percentage of obese people was 23.4%.

According to smoking status, the patients’ distribution by study groups was homogenous. Although the group with pseudoangina recorded the lowest rate of smoking patients (5.3%), there were no statistical differences between reflux laryngitis (18.1%) or GERD-related asthma patients (25%) (p=0.234).

Biological features. Dyslipidemia was found in 57.9% of patients presenting non-cardiac chest pain, which is a significantly higher frequency in comparison with the other two groups (24.5% for laryngitis and 37.5% for asthma) (p=0.013).

*Helicobacter pylori* infection was identified in 52.6% of all GERD patients, without any significant statistically differences between study groups; the fewest cases of infection with *Helicobacter pylori* were identified in the pseudoangina group (p=0.619).

Endoscopic features. The percentage of patients presenting esophagitis on UDE examination was found to be higher in the group with non-cardiac chest pain (84.2%) compared to the other two groups (79.8%, 75% respectively) (p=0.115). Statistical analysis showed Barrett's esophagus in only 6.6% of GERD patients, but with no significant differences between the study groups (p=0.457). Hiatus hernia occurred in 63.2% of pseudoangina patients and in only 36.2% and 41.7% of patients with laryngitis and asthma, respectively (p=0.094).

DISCUSSION
Our study is one of the few studies on extradigestive GERD conducted in our country. It is known that GERD with or without extradigestive manifestations is found in approximately equal proportions in both genders, with a slight tendency towards males (1, 2). In our study there was a gender homogeneity of the study groups, with a slightly higher frequency of women in the group with chest pain of non-cardiac cause.

GERD can occur at any age, but it is most commonly diagnosed after 40 years
The age of our patients showed wide variations in the three study groups. The mean age was 50 years both in patients with laryngitis and asthma, but in the pseudoangina group the mean age was significantly higher (58 years), suggesting that age is a risk factor for this category of GERD patients. The highest frequency of young patients was recorded in the group with laryngitis, while older patients were most numerous in the group with pseudoangina.

In the literature (5, 6, 7) it is postulated that smokers, obese and dyslipidemic patients are more likely to have GERD. In our study, a quarter of asthma patients were smokers, with a 1.57 times higher relative risk of developing GERD. It appears that non-smoking status may be a protective factor in patients with pseudoangina, but this result cannot be extrapolated to general population. We found obesity in less than a quarter of extradigestive GERD patients, of which half were in group III. The highest percentage of patients with dyslipidemia was found in the group with non-cardiac chest pain. The relative risk to develop GERD of these patients is 3 times higher, which reinforces the idea that dyslipidemia is a factor contributing to the development of GERD.

It is well known that typical symptoms of reflux (heartburn/regurgitation) may be absent in patients with extradigestive GERD in a percentage that reaches 50% (8, 9). We obtained similar results, an increased proportion of patients experiencing both typical and extradigestive manifestations being identified in the asthma group.

As to the endoscopic features, lesions of esophagitis were observed in a high percentage of our patients (62.8%), especially in those with pseudoangina, result that is not consistent with studies in the literature (10, 11). Barrett's esophagus has been identified in a minority of cases regardless of dominant extradigestive manifestation. Hiatus hernia, known as a contributing factor in GERD (12), was present in comparable percentages in the laryngitis and asthma group, exceeding 50% of cases only in the pseudoangina group.

The literature data referring to the association of *Helicobacter pylori* infection and GERD are contradictory. Some studies (13, 14, 15) support the protective role of this bacteria in patients with GERD, while other studies (16, 17) postulate that *Helicobacter pylori* infection is a favorable factor in GERD. In our patients, *Helicobacter pylori* infection was identified in just over half of the cases, the lowest frequency being in the group with pseudoangina. This result would suggest that in this category of individuals *Helicobacter* infection may play a protective role in the development of GERD (RR = 0.61), but the result cannot be extrapolated to the general population.

**CONCLUSIONS**

Our study supports the idea that extradigestive manifestations of GERD are frequent and heterogeneous. There are differences between patients with GERD and chronic laryngitis, asthma and non-cardiac chest pain in terms of demographic, clinical, biological and endoscopic features. We demonstrated that extra digestive manifestations correlate with smoking, obesity and dyslipidemia, as contributing factors. The typical symptoms are absent in about half of extradigestive GERD cases, making the diagnosis being sometimes difficult. It is obvious that *Helicobacter pylori* infection influences the course of GERD, but is still not clear if it is in a positive or a negative way.
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REFERENCES