Epidemiological and clinical risk factors for non-erosive reflux disease, erosive esophagitis and Barrett’s esophagus in Russia

Abstract

The aim of the study was to identify the epidemiological and clinical factors predisposing to non-erosive reflux disease (NERD), erosive esophagitis (EE) and Barrett’s esophagus.

Materials and methods: 1433 patients with GERD from Moscow, Moscow region, St. Petersburg and Leningrad region were studied. During the study complaints and anamnestic data were gathered, anthropometry, tests for H. pylori infection and upper endoscopy were performed. Spearman rank correlation was used to identify the correlation of clinical characteristics with NERD, EE and Barrett’s esophagus. 880 patients with GERD (407 with NERD, 443 with EE, 27 with Barrett’s esophagus, 3 with esophageal stricture) were selected for correlation analysis due to the presence of all necessary parameters.

Results: The prevalence of two main GERD phenotypes - EE and NERD - was approximately equal in the patients of Russian megapolises. Male gender was significantly negatively correlated with NERD development (p=0.002011). An inverse correlation was found between NERD and older age groups (p=0.002459), high weight circumference (WC) (p=0.003733), long duration of GERD symptoms (p=0.012984), the results of the Gerd-Q<8 points (p=0.040030). In the group of patients with EE grade A-B, a significant inverse correlation was revealed with age over 40 years (p=0.002708), high body mass index (BMI) (p=0.020957), and high WC (p=0.001293). The male gender (p=0.000108) and the duration of GERD symptoms more than 3 years (p=0.028292) were significantly associated with severe grades of EE development. The male gender (p=0.002011) and not using of PPIs over the past 6 months (p=0.015930) were positively associated with Barrett’s esophagus.

Conclusion: Female gender, young age, normal BMI and WC, short duration of symptoms and Gerd-Q less than 7 points were positively associated with NERD compared with EE and Barrett’s esophagus. Female gender, young age, normal BMI and WC, short duration of symptoms and Gerd-Q less than 7 points were positively associated with NERD development.

Keywords: gastroesophageal reflux disease, erosive esophagitis, non-erosive reflux disease, proton pump inhibitors, heartburn, Barrett’s esophagus

Abbreviations: GERD, gastroesophageal reflux disease; EE, erosive esophagitis; NERD, non-erosive reflux disease; PPIs, proton pump inhibitors

Key summary

a. GERD is a widespread disease, which is associated with increased risk of Barrett’s esophagus and esophageal adenocarcinoma. Moreover, the frequency of GERD is constantly increasing, which may be associated with an increase in the incidence of obesity and other metabolic diseases. Nowadays the prevalence of GERD in North America and in Western Europe is up to 27.8% and 25.9% respectively. In Russia, GERD prevalence ranges from 13.3 to 23.6% in different regions.

b. However, no data on risk factors predisposing to the development of non-erosive reflux disease, erosive esophagitis and Barrett’s esophagus in Russia is available.

I. What are the significant and/or new findings of this study?

a. We showed that female gender, young age, normal BMI and WC, short duration of GERD symptoms and Gerd-Q results<7 points were positively associated with NERD.

b. We showed that male patients with long-term GERD symptoms who do not use PPIs are at high risk of Barrett’s esophagus.

Introduction

Gastroesophageal reflux disease (GERD) is one of the most common diseases in developed countries. Many studies have shown that GERD has a high worldwide prevalence varying from 8% to 33% and involves all age groups and both genders. Moreover, the frequency of GERD is constantly increasing, which may be associated with an increase in the incidence of obesity and other metabolic diseases. Nowadays the prevalence of GERD in North America and in Western Europe is up to 27.8% and 25.9% respectively. In Russia, GERD prevalence ranges from 13.3 to 23.6% in different regions.

According to the modern concept of GERD spectrum, patients with GERD can be divided into three main phenotypes: non-erosive reflux disease (NERD), erosive esophagitis (EE), and GERD with complications, such as Barrett’s esophagus, esophageal stricture, esophageal adenocarcinoma and pulmonary fibrosis. The NERD phenotype represents the majority of patients with GERD, and is diagnosed in approximately 70% of the patients, while the EE prevalence is about 30%. Moreover, based on the upper endoscopy and impedance pH-monitoring results patients with NERD can be subdivided into disorders with different pathways and therapeutic options: NERD with catarrhal esophagitis, endoscopically negative GERD with pathological acid exposure time (AET) and positive symptom-association probability (SAP) and hypersensitive esophagus with normal AET and positive SAP. The functional heartburn, which is characterized by negative SAP, normal AET and absence of esophagus mucosa lesions, is included into functional disorders, so-
called Gut-Brain axis disorders. GERD phenotypes can succeed each other, thus in 10% of cases NERD can transform into EE.2

There is no «gold standard» for the diagnosis of GERD nowadays. Most of the clinical practice guidelines have developed stepwise diagnostic algorithms depending on the initial characteristics of the patient.9-12 The main diagnostic methods for GERD in real clinical practice include The Reflux Disease Questionnaire (GerdQ), PPI test, empirical proton pump inhibitor (PPI) therapy for 12 weeks, upper endoscopy and biopsies, impedance pH-monitoring, but each of these methods has its own limitations. Some studies have showed that Helicobacter pylori (H. pylori) infection is associated with the development of GERD. According to these data it is recommended to identify H. pylori among patients with GERD and initiate eradication therapy if the result is positive. H. pylori infection is widespread in Russia. According to our data around 50% of patients with different stomach diseases and 42% of patients with dyspepsia are infected with H. pylori infection in Russia.13,14 And the prevalence of H. pylori infection among doctors (general practitioners) in Saint-Petersburg is around 60%.15 But some researches deny any relationship between GERD and H. pylori.16,17

Knowledge of risk factors for NERD, EE and Barrett’s esophagus development helps to determine optimal treatment and surveillance for each patient with heterogeneous GERD phenotypes. Risk factors associated with the development of GERD were studied in different researches.9-19 Mazzoleni F. et al. in randomized clinical trial HEROES-GERD showed that combination of increased body mass index and waist circumference predicts new-onset esophagitis.17 The 12-month follow-up esophagitis rates for overweight and normal body weight patients were 13.6% (29/213) and 6.0% (10/167), respectively (p=0.015); rates for patients with and without increased baseline waist circumference were 15.4% (24/156) and 6.7% (15/224), respectively (p=0.006). Dietary habits (fat and spice food, carbonated drinks, fermentable carbohydrates), hiatal hernia, comitant gastroenterological diseases, comitant medications (antibiotics, calcium-channel blockers, bisphosphonates), genetic factors18 and psychological status of the patient19 were determined to be associated with GERD occurrence. According to Schmidt M. et al. demographic, lifestyle, and clinical factors as well as GERD symptoms were associated with Barrett’s esophagus development, suggesting that a combination of risk factors could be useful in developing individualized screening efforts for patients with Barrett’s esophagus and GERD in Germany.20

The first-line medical therapy of GERD is anti-secretory drugs, most commonly PPIs. However, clinical practice data showed that about half of patients were refractory to PPI. In 20-50% of cases symptoms of GERD and/or endoscopic lesions of esophagus mucosa persisted during treatment with PPI for 8 weeks.17,21 In 50-90% of patients, during the PPI therapy or within a year after the withdrawal of PPIs, the symptoms of the disease recurred.22,23 Furthermore, there are differences between responses to PPI therapy in patients with EE and typical reflux symptoms and patients with NERD: the response to standard dose of PPI in EE patients is about 55.5%, whereas the NERD patients have a rate of 36.7%.22,24 There are several explanations for PPI non-response or partial response, such as low compliance to prescribed therapy and inappropriate timing of administration, which may reduce the effect of the drug; individual pharmacokinetics of PPIs; weakly acidic reflux and remaining of alkaline reflux during PPI therapy.22,23 Non-GERD conditions may also cause symptoms similar to GERD: Crohn’s disease of upper GI tract, eosinophilic esophagitis, esophageal achalasia and others. In that cases non-response to PPI treatment may also occur.

The aim of the study was to identify the epidemiological and clinical factors predisposing to non-erosive reflux disease (NERD), erosive esophagitis (EE) and Barrett’s esophagus in Russian population of patients.

Materials and methods

The study included 1433 patients with GERD from Moscow, Moscow region and St. Petersburg. Written, informed consent was obtained from each patient included in the study. This study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the local ethical committee of Federal State Budgetary Educational Institution of Higher Education “North-Western State Medical University named after I.I. Mechnikov” of the Ministry of Health of the Russian Federation on 04.04.2018.

There were 595 (42%) men and 838 (58%) women with the average age 48±16years (from 7 to 91years). The study design included 3 visits with an interval of 4 weeks, during which complaints and anamnestic data were gathered, anthropometry, upper endoscopy, tests for H. pylori infection and adherence evaluation were performed. For anti-secretory effect rabeprazole was prescribed for most of the patients (n=1333, 96%).

The obtained data were analyzed by parametric and non-parametric statistical methods with statistical programme «SPSS». Correlation analysis with Spearman rank correlation was used to identify the correlation of clinical characteristics with NERD, EE and Barrett’s esophagus. 880 patients with GERD (407 with NERD, 443 with EE, 27 with Barrett’s esophagus, 3 with esophageal stricture) were selected for correlation analysis due to the presence of all necessary parameters.

As potential risk factors for NERD, EE and Barrett’s esophagus development were suggested the following: age, gender, body mass index (BMI) and waist circumference (WC), smoking, H. pylori presence, hiatal hernia, duration of symptoms, previous PPIs therapy, concomitant therapy.

Results

Analysis of age and gender characteristics of patients showed that GERD was diagnosed in all age groups. Among male patients the most common was the age group 30-39 years (30%), among female – age group 60-69 years (23%). These results correspond with published data, according to which the incidence of GERD is higher in the older age groups.

The number of patients with the high BMI was 895 (62.5%). A direct moderate association between BMI and the age of patients was found (Spearman’s ratio=0.39). The high value of WC was detected in 193 (39%) men and in 380 (39 %) women.

Overweight and obesity are known to be associated with the development of GERD. Mazzoleni F. et al.17 in a randomized clinical trial of patients with functional dyspepsia HEROES-GERD (n=404) showed that EE is significantly more frequent in patients with overweight (p=0.015) compared with patients with normal body weight (13.6% and 6.0% respectively). Significant differences were also found in the prevalence of EE depending on the WC: 15.4% in patients with high WC values and 6.7% in patients with normal WC values (p=0.006).17

914 (65%) patients didn’t smoke, 200 (14%) patients were smokers in the past, 299(21%) patients were current smokers. According to χ2-test no significant differences were found between smoking and the...
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The distribution of patients with GERD included in the correlation analysis according to the endoscopic findings is shown in the Figure 1. EE was detected in 443 (50.3%) patients, NERD with/without catarrhal esophagitis – in 407 (47%). The prevalence of two main GERD phenotypes - EE and NERD - is approximately equal in the population of Russian patients. However, according to published data, in the last decade, prevalence of NERD is higher, than EE.

Table 1 Spearman Rank Order Correlations for NERD

| Variables                                      | Valid | Spearman | t(N-2) | p-level |
|------------------------------------------------|-------|----------|--------|---------|
| no visible changes of esophageal mucosa & male gender | 880   | -0.103983 | -3.09793 | 0.002011 |
| Catarrhal esophagitis & male gender           | 880   | -0.043592 | -1.29290 | 0.196385 |
| Catarrhal esophagitis & smoking               | 880   | 0.000864  | 0.02560 | 0.979583 |
| Catarrhal esophagitis & age group             | 880   | -0.101963 | -3.03709 | 0.002459 |
| Catarrhal esophagitis & BMI                   | 880   | -0.065762 | -1.95283 | 0.051158 |
| Catarrhal esophagitis & WC                    | 880   | -0.097660 | -2.90768 | 0.003733 |
| Catarrhal esophagitis & Duration of symptoms  | 880   | -0.083715 | -2.48929 | 0.012984 |
| Catarrhal esophagitis & GerdQ                 | 880   | -0.069237 | -2.05649 | 0.040030 |
| Catarrhal esophagitis & previous PPIs treatment | 880   | 0.023804  | 0.70553 | 0.480666 |

Table 2 Spearman Rank Order Correlations for EE

| Variables                                      | Valid | Spearman | t(N-2) | p-level |
|------------------------------------------------|-------|----------|--------|---------|
| EE grade A-B & Male gender                     | 880   | -0.030047 | -0.89074 | 0.373315 |
| EE grade A-B & Smoking                         | 880   | -0.020031 | -0.59364 | 0.552903 |
| EE grade A-B & Age group                       | 880   | -0.100983 | -3.00761 | 0.002708 |
| EE grade A-B & BMI                             | 880   | -0.077821 | -2.31293 | 0.020957 |
| EE grade A-B & WC                              | 880   | -0.108300 | -3.22802 | 0.001293 |
| EE grade A-B & Duration of symptoms            | 880   | -0.035362 | -1.04847 | 0.294711 |
| EE grade A-B & GerdQ                           | 880   | -0.036374 | -1.07850 | 0.281106 |

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Table Continued...

| Variables                        | Valid | Spearman | t(N-2)   | p-level |
|----------------------------------|-------|----------|----------|---------|
| EE grade A-B & previous PPIs treatment | 880   | -0.000911| -0.02699 | 0.978477|
| EE grade C-D & Male gender        | 880   | 0.130162 | 3.889924 | 0.000108|
| EE grade C-D & Smoking            | 880   | 0.036444 | 1.080596 | 0.280174|
| EE grade C-D & Age group          | 880   | 0.015645 | 0.463639 | 0.643021|
| EE grade C-D & BMI                | 880   | 0.019657 | 0.582572 | 0.560331|
| EE grade C-D & WC                 | 880   | 0.000452 | 0.013399 | 0.989312|
| EE grade C-D & Duration of symptoms | 880 | 0.073937 | 2.196841 | 0.028292|
| EE grade C-D & GerdQ              | 880   | 0.051355 | 1.523709 | 0.127941|
| EE grade C-D & previous PPIs treatment | 880 | -0.015325| -0.454151| 0.649832|

The male gender (p=0.007505) and not-using of PPIs over the last 6 months (p=0.015930) were positively correlated with Barrett’s esophagus development.

Conclusion

The prevalence of two main GERD phenotypes - EE and NERD - is approximately equal in the population of Russian megalopolises patients. Female gender, young age, normal BMI and waist circumference, short duration of symptoms and Gerd-Q results less than 7 points were positively associated with NERD development compared with erosive esophagitis among Russian patients. Male patients with long-term GERD symptoms who do not take PPIs are at high risk of Barrett’s esophagus development.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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