AJPMHS GLOBAL RESEARCH NETWORK

AMERICAN Journal of Pediatric Medicine and Health Sciences
Volume 01, Issue 08, 2023 ISSN (E): 2993-2149

Peculiarities of the Relationship between Immunological Parameters and Endothelial Dysfunction in Patients with Bronchial Asthma, Chronic Obstructive Pulmonary Disease and Their Combination

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Abstract: To date, many studies have defined COPD-bronchial asthma crossover syndrome as a phenotype of COPD. Patients with a cross between bronchial asthma and chronic obstructive pulmonary disease (COPD) have differences with patients with isolated bronchial asthma (BA) and chronic obstructive pulmonary disease (COPD). Separation of such patients into a special group seems to be justified and appropriate from the standpoint of pathophysiology, clinic and therapy.

Key words: Chronic obstructive pulmonary disease, bronchial asthma, endothelial dysfunction.

Introduction. Chronic obstructive pulmonary disease (COPD) is a common disease with high global morbidity and mortality. COPD is characterised by poorly reversible airway obstruction, as evidenced by spirometry, and includes small airway obstruction (chronic obstructive bronchiolitis) and emphysema, which result in air retention and dyspnoea in response to exercise. The most common risk factor for developing COPD is cigarette smoking, but other environmental factors such as exposure to indoor air pollutants, especially in developing countries, can influence the risk of COPD. Not all smokers develop COPD, and the reasons for the predisposition to the disease in these individuals have not been fully elucidated. Although the mechanisms underlying COPD remain poorly understood, the disease is associated with chronic inflammation that is usually resistant to corticosteroids. In addition, COPD involves accelerated lung aging and an abnormal repair mechanism that may be induced by oxidative stress. Acute exacerbations, which are mainly caused by viral or bacterial infections, are important because they are associated with a poor prognosis. The mainstay of treatment of stable disease is the use of long-acting inhaled bronchodilators, whereas corticosteroids are primarily effective in patients who have concomitant features of asthma, such as eosinophilic inflammation and greater reversibility of airway obstruction. With the exception of smoking cessation, no treatment modality slows disease progression. More research is needed to better understand the mechanisms of the disease and to develop new therapies that reduce disease activity and progression.

Although the mechanisms of bronchial asthma and COPD have been studied worldwide, a number of scientific studies are being conducted to analyse the pathogenetic mechanisms in the principles of prevention and treatment, measures to prevent the disease and to establish a fundamental basis for early diagnosis.

Purpose of the study: to improve the efficiency of early and differential diagnosis taking into account immunological parameters of AD, COPD and their combination.

Materials and methods of the study: During the research we studied 123 patients. We divided them into 3 groups. The first group consisted of 43 patients with bronchial asthma, the second group consisted of 41 patients with chronic obstructive pulmonary disease and the third group consisted of 39 patients with combined pathology.

The study was performed in several stages. At the first stage all patients underwent initial complex anamnestic, clinical, laboratory and instrumental study, which included: general clinical examination, interview of patients, instrumental study and immunological study in blood and EAB.

The concentration of cytokines IL-4, IL-6 and TNF-α was determined by enzyme immunoassay method using test systems Vector-Best (Novosibirsk, Russia). The principle of ELISA-4IL kit operation is based on the "sandwich" version of immunoenzyme analysis. In order to perform this version two monoclonal antibodies with different epitope specificity to IL-4 were used. One was immobilised in solid phase (on the inner surface of the wells) and the other was conjugated with peroxidase. In the first step of the assay, IL-4 present in the calibration and test samples binds to the immobilised antibodies on the inner surface of the wells. In the second step of the assay, immobilised IL-4 interacts with the secondary antibody-peroxidase conjugate. The amount of bound conjugate is directly proportional to the amount of IL-4 in the punctate.

NO metabolism was studied as follows: the concentration of stable NO metabolites (NO2/NO3) was investigated in blood and FVC using Griess reagent. FVC was collected by the method of G.I. Sidorenko et al. (1980), modified by us.

Results of the study. To detect endothelial dysfunction we studied the ratio of NO2 and NO3 indices both in EFV and in blood. The results of these values, which were obtained in 20 people, defined by us as "practically healthy", were taken as normal in our study: the ratio of NO2/NO3 in blood -13,43-14,83 μmol/l and in EFV 5,2-6,92 μmol/l. The control group consisted of 20 practically healthy individuals (12 males and 8 females) aged 49.13 ± 4.67 years. Volunteers from the control group were without chronic diseases, without bad habits and did not take various kinds of drugs. When comparing the groups of AD and COPD patients in the acute stage, it was revealed that both AD and COPD patients had high values of NO2/NO3 ratio in contrast to practically healthy individuals, but it should be emphasised that COPD patients had statistically high values in blood in relation to AD patients ($P<0,01$) and also in EFV ($P<0,001$), this confirms that endothelial dysfunction is more pronounced among COPD patients. In the remission stage, we found an identical pattern.

When comparing COPD and BA+COPD patients in the stages of exacerbation and remission, we found also high indices in both groups, but statistically significantly high in COPD patients both in blood ($P<0,05$) and in EFV ($P<0,001$).

When comparing patients with AD and AD+COPD in the stage of exacerbation in contrast to potentially healthy patients the NO2/NO3 ratio was statistically significantly high in patients with AD as well as in patients with combined pathology, but it should be noted when comparing patients with AD and AD+COPD in the stage of exacerbation there was no statistically significant difference when determining the indicators in blood and in EFV. When studying these parameters between the same groups in remission stage, a statistically significant difference was noted, expressed in increased concentrations of NO2 and NO3 in EFV of patients with BA+COPD in comparison with patients with AD.

To determine the significance of immunological indicators, NO2/NO3 ratio in the course of COPD, AD, AD+COPD, a number of correlation analyses were performed to identify the relationship between cytokine indicators (IL-4, IL-8) and NO2/NO3 both in blood and in EAB with the subsequent construction of a correlation graph, equation diagram and approximation value.

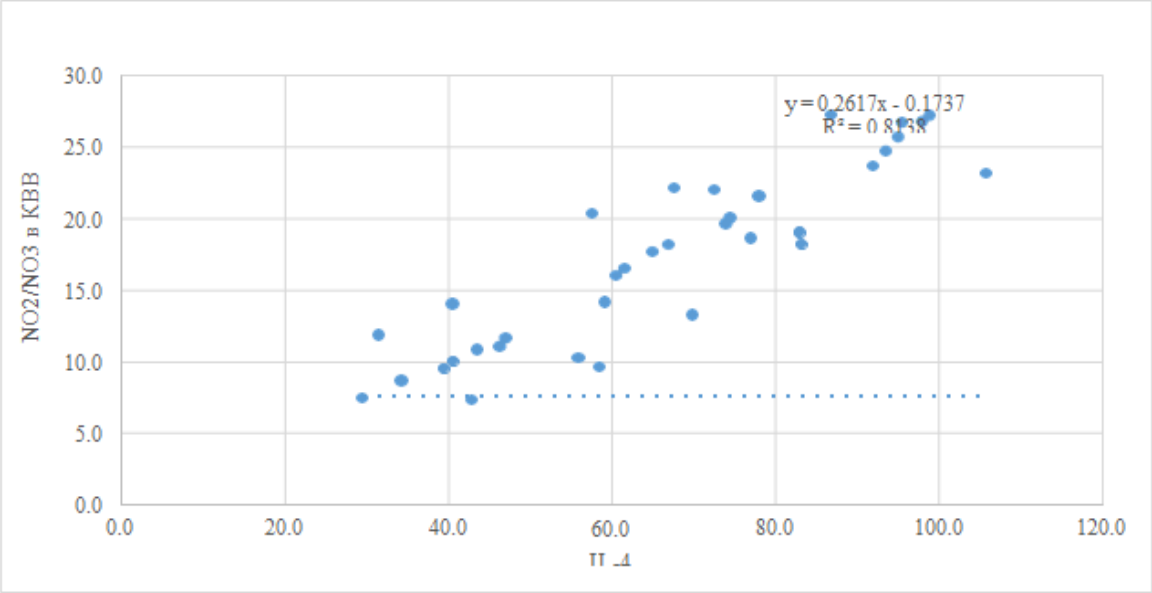

Figure 1: Correlation plot of IL-4 and NO2/NO3 in the blood of AD patients in the exacerbation stage (P<0.001).

The data of patients with bronchial asthma shown in Figure 1 show high uniform crowding of indicators in the form of almost identical small deviation of points relative to the trend line. The obtained data indicate a very high direct correlation between IL-4 and NO2/NO3 indices in the blood of BA patients in the exacerbation stage (r=0.90), which indicates the validity of using these immunological indices in diagnosing and determining the course of the disease.

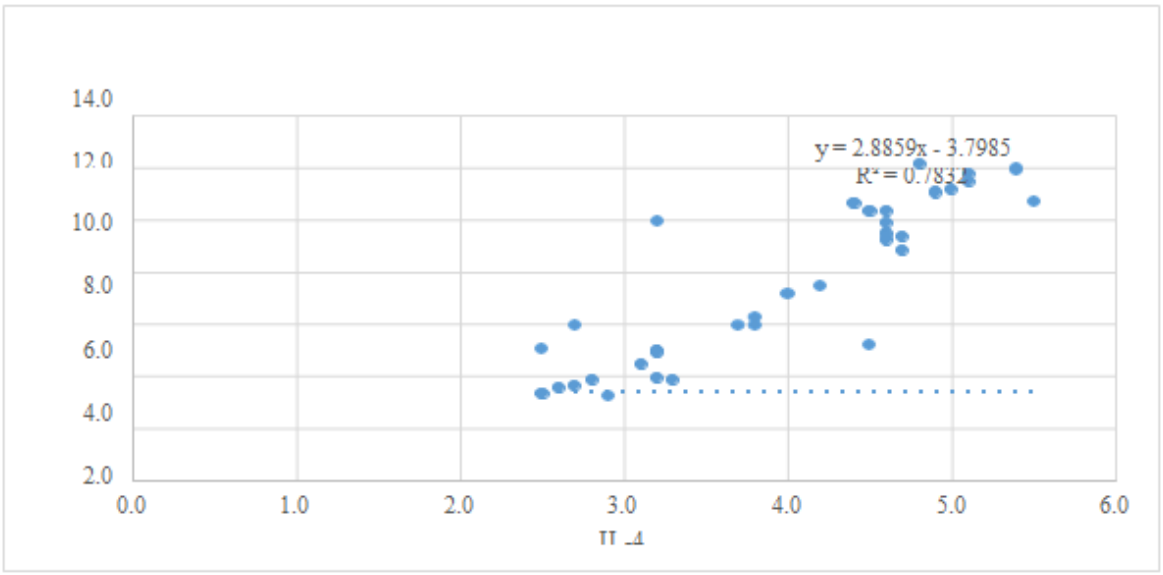

Figure 2: Correlation plot of IL-4 and NO2/NO3 in EFV of AD patients in the exacerbation stage (P<0.01).

A similar picture was observed in the study of these indicators in EHF, shown in Figure 2, even greater crowding of indicators is noted, only a small number of deviation points relative to the trend line. The obtained data testify to high direct correlation between IL-4 and NO2/NO3 indices in EHF of AD patients in the stage of exacerbation (r=0,88), which indicates the validity of using these immunological indices in diagnostics and determination of the course of the disease.

The study of indicators of patients with bronchial asthma, shown in Figures 3 and 4 also shows a high uniformity of the indicators with an insignificant amount of small deviation of points above

relative to the trend line, which indicates a very high direct correlation between the indicators of IL- 8 and NO2/NO3 in the blood of patients with BA in the acute stage (r=0,91) and a high direct correlation between the indicators of IL-8 and NO2/NO3 in the EHF of patients with BA in the acute stage (r=0,88).

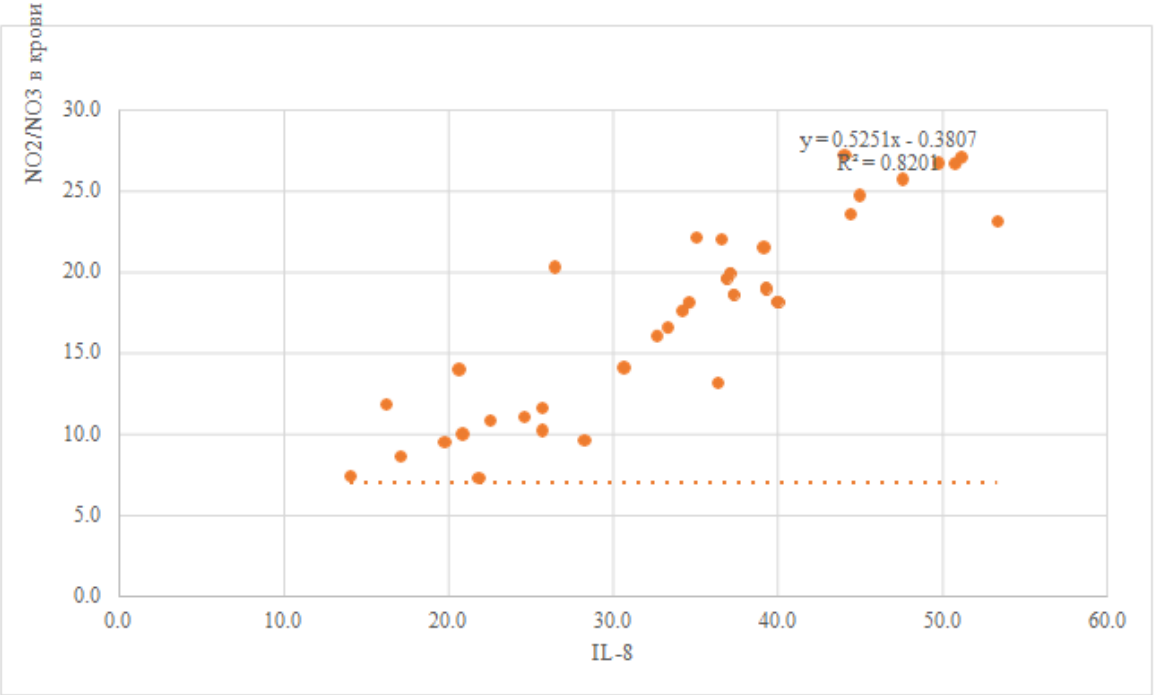

Figure 3: Correlation plot of IL-8 and NO2/NO3 in the blood of AD patients in the exacerbation stage (P<0.01).

The study data shown in Figures 5 and 6 show high uniform crowding of indicators in the form of almost identical small deviation of points relative to the trend line. The obtained data indicate a very high direct correlation between IL-4 and NO2/NO3 indices in blood and EHF of COPD+BA patients in the stage of exacerbation (r=0,88; r=0,89), which indicates the validity of using these immunological indices in diagnosing and determining the combined course of diseases.

When studying the correlation relations of IL-8 and NO2/NO3 ratio in blood and EHF of COPD+BA patients in the stage of exacerbation, shown in Figures 7 and 8, it was noted that against the background of crowding of indicators, several points were observed that were at a great distance from the trend line when studying the indicators in both blood and EHF of COPD+BA patients. At the same time, the obtained correlation data indicate a high direct correlation between IL-8 and NO2/NO3 indices in blood and EHF of COPD+BA patients at the stage of exacerbation (r=0,83; r=0,86).

Based on the conducted correlation studies of IL-4, IL-8, TNF-α, IgE indices with the indices of endothelial dysfunction in the groups of patients with BA, COPD and COPD+BA, the final correlation tables were compiled (Table 1 and 2)

Table 1. Correlation matrix of basic immunological indices and NO2 and NO3 in blood in patients with BA, COPD and COPD+BA

Readings	NO2 and NO3 in the blood		
	BA (r)	COPD (r)	COPD+BA (r)
IL-4 in blood	0,90	0,80	0,88
IL-8 in blood	0,91	0,81	0,83

Table 2. Correlations (r) between cytokine indices and NO2 and NO3 in EFV in patients with AD, COPD and COPD+BA

Indices	NO2 and NO3 in the EAC		
	BA (r)	COPD (r)	COPD+BA (r)
IL-4 in EHF	0,88	0,80	0,89
IL-8 in EAC	0,88	0,80	0,86

It should be noted a very high strength of direct correlation in patients with bronchial asthma between IL-4, IL-8 and endothelial indices in blood, which proved the essential role of immunological indices in the course of the disease. It is also necessary to note the high strength of direct correlation dependence in patients with BA, COPD and COPD+BA between the rest of immunological and endothelial indices, which indicated a high correlation of disturbed immunological and endothelial status in patients with chronic respiratory pathologies.

Conclusions: Thus, the conducted studies showed that the patients had impaired immune response, which was manifested in hyperproduction of various interleukins, which had a direct correlation with the disease clinic. The clear directionality of immune metabolism and their expression indicate an important pathogenetic role of immune mechanisms, which leads to delayed recovery processes of AD, COPD and AD+COPD in the development and progression of changes in the state of immune and endothelial systems.

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