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Стаття надійшла 28.03.2020 р.

DOI 10.26724/2079-8334-2021-1-75-119-124
UDC 616.24:616.329.-002-071

G.V. Osyodlo, S.A. Bychkova, I.P. Katerenchuk[1], M.M. Seliuk, A.P. Kazmirchuk[2]
Ukrainian Military-Medical Academy, Kyiv
[1]Ukrainian Medical Stomatological Academy, Poltava
[2]National Military Medical Clinical Center "The Main Military Clinical Hospital" Kyiv

CURRENT ISSUES IN DIAGNOSING THE RESPIRATORY MANIFESTATION OF GASTROESOPHAGEAL REFLUX DISEASE

svetlana_bichkova@yahoo.com

The purpose of the study was to determine the leading extraesophageal symptoms, disturbance of spirometric indices, changes in the immune system and production of nitric oxide in patients with gastroesophageal reflux disease. Bronchopulmonary manifestation of gastroesophageal reflux disease was a cough syndrome, which was characterized by the presence of non-intensive, unproductive cough with a small amount of mucous sputum and was combined, in most cases, with the hoarseness of the voice. Cough syndrome during gastroesophageal reflux disease was characterized by a lack of obstructive changes in the study of external respiration indices and elevated levels of proinflammatory cytokines in the blood serum. It was determined the higher nitric oxide content in platelets in patients with respiratory manifestations of gastroesophageal reflux disease.

Keywords: gastroesophageal reflux disease, cough syndrome, proinflammatory cytokines, chronic obstructive pulmonary disease

Г.В. Осьодло, С.А. Бичкова, І.П. Катеренчук, М.М. Селюк, А.П. Казмірчук

АКТУАЛЬНІ ПИТАННЯ ДІАГНОСТИКИ РЕСПІРАТОРНИХ ПРОЯВІВ ГАСТРОЕЗОФАГЕАЛЬНОЇ РЕФЛЮКСНОЇ ХВОРОБИ

Метою роботи було визначення провідних респіраторних позастравохідних симптомів, порушення спірометричних показників, змін в імунній системі та продукції оксиду азоту у хворих на гастроезофагеальну рефлюксну хворобу. Для вирішення поставленої мети було обстежено 94 військовослужбовці чоловічої статі, які звернулися за медичною допомогою з приводу наявності синдрому кашлю. Основним респіраторним проявом гастроезофагеальної рефлюксної хвороби був неінтенсивний малопродуктивний кашель із виділенням невеликої кількості мокроти слизового характеру, який поєднувався, у більшості випадків, із осиплістю голосу. Синдром кашлю характеризувався відсутністю обструктивних змін при дослідженні показників функції зовнішнього дихання та підвищеним рівнем прозапальних цитокінів у сироватці крові. Було встановлено високий рівень оксиду азоту в тромбоцитах у хворих із респіраторними проявами гастроезофагеальної рефлюксної хвороби.

Ключові слова: гастроезофагельна рефлексна хвороба, синдром кашлю, прозапальні цитокіни, хронічне обструктивне захворювання легень

The study is a fragment of the research project "Epidemiological, therapeutic and pharmacoeconomic features of topical therapeutic pathology in servicemen and employees of the Armed Forces of Ukraine in the conditions of the Joint Forces Operation, "Vydnokray", state registration No. 0120U101854.

The worldwide organization of gastroenterologists has recognized gastroesophageal reflux disease (GERD) as a leading disease in the 21st century, which afflicts 20 to 50 % of the population of different countries, which also causes a decrease in the life quality, work capacity and the development of a number of complications, such as Barrett's esophagus [1, 3].

Due to the wide distribution and presence of extraesophageal manifestations caused by pathological reflux, GERD has become relevant not only for gastroenterologists but also for related specialties. Today, this disease is more often considered not as a "gastroenterological", but as an "internal" pathology, and the symptoms of the disease are divided into esophageal and extraesophageal [3, 12]. Typical esophageal symptoms are epigastric burning (83 %), acid or belching (more than 50 %), dysphagia (19 %), less often chest pain and hiccups. Frequent abdominal manifestations of GERD include epigastric pain, early satiety syndrome, vomiting, and stomach heaviness after eating, and flatulence. Much attention has recently been given to the study of comorbid pathology, namely the combined course of GERD and other diseases such as functional dyspepsia, irritable bowel syndrome, pancreatitis, coronary heart disease and heart rhythm disorders, obesity, chronic obstructive pulmonary disease (COPD), bronchial asthma, hypertonic disease, etc. [1, 13].

It should be noted that GERD combined with another somatic pathology, acquires certain features, complaints that are not always inherent in the pathology of the gastrointestinal tract are coming to the fore. One of manifestations of the atypical course of GERD may be a cough syndrome, which becomes a main complaint of the patient. The mechanism of cough development in GERD is the realization of vagus-mediated esophageal and tracheobronchial reflex [3]. Two-thirds of patients with this condition may have no other gastrointestinal symptoms, although they may complain of epigastric burning after eating. Increased acidity in the lower esophagus is a prerequisite for the occurrence of chronic cough [3, 8]. In this case, it is important to access the duration, frequency of episodes of reflux, and also to establish a correlation with cough episodes [1, 3].

It is the cough syndrome and shortness of breath that cause patients to seek medical help from pulmonologists and therapists. If the patient has such modifying factors as smoking or hereditary predisposition to allergic diseases with manifestations of bronchial hypersensitivity, the question of performing a differential diagnosis for the correct verification of the underlying disease urgently arises. The pulmonologist should exclude such bronchoobstructive diseases as COPD, which is usually manifested by wet cough, but is very rarely detected at the early stages, when a cough is the only manifestation [10, 11] and bronchial asthma, namely cough option.

Over the last decade, the problem of diagnosis and treatment of extraesophageal manifestations of GERD has become especially relevant for servicemen of the Armed Forces of Ukraine. This is due to the widespread prevalence of GERD among this contingent [3], the widespread use of smoking on the background of significantly increased psycho-emotional burden, constant work in stress. Moreover, due to the location of certain categories of military, where access to specific instrumental research may be limited and different prognosis for military service, as the degree of suitability for GERD with extraesophageal manifestations, COPD or asthma differs significantly.

The purpose of the study was to determine the leading extraesophageal symptoms, disturbance of spirometric indices, changes in the immune system and production of nitric oxide in patients with gastroesophageal reflux disease.

Materials and methods. In order to access the presented purpose, 94 male patients were examined, who sought medical help for cough syndrome. They were divided into two groups. Group 1 (48 patients) consisted of GERD patients, who had extraesophageal bronchopulmonary manifestations; group 2 consisted of 46 patients with first time diagnosed COPD. Mean age of the patients constituted (47.6±3.4) years; all patients were on examination and hospitalised in the clinics of National Military-Medical Clinical Centre.

The GERD diagnosis was established pursuant to the Unified clinical protocol of primary, secondary (specialised) medical care "Gastroesophageal reflux disease" (Order of MoH of Ukraine No. 943), 2013 [9]. When establishing a clinical diagnosis, the extent of damage to the esophagus was determined after an endoscopic examination (A, B, C, D) according to the Los Angeles Classification (1994). To verify the type of reflux and association indices (symptom index), patients underwent long-term pH impedance monitoring using the original Ukrainian computer system of esophago−gastro−impedance−pH monitoring.

The COPD diagnosis was established pursuant to the Order of MoH of Ukraine [2]. All COPD patients underwent the course of the disease assessment test (COPD Assessment Test, CAT) and the assessment of dyspnea intensity was carried out by the modified dyspnea scale − Medical Research Council Dyspnea Scale (mMRC) [2]. The assessment of clinical symptoms of bronchopulmonary system damage was performed with the help of rating scale of I. V. Suvorkina (2005) [6]. Spirography was performed on the "Spirosift SP-5000" (Fucuda Denshi, Japan). The levels of pro− and anti-inflammatory cytokines, IL-17A, interferon-γ (IFN-γ), and the content of soluble sICAM-1 sVCAM adhesion molecules were determined using Ukraine-certified enzyme multiplied immunoassay kits based on Pro Con (Russia) and

Diaclon (France) companies methodology, a transforming growth factor-β (TGF-β) – "Genzyme diagnostics". The content of subpopulations of lymphocytes with the CD54+, CD11b+ and CD62L+ phenotypes was determined by indirect immunofluorescence using monoclonal antibodies.

Statistical data was processed using the Microsoft XP Excel application program package, as well as the standard version of the Statistical Package for the Social Sciences (SPSS) 17.0.

Results of the study and their discussion. All patients sought medical help for cough syndrome, as mentioned above. After a detailed examination, two groups of patients were identified: group 1 − patients without radiological or functional signs of damage to the bronchopulmonary system, who on the basis of clinical manifestations, FEGDS results and intraesophageal impedance−pH monitoring were diagnosed with GERD, but they had various respiratory symptoms (cough with sputum, dyspnea, shortness of breath , etc.). Numerical access of long-term intraesophageal impedance − pH monitoring allowed to establish the structure of gastroesophageal reflux in patients of this category, they had mainly weakly acidic (38.2±4.7 %), acidic (32.5±4.2 %), rarely slightly alkaline (19.8±2.3 %) and mixed (9.5±3.7 %) episodes of reflux. The Symptom Index in the group was 71.2±6.8 %.

Group 2 − patients with newly diagnosed COPD, in whom the cough was caused by bronchial lesions, because this group of patients was older than 40 years, had a long smoking history and clinical and functional signs of the disease (cough with sputum, shortness of breath during exercise; according to spirometry − decrease in FEV1/FVC <70 %, irreversible bronchial obstruction, increase in FEV1 <12 %.

Table 1 shows basic clinical, demographic characteristics of the patients, and states the main complaints of all three groups of patients.

Table 1

Clinical characteristics of examined patients (M±m)

Clinical features	1-st group (n=48)	2-nd group (n=46)	p*
Mean age, years	46.3±3.2	48.9±2.8	p>0.05
Body mass index, kg/m^2	25.5±1.5	30.3±1.8	p<0.05
Smocking, n (%)	26 (54.2%)	46 (100%)	p<0.05
Smocking index, pack/years	19.4±2.5	26.8±4.9	p>0.05
Epigastric burning sensation, n (%)	33 (68.8%)	-	
Regurgitation sensation, n (%)	37 (77.1%)	2 (4.3%)	p<0.05
Sour regurgitation sensation, n (%)	32 (66.7%)	-	
Acute disease onset , n (%)	29 (60.4%)	3 (6.5%)	p<0.05
Cough, points	1.3±0.1	2.8±0.2	p<0.05
Sputum, points	1.1±0.1	3.2±0.3	p<0.05
Sputum's nature: mucus, n (%) mucus-pus, n (%) pus, n (%)	 26 (54.2%) - -	 33 (71.7%) 13 (28.3%) -	p<0.05
Voice hoarseness, n (%)	27 (56.3%)	12 (26.1%)	p<0.05
Feeling short of breath, n (%)	13 (27.1%)	16 (34.8%)	p>0.05
Dyspnea according to mMRC, points	0.3±0.01	1.1±0.1	p<0.05
CAT , points	-	7.5±0.8	
Harsh respiration, n,%	-	39 (84.9%)	
Scattered dry rales, n,%	-	31 (67.4%)	
Sa O2, %	98.6±1.2	96.6±0.8	p>0.05

Note: p – probability of indices' difference

The main complaint in all groups of patients was cough, but its intensity was significantly higher in patients with COPD, severe coughing was accompanied by sputum expectoration in daily amount of 30 and more ml, which usually excreted in the morning with severe cough. The type of sputum in 71.7 % was predominantly mucous, in 28.3 % − mucus-pus.

It should be noted that in the group of patients with GERD, one of the main complaints was also cough, but its intensity was lower in probability compared to the group 2 of patients. The cough was accompanied by the excretion of a small amount of sputum of the mucous nature in 54.3% of patients. 27 patients (56.3 %) were found to have hoarse voices. Such classic signs of GERD as epigastric burning, eructation and acid eructation were expressed in 1 group of patients in 68.8 %, 77.1 % and 66.7 %, respectively, but they were not the dominant complaints.

Despite the relatively young age of the examined patients in both groups, such a complaint as shortness of breath was detected (p> 0.05), although Sa02 in both groups of patients was normal. Particular attention was paid to the fact that all patients of group 2 were smokers or former smokers with a high smoking index. However, 54.2 % of patients of group 1 were also smokers, indicating that this habit is a provocative factor in the development not only of the pathology of the respiratory organs, but also of the

gastrointestinal tract. As can be seen from the data presented in table 1, patients of group 2 showed a significant increase in the body mass index (BMI) compared with patients of group 1. Thus, in the initial examination, all patients appealed for medical assistance for cough syndrome; its intensity, the presence or absence of sputum could not always indicate a lesion of the bronchopulmonary system. As a separate diagnostic criterion can serve only the acute beginning of the development of cough syndrome, which is more common in patients with GERD (60.4 % of patients), while in patients with COPD with the phenotype of chronic bronchitis, the cough developed gradually, and its intensity increased over time. Physical signs of the bronchopulmonary system lesions (harsh breath, scattered dry rales) were detected in patients with COPD. In addition to cough with expectoration, in patients of group 1 were noticed complaints of epigastric burning, sensation of eructation including with acid content. In the initial examination of all patients, the study of the external respiration function (ERF) indices was performed to confirm or exclude obstructive diseases of the respiratory organs.

Table 2

Spirometric indices of examined patients (M±m)

Indices	1-st group (n=48)	2-nd group (n=46)	p*
FEV 1, %	86.1±3.2	74.9±2.8	p<0.05
FVC, %	83.7±2.1	77.5±3.3	p <0.05
FEV1/FVC	88.2±3.4	65.3±2.6	p<0.05
PEF	82.5±3.6	72.2±3.8	p<0.05
MEF 25-75 %	82.8±2.1	71.4±3.3	p<0.05
VC, %	93.5±4.8	94.8±4.6	p>0.05
FEV1 gain, %	3.6±0.8	4.7±1.1	p>0.05

Note: p – probability of indices' difference

The analysis of the indices presented in Table 2 showed that in the group of patients with GERD (group 1), all indices were preserved, and no obstructive or restrictive changes were detected. In group 2 of patients diagnosed with "first time diagnosed COPD, Group A", there were found obstructive disorders that were manifested by a probable decrease in FEV 1, forced vital capacity (FVC), Maximum exhalation force (MEF from 25–75 % FVC) with a level of obstruction corresponding to GOLD 1, in a small number of patients – 7 people – GOLD 2. In addition, the ratio of FEV1/FVC less than 70 %, which is one of the diagnostic criteria for COPD, was noted in these patients, the obstruction was accessed as irreversible during the bronchodilation test (gain of FEV1 was 4.7±1.1% in group 2).

An immunological examination performed for all groups of patients, which included the determination of serum concentration of pro- and anti-inflammatory cytokines, the level of soluble adhesion molecules, as well as the expression of activation adhesive molecules on peripheral blood lymphocytes in the examined patients (table 3). It is known that there is an imbalance in T-cell subpopulation in patients with GERD, which plays a key role in modulating the functions of immunocompetent cells, and a significant role in the relapse of the disease and promotes changes in the cellular structure of the esophagus mucosa with the formation of intestinal metaplasia. In those areas, there is a decrease in apoptosis, proliferation processes are activated, and the activity of glutathione-S-transferase decreases, which, in turn, leads to a decrease in the protection of cells of the esophagus mucosa from free oxygen radicals and the formation of erosive lesions [14].

Table 3

Immunological characteristics of the examined patients (M±m)

Indices	1-st group (n=48)	2-nd group (n=46)	p
$CD54^+$lymphocytes, %	12.6±0.8	18.2±0.5	p0.05
$CD11b^+$lymphocytes, %	21.5±1.4	33.2±1.6	p<0.05
$CD62L^+$lymphocytes, %	28.3±1.2	40.9±1.6	p<0.05
TNF-α, pg/ml	113.6±4.2	82.7±3.9	p<0.05
IL-1β, pg/ml	106.8±5.2	79.42±3.6	p<0.05
IL-6, pg/ml	14.3±0.6	23.9±1.2	p<0.05
IFN-γ, pg/ml	48.6±2.9	83.9±2.3	p<0.05
IL-4, pg/ml	20.1±0.9	19.7±0.8	p>0.05
TGF-β, pg/ml	39.4±4.1	62.3±3.4	p<0.05
IL-17A, pg/ml	17.3±2.7	20.3±1.1	p<0.05
sVCAM, pg/ml	18,6±1.2	22.3±1.6	p>0.05
sICAM-1, ng/ml	175.5±11.3	228.3±15.4	p>0.05

Note: p – probability of indices' difference

Patients with GERD showed a significantly higher level of proinflammatory cytokines in serum, namely, TNF-α and IL-1β, against the background of the preserved level of anti-inflammatory IL-4, as well as TGF-β and IL-17. In addition, in this group of patients, there was noted the normal content of serum soluble sVCAM and sICAM-1 adhesion molecules and the expression of activation adhesive molecules on lymphocytes, which is directly related to the activation processes of the immune system cells (CD4+lymphocytes) in response to irritation of mucous membrane of the gastrointestinal tract with hyperproduction of proinflammatory cytokines. It has been detected the activation of the T-helper cells type 1 of the immune system with a significant prevalence of IFN-γ in blood serum as opposed to other proinflammatory cytokines in the blood of the patients 2 group. At the same time, an increase in TGF-β serum concentration was found, which is an immunological feature of bronchial remodelling and the formation of irreversible bronchial obstruction [11]. In addition, an individual analysis of the IL-17A serum concentration found that patients with GOLD 2 level of obstruction (7 persons) had a significantly higher IL-17A level compared to the mean in the group – 27.3±2.9 pg/ml while the middle level was 20.4±1.1 pg/ml. During an immunological examination, in patients with COPD, high serum concentration of soluble adhesion molecules and high expression of adhesive markers on activated lymphocytes were also detected. Thus, intense inflammatory process with high levels of proinflammatory cytokines leads to stronger activation of immunocompetent cells and their synthesis of adhesive molecules. The high serum concentration of the soluble adhesion molecule sICAM-1, in addition, was combined with increased expression of the ICAM-1 receptor on peripheral blood lymphocytes, the content of CD54 + lymphocytes was significantly higher than in patients of group 1 by 44.4 % ($p<0.05$). In addition, an increased percentage level of CD62L+ lymphocytes in patients with COPD was found, this is due to that L-selectin (CD62L) provides the attachment of lymphocytes to the endotelial wall.

The concentration of NO in neutrophilis and platelets in patients with respiratory manifistations with GERD was studied.

Table 4

NO concentration of neutrophils and platelets in patients with respiratory manifestations of GERD (M ± m)

NO level	Patients with respiratory manifestations of GERD (n=26)	Patients with GERD (n=26)	Almost healhy people (n=26)
NO_1	2.8±0.51	2.55±0.45	0.79±0.05
NO_2	3.71±0.79	2.44±0.41*	0.77±0.08

Notes: * − the probability of the difference between the groups of patients, $p<0.05$; NO1− NO concentration in neutrophils (nmol/1 · 106 cells·min.); NO2 − NO concentration in platelets (nmol/1 · 106 cells · min.)

In patients with GERD without respiratory manifestations, the level of neutrophils's NO exceeded the control values by 3.3 times ($p<0.05$), and platelets's NO − by 3.17 times ($p<0.05$) (table 4). In the group of patients with GERD with respiratory manifestations, the level of neutrophils's NO exceeded the control values by 3.6 times, and the indicators of NO content in platelets (controlled by constitutive NOS) − by 4.82 times ($p<0.05$). Thus, in patients with respiratory manifestations of GERD, a significantly elevated level of NO was detected in platelets.

There was also found a high positive correlation between serum IL-1β level and platelets's NO level ($r=0.632$) and between TNF-α serum level and platelets's NO ($r=0.613$).

Thus, the main causes of pathological gastroesophageal reflux were considered to be the primary decrease in pressure and transient relaxation of the lower esophageal sphincter [4], due to increased production of nitric oxide [5, 15]. NO has a unique ability to relax smooth muscles, but there were data on specific effects of NO produced by different sources [4, 5]. Thus, NO, synthesis by leucocytes and neurons, regulated intestinal motility, caused relaxation of the round muscles of the rectum, tonic inhibits the pylorus [5, 15]. The main enzyme of nitric oxide biosynthesis − NO synthase (NOS) exists in two forms: constitutive and inducible NOS. Constitutive NOS, which are also contained in platelets − less powerful enzymes than inducible, they are calcium- and calmodulin-dependent, but function relatively autonomously in relation to environmental factors and regulatory systems of the macroorganism [10]. At the same time, more potent calcium-independent inducible NOS is induced by cytokines. It is found in neutrophils, as well as in macrophages, hepatocytes, fibroblasts, monocytes, lymphocytes, Kupffer cells, eosinophils and is activated by antigens of microorganisms and some pro-inflammatory cytokines.

Overall, the high concentration of NO in patients with respiratory manifestations of GERD was characterized by higher NO content in platelets, which is due to the development of neutrophilic inflammation and hyperproduction of proinflammatory cytokines in respiratory manifestations of GERD due to constant prolonged irritation of the respiratory mucosa with acidic contents [7]. Due to prolonged activation, neutrophils synthesize excess pro-inflammatory cytokines for a long time and in high

concentrations, which led to depletion of their functional activity relatively on NO production. The production of NO by platelets depended little on other factors, including various cytokines, did not depend on external factors and therefore compensatory increases, which provides the pathogenetic role of NO in the development and progression of GERD.

Conclusions

1. GERD is a multiple-symptom disease, which is characterized by extraesophageal manifestations. Bronchopulmonary manifestation of GERD are a cough syndrome characterized by the presence of a non-intensive, unproductive cough with a small amount of mucous sputum and is combined, in most cases, with the hoarseness of the voice.

2. Cough syndrome during GERD is characterized by a lack of obstructive changes in the study of indices of external respiration and elevated levels of proinflammatory cytokines in the blood serum.

3. Increased content of neutrophils's and platelets's NO in patients with extraesophageal manifestations of GERD indicates its important role in the course of respiratory manifestations and depends on increased levels of pro-inflammatory cytokines.

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Стаття надійшла 26.02.2020 р.