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ENGLISH VERSION: NEW DIAGNOSTIC POSSIBILITIES FOR DETERMINING THE NATURE OF RESPIRATORY SYMPTOMS IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE*

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As of today, it is not completely known why there is a large number of eosinophils in the peripheral blood of some patients with chronic obstructive pulmonary disease (COPD) in the stable phase of the pathological process: it possibly evidences of the mistaken diagnosis of COPD instead of bronchial asthma (BA); possible respiratory symptoms in these patients due not only to the action of air pollutants, and hypersensitivity to household, epidermal, mold allergens; perhaps these are the cases of overlap syndrome. Recently, in order to address some of the issues mentioned above, new diagnostic possibilities have appeared, among them – the method of molecular allergy diagnosis Phadiatop, which allows to determine the molecular structure of allergenic proteins, "guilty" of the body's sensitization to certain allergens. If the Phadiatop test sample results are positive, it is necessary to define a group of inhaled allergens, and then – the specific allergens in groups with the positive result. The negative Phadiatop test result means that the allergic-like symptoms are not caused by respiratory allergies, therefore, it is necessary to carry out studies of other organs and systems (digestive, immune, endocrine, etc.). We conducted a pilot study in 12 patients (average age – 65.0 ± 3.8 years, 7 men, and 5 women) with a long verified diagnosis (more than 5 years ago) of COPD stage III. Determining the level of eosinophil and total IgE in the blood, as well as the study of the Phadiatop test were conducted in the dynamics on the background of the planned treatment of patients – at their inclusion in the study, after 6 and 12 months. The results showed that the presence of signs of respiratory allergosis in COPD patient (according to Phadiatop test) are most often accompanied by increased levels of eosinophils and / or total IgE level in blood. However, in a certain proportion of patients with laboratory evidence of respiratory allergosis these indicators can be normal. Increased total IgE levels in the blood of COPD patient without the confirmed presence of signs of respiratory allergosis (according to the Phadiatop test) narrows the scope for further diagnostic search in the direction of another (non-respiratory) disease. Taking into account the data that the Phadiatop test results may change in the dynamics of patients' follow-up, it can be assumed that the manifestations of respiratory allergosis may change over time. Since the Phadiatop test is more sensitive and specific for the detection of symptoms of respiratory allergosis, it should be more widely used at the stages of screening and follow-up of patients with COPD (instead of determining the level of blood eosinophils and / or total IgE).

Key words: chronic obstructive pulmonary disease, inhaled allergens

Numerous pulmonologists have long ago admitted the fact that in some patients with chronic obstructive pulmonary disease (COPD) during infectious exacerbation, the signs of eosinophilic inflammation are increased, and its marker appears in the peripheral blood, namely, the elevated levels of eosinophils. It is not known, why these changes actually occur and why in these particular patients. As for the stable phase of COPD, even more questions arise: are there COPD patients with increased levels of eosinophils? If the answer is "yes", what rate of increase is the most characteristic for them? Is this not the case of wrongly diagnosed COPD instead of bronchial asthma (BA)? Are the respiratory symptoms in patients with COPD due to not only influence of air pollutants (tobacco smoke, industrial factors), but also to household hypersensitivity, epidermal and mold allergens (that is, maybe it is the overlap syndrome?), etc.

Recently, in order to address some of the issues mentioned above, new diagnostic possibilities have appeared. One such possibility is the use of molecular method of allergy diagnosis, namely the Phadiatop test, – the new level of verification of allergic diseases [2, 5, 6]. This method allows us to determine the molecular structure of allergenic proteins, "guilty" of the body's sensitization to certain allergens.

The Phadiatop test is developed by Pharmacia Diagnostics. This is the comprehensive screening study, by means of which one can determine predisposition of allergic reaction to key inhaled allergens and thus clarify the nature of eosinophilic inflammation and confirm (or rule out) the signs of the allergic nature of respiratory symptoms, especially in patients with broncho-obstructive pathology. It allows us to determine the increase of specific immunoglobulin E (IgE) to both allergens of different groups, such as pollen, mold, mites, animal allergens, cockroaches and others. From the results of the study it will not be known, to which allergen the antibodies increase was found, but in the negative result, the possible allergic reactions to most frequently inhaled will be excluded. The analysis verifies the presence of atopy – personal or family predisposition to production of specific IgE in response to allergens' normal action. The higher the level of IgE-antibodies is, i.e. the degree of atopy, the higher the risk of symptomatic allergy is.

This method is innovative, based on immunofluorescence technique, and it provides 300 times more sensitiveness than enzyme multiplied immunoassay (ELISA) and is more specific. For the diagnosis of allergic diseases, the serum is studied via this method without hemolysis and chyle, Phadia 100 analyzer is applied using ImmunoCAR test system (Phadia AB).

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If the result of the Phadiatop test samples turns positive, it is necessary to conduct the following studies with certain groups of allergens (house dust, pets, mold, grass, weeds, egg white, milk, fish, wheat, soybeans, etc.). At the last stage, if necessary, it is needed to determine specific allergens in groups with the positive result. If the result of the Phadiatop test samples is negative, the likelihood of allergic symptoms or disease is minimal, amounting to almost zero. This means that the reason that caused symptoms similar to allergic in patient is not allergy, and therefore one should conduct the study of other organs and systems (digestive, immune, endocrine, etc.).

The Phadiatop test is safe for patients and can be carried out without restrictions - regardless of skin condition, medication (including antihistamines), disease activity, the presence of pregnancy; it can be conducted in children, even infants, as well as in elderly people.

It should be recalled that the level of total IgE is increased only in 50% of people sensitive to inhaled allergens.

Thus, the aim of our research was to determine the diagnostic significance of the Phadiatop test in order to establish the nature of respiratory symptoms in COPD within the framework of pilot study.

Materials and methods

The study included 12 patients with COPD of stage III (average age - 65.0 + 3.8 years, 7 men, 5 women). The diagnosis of COPD in all patients had been verified more than 5 years ago, and according to the results of long-term follow-up of patients it is not in doubt (all patients were active or former smokers with duration of smoking habit for over 10 years; according to spirometric monitoring, all patients had pronounced irreversible or partially reversible bronchial obstruction, no patient had history of asthma attacks as the main clinical sign of another possible broncho-obstructive disease − bronchial asthma).

The formulation of the diagnosis of COPD and its stage was performed according to the order of Ministry of Public Health of Ukraine No. 555 as of 27.06.2013 [1].

All examined patients were compliant and received the long-term routine therapy (over one year) that included inhaled corticosteroids (ICC) and long-acting β_2-agonist (combined salmeterol / fluticasone propionate (25/250 mcg) in 2 inhaled doses 2 times per day), and if necessary − short-acting β_2-agonist salbutamol (in 2 inhaled doses per administering).

At the stage of patients' inclusion in the study (at visit 1) all patients underwent the assessment of clinical symptoms; the degree of ventilation disorders, the level of blood eosinophils and total IgE, and the Phadiatop test index were determined. After 6 and 12 months (at visits 2 and 3) clinical and functional studies were re-conducted, serum total IgE and the Phadiatop test parameters were determined.

Throughout the study, patients received routine therapy.

Clinical symptoms were assessed for severity of COPD symptoms in general, using the COPD test score (COPD Assessment Test (CAT)) [4]. Total points for CAT, less than 10, were considered as "a small number of COPD symptoms," and more than 10 − as "a large number of COPD symptoms".

The study of ventilatory lung function with determining the level of parameters (forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), and their ratio − FEV_1 / FVC) was conducted by means of the computer spirometry with measurement of the loop "flow-volume" using the apparatus «Master Screen Body/Diff» («Jager», Germany). All figures were calculated as a percentage of appropriate values calculated by Knudson (1983). Spirometry was performed in the morning on an empty stomach.

Bronchial reversibility test was conducted with 400 mcg salbutamol; thus the level of FEV_1 to inhalation of salbutamol (in pre-dose) and 15-20 minutes after inhalation (post-dose) was determined.

Clinical blood analysis with leukocyte count was conducted in the morning on an empty stomach. Number of eosinophils was defined as the absolute (referential values − 0.00-0.56 g/l) and relative (the referential value − 0.0-6.0%) indices.

Quantitative level of total IgE in serum of patients with COPD was determined by immunofluorescence method (referential values − 0.0-113.0 IU/ml).

The Phadiatop test was performed by immunofluorescence method using the ImmunoCAR test kits. In referential values 0-0.35 kU/l the result was considered negative, in values higher than 0.35 kU/l − positive.

Statistical analysis of the results was performed with the standard package of functions of «MS Excel».

Results and discussion

Analysis of the results showed that at the time of patients' inclusion in the study, all of them had relatively high severity of clinical symptoms (according to CAT) as well as rather manifested bronchial obstruction (by FEV_1 level; in all patients FEV_1 / FVC ratio was lower than 0.7) (Table 1).

Table 1

Average levels of clinical, functional and laboratory parameters in examined patients with COPD at visit 1

No.	Parameters	Parameter values
1.	CAT, points (M±m)	15.91±0.80
2.	FEV_1 level, % of proper value (M ± m): - In pre-dose - In post-dose	 42.53±3.18 45.30±2.80
3.	The level of blood eosinophils: - Abs. (M ± m) - % (M ± m)	 0.39±0.08 5.63±1.13
4.	IgE, IU / ml	273.5±101.2

The attention has been drawn to the fact that no patient at visit 1 had total CAT points, less than 13; in one patient, this figure amounted to 24; in the rest, it ranged from 13 to 17. Thus, all patients had "a large number of COPD symptoms" despite the fact that, apparently, against the long-term use of ICC and bronchodilators of prolonged action they would have to manifest significantly less symptoms of the disease.

The latter suggests that drugs that are recommended today for patients with COPD (according to both national

and European standards [1, 5]), are still unable to resolve all the clinical symptoms of the disease even when patients are absolutely compliant and committed to the therapy prescribed by the doctor. There are grounds for the need to ascertain the reasons for the pathological process prolongation with outlining new pathogenetic links of COPD formation, as well as for justification of new approaches to the planned treatment of patients with future development of new groups of effective drugs. One of these areas can be clarification of issues related to the contribution of eosinophilic inflammation and / or respiratory allergies (most frequent sensitization to inhaled allergens) in the pathogenesis of COPD, and therefore the impact of these processes on the certain instability of patients' condition.

Regarding blood eosinophilia, we have found that in some patients with COPD, it can be observed not only in the acute phase (which is indicated in the literature [1, 3]), but in the stable phase of the pathological process, and against the backdrop of long-term use of planned treatment, including ICC. Thus, in 4 out of 12 (33.3%) observed patients, the increased percentage of blood eosinophils was revealed, in two of them − also the increase of their absolute amount. Individual analysis showed that patients with only percentage elevated levels of eosinophils, the blood levels of total IgE was normal (7.1 and 29.2 IU/ml), and the index of Phadiatop test was negative, whereas in higher both percentage and absolute eosinophil blood levels, total IgE was significantly higher than norm (304.3 and 1039.3 IU/ml), and the rate of the Phadiatop test was positive.

Interesting was the fact that during the subsequent visits (2 and 3) in one patient with initially normal level of total IgE and negative Phadiatop test result, the parameters have changed (IgE reached the level of 188.1 IU/ml at visit 2 and 324.1 IU/ml at visit 3 and the Phadiatop test turned positive, it is possible that he contacted with the allergen); in another patient, the figures remained without significant changes. In initially elevated total IgE and positive test Phadiatop (during the subsequent visits 2 and 3) in one patient the parameters did not change, while in another patient with levels of total IgE, higher than norm by almost 10 times, the Phadiatop test turned negative (most probably, he withdrew from the contact with the allergen).

In patients with initially normal levels of eosinophils both in percentage and in absolute terms (in 8 out of 12 (66.6%) observed patients) the levels of total IgE and the Phadiatop test results were different. In half of them (4 out of 8 (50%)) the total serum IgE was normal, and the Phadiatop test was negative. In the other half of patients, the results were as follows: in one patient with normal levels of total IgE (41.1 IU/ml) the Phadiatop test was positive; in another one, on the contrary, with increased levels of total IgE (488.9 IU/ml), the Phadiatop test was negative; in two persons, total IgE levels were elevated (426.8 and 804.7 IU/ml) and the Phadiatop test indicators were positive.

At the stages of observation of all 8 patients, mentioned above (at visits 2 and 3) the Phadiatop test results and total IgE did not change.

It should be added that clinical symptoms in examined COPD patients in the dynamics of observation (at visits 2 and 3) remained quite distinct − in all patients the CAT total score remained higher than 10.

The obtained results, although in the rather modest sample group of patients, have provided us with a number of scientific thoughts, which we consider as necessary to be shared.

1. According to the severity of clinical symptoms in patients with COPD (by CAT) the doctor can neither confirm nor deny the presence of respiratory allergies. In order to address this issue, it is necessary to conduct special diagnostic search. It is possible that patients with severe bronchial obstruction, absence of clinical symptoms of respiratory allergies and presence of its laboratory signs have the overlap syndrome.

2. Increased levels of eosinophils and total IgE in the blood of patients with COPD do not always reflect the presence of respiratory allergies. These changes may have another cause of systemic allergic reactions, such as intestinal helminthiasis (it is known as IgE is involved in the formation of protective antihelminth immunity).

3. The presence of laboratory signs of respiratory allergies in COPD patient (according to the Phadiatop test) is still most often accompanied by increased levels of eosinophils and / or total IgE levels in the blood. However, one should remember that in some patients with laboratory signs of respiratory allergies both blood levels of eosinophils and levels of total IgE may be normal. The latter indicates the presence of respiratory allergies in patients with the prevalence of local characteristics over the systemic ones and does not preclude the need for further diagnostic search of causes of respiratory allergies (including the determination of allergen-specific IgE levels), and justifies the choice of inhaled route of administering drug to eliminate relevant pathological changes.

5. Increased total IgE in the blood of patients with COPD without confirmation of signs of respiratory allergies (according to the Phadiatop test) narrows the scope for further diagnostic search toward another (non-respiratory) disease.

6. Since Phadiatop test is more sensitive and specific for detection of respiratory allergies, it should be used as widely as possible at the stage of screening patients (including patients with COPD), instead of determining the level of eosinophils blood and / or total IgE.

7. Taking into account the data on the possible changes of the Phadiatop test result in the dynamics of patients' observation, it can be assumed that the manifestations of respiratory allergies can vary in time (possibly depending on the season).

Thus, all of the above allowed us to conclude that:

1) the conducted pilot study demonstrated that the Phadiatop test is a valuable tool for the diagnosis of respiratory allergies (allergic respiratory sensitization) in patients with COPD and can reveal the nature of respiratory symptoms in many of them;

2) our results draw attention to the need for better understanding of the problem and further research involving a greater number of patients.

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