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PECULIARITIES OF IMMUNOLOGICAL RESPONSE IN PATIENTS WITH OVERCROSSED BRONCHIAL ASTHMA AND COPD

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✓ ***Resume***

This article discusses the issues of immunological status in patients with asthma, COPD and ACO. A correlation analysis of 10 clinical and immunological parameters was carried out, on the basis of which (IL-8 va IFNy) an index for the prognosis of the course of the disease of bronchial asthma and COPD overlap was developed, which makes it possible to predict the course of the disease and the choice of adequate therapy.

Keywords: BA, COPD, ACO, cytokines, IgE, correlation analysis.

ОСОБЕННОСТИ ИММУНОЛОГИЧЕСКОГО РЕАГИРОВАНИЯ У БОЛЬНЫХ С ПЕРЕКРЕСТОМ БРОНХИАЛЬНОЙ АСТМЫ И ХОБЛ

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✓ ***Резюме***

В данной статье рассматриваются вопросы иммунологического статуса у больных БА, ХОБЛ и ПБАХ. Был проведен корреляционный анализ 10 клинико-иммунологических параметров, на основе которых (IL-8 va IFNy) был разработан индекс прогноза течения заболевания перекрёста бронхиальной астмы и ХОБЛ, позволяющий прогнозировать течение заболевания и выбора адекватной терапии.

Ключевые слова: БА, ХОБЛ, ПБАХ, цитокины, IgE, корреляционный анализ.

BRONXIAL ASTMA VA O'SOK KESISHMASI BO'LGAN BEMORLARDA IMMUNOLOGIK JAVOBNING XUSUSIYATLARI

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✓ ***Resume***

Ushbu maqolada astma, O'SOQ va BAO'Q bilan kasallangan bemorlarning immunologik holati masalalari muhokama qilinadi. 10 ta klinik va immunologik ko'rsatkichlarning korrelyatsiya tahlili o'tkazildi, uning asosida (IL-8 va IFNy) bronxial astma va O'SOQ kasalligining o'zaro bog'liqligi prognozi uchun indeks ishlab chiqildi, bu esa: kasallikning vater kechishini tanlashni bashorat qilish.

Kalit so'zlar: BA, O'SOQ, BAO'Q, sitokinlar, IgE, korrelyatsiya tahlili.

Relevance

In our country, as well as throughout the world, the trend of diseases of the bronchopulmonary system, such as asthma, COPD, is growing. The combination of bronchial asthma and COPD increases the risk of developing complications of the underlying and concomitant diseases, which in turn puts this problem among the most pressing. [2, 3, 8, 15].

The issue of fundamental importance in modern practical medicine is the relationship between the formation of the layering of chronic diseases, such as asthma and COPD, with the processes occurring in the bronchopulmonary system or with changes in the immune system. According to many authors,

the cause of overlapping or layering of bronchial asthma and chronic obstructive pulmonary disease is various immune disorders that cause a decrease in the body's resistance to microbial infection [1, 9, 14].

A group of other scientists believes that ACO has a different combination of immune disorders, which is a consequence of the development of two separate pathologies. In some cases, Th2-type atopy and inflammation of the airways, eosonophilia, elevated IgE levels, with the participation of cytokines such as IL-4, IL-5 and IL-9, can be observed in patients with ACO. And other patients with ACO may have signs of COPD, neutrophilia and an imbalance of such cytokines as IL-6, IL-8 and tumor necrosis factor [4,7,20,25].

The study of cytokines shows their significant and diverse role in the development of immune, allergic and inflammatory reactions in respiratory diseases. Emerging data on the nature and functions of these mediators complement the understanding of the pathogenesis of pulmonary diseases. As the role of cytokines becomes clear, it becomes possible to control the inflammatory process and other pathophysiological consequences of lung damage [5, 6, 11,16].

Based on the above, the purpose of our study is to study the characteristics of the immune status in patients with overlapping bronchial asthma and COPD.

Materials and methods

We have studied the state of the immune system in 159 patients with bronchopulmonary diseases. Of these, 62 patients with BA, 67 patients with COPD and 30 patients with ACO. 20 practically healthy people made up the control group.

The inclusion criteria for the study were patients with an established diagnosis of asthma and/or COPD aged 18 to 75 years.

Exclusion Criteria:

- heart disease (acute myocardial infarction)
- the presence of cerebrovascular diseases (stroke, transient ischemic attacks
- malignant neoplasms
- severe kidney or liver failure
- Pregnancy or breastfeeding in women
- severe endocrine pathologies
- severe autoimmune condition

Quantitative assessment of the levels of IL-4, IL-8, TNFα, IFNγ was carried out using test systems (LLC "Cytokin", St. Petersburg) by enzyme-linked immunosorbent assay.

Statistical processing of the obtained data was carried out by the method of variation statistics according to Fisher-Student and used Pearson's χ^2 test.

Result and discussion

In our studies, we conducted a comparative analysis of pro- and anti-inflammatory cytokines in the studied groups (IL-4, IL-8, TNFα, IFNγ) (Table 1).

Table 1

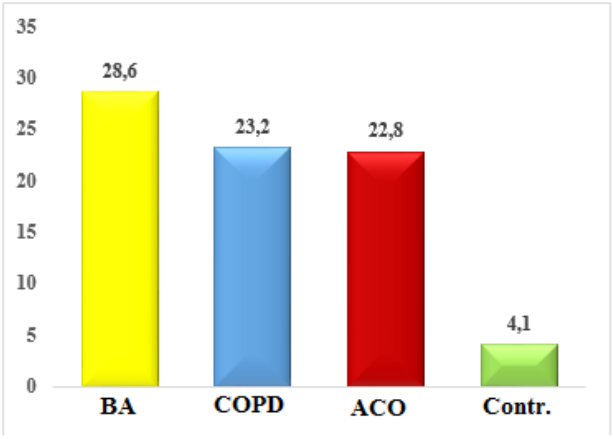
The concentration of cytokines in the group of subjects

	BA (n=62)	**COPD (n=67)**	**ACO (n=30)**	**Counter.**
IL-4	28.6±1.7*	23.2±1.5	22.8±1.2	8.7±0.3
IL-8	18.7±1.4	27.8±1.3	39.6±1.1*	11.6±0.4
TNF-α	35.3±2.5	39.7±2.2	46.2±1.7*	21.4±0.1
IFN-γ	11.7±0.6	14.3±1.5*	12.4±0.2	19.1±0.9

*Note: *Values are significant in relation to the control group (P<0.05-0.001)*

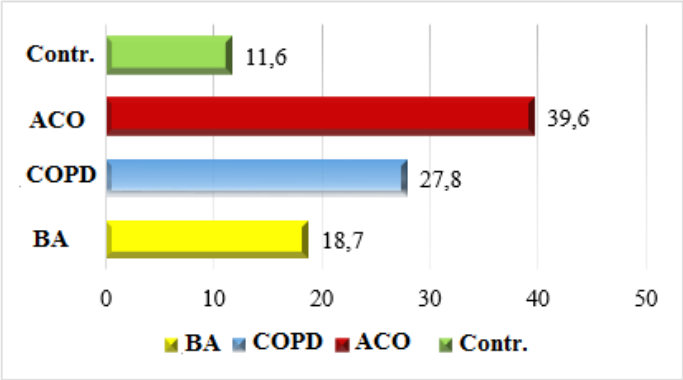
According to many authors, cells synthesizing Th2-type cytokines dominate in the airways affected by asthma. CD8+ cells, eosinophils, and mast cells produce IL-4, which, in turn, possibly causes bronchial tree hyperreactivity [10, 13, 19, 24]. Our data confirm that the levelIL-4 was the highest in

the BA group - 28.6 ± 1.7 pg/ml, which was significantly higher by 3.97 times than in the COPD group and 1.25 times more than in the ACO group. (P<0.01) (Pic. 1.)



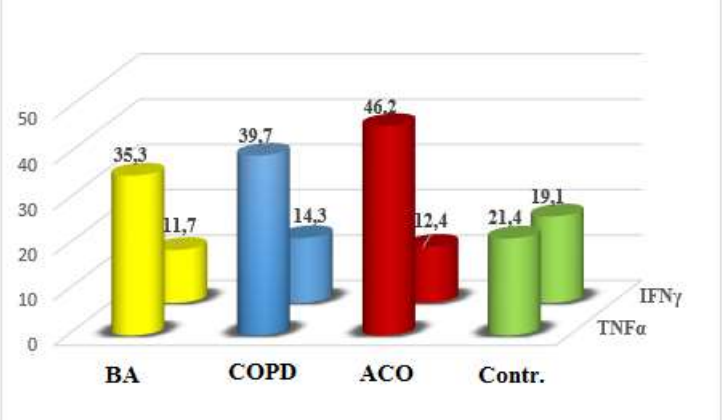
Pic. 1. The level of IL-4 in the groups of subjects

In chronic obstructive pulmonary disease and ACO, an increase in the content of IL-8 in sputum is observed, which is associated with the involvement of neutrophils in the inflammation focus [12].In our study, the concentration of IL-8 was high in the ACO group - 39.6 ± 1.1 pg/ml, which was significantly higher by 2.1 times compared with the BA group and 1.42 times higher in COPD.(P<0.01)(Pic.2)



Pic. 2. The level of IL-8 in the groups of subjects

When studying the concentration of tumor necrosis factor, there were no significant differences between the BA and COPD groups; in the ACO group, the concentration TNFα was increased 1.3 times compared with other groups (46.2 ± 1.7 pg/ml).(P<0.01).The increase in the level of TNFα in the ACO group is possibly associated with a more intense inflammatory process in the lungs.



Pic. 3. The level of TNFα and IFNγ in the groups of subjects

Interferon gamma is an indicator of the Th1 immune response, which is more characteristic of a non-allergic inflammatory process. Level IFNγ was reduced in all the studied groups, but its lowest concentration was observed in the BA group 11.7±0.6.(P<0.01)(Pic.3.).

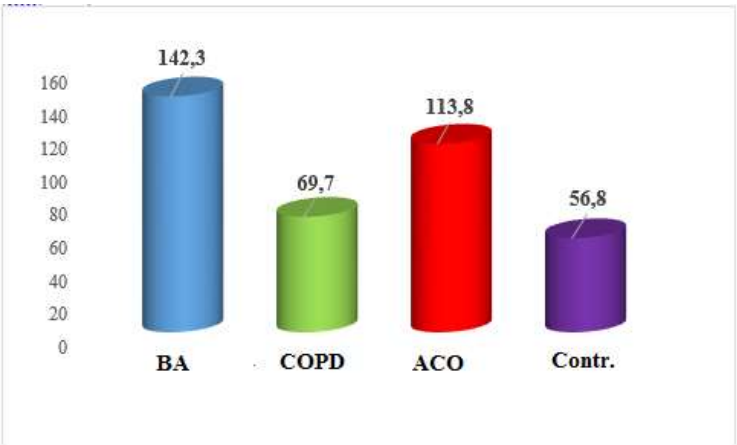
Thus, a comparative analysis of the indicators of pro- and anti-inflammatory cytokines in patients during exacerbation of BA, COPD and ACO revealed that IL-4 synthesis was the highest in the group of patients with bronchial asthma and was 3.97 times higher than in the group with COPD and 1 .25 times more than in the ACO group (P ≤ 0.01). The concentration of IL-8 was high in the ACO group - 39.6 ± 1.1 pg/ml, which was significantly higher by 2.1 times compared with the BA group and 1.42 times higher in COPD.(P<0.01). When studying the concentration of tumor necrosis factor, there were no significant differences between the BA and COPD groups; in the ACO group, the concentration TNFα was increased 1.3 times compared with other groups (46.2 ± 1.7 pg/ml).(P<0.01). Level IFNγ was reduced in all the studied groups, but its lowest concentration was observed in the group with BA 11.7±0.6 (P<0.01). The results obtained reflect the type and intensity of airway inflammation. The high values of the studied cytokines confirm their role in bronchial remodeling and contribute to the irreversibility of obstruction in these pathologies. Perhaps this is due to the chronic course of both eosinophilic and neutrophilic airway inflammation. Undoubtedly, these cytokines play an important role in the pathogenesis of BA, COPD, ACO and can serve as markers of the severity of the pathological process.

The main biological role is the unique ability to bind to the surface of human mast cells and basophils [17, 21, 23].

IgE is synthesized mainly by plasma cells localized in the mucous membranes.

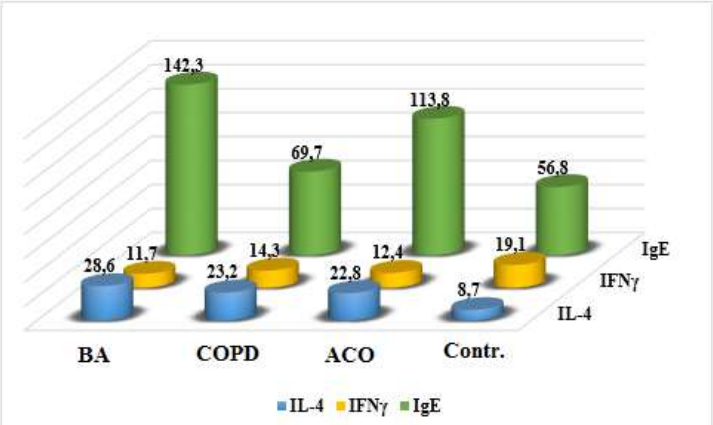
In an immediate hypersensitivity reaction, specific antibodies (reagins) are detected in the body that have the ability to sensitize their own tissues - IgE.

The results of our studies showed that in bronchial asthma there is a sharp tendency to increase the level of IgE (142.3±0.9 ng/ml versus 56.8±0.6 pg/ml in control). (P<0.01).



Pic.4. IgE level in examined patients (ng/ml) with BA, COPD, ACO

In patients with COPD and ACO, the level of IgE was increased by 1.2 and 2 times, respectively, averaging 69.7±1.3 ng/ml and 113.8±1.6 ng/ml versus 56.8±0 .6 ng/ml, (P<0.01) (Pic. 4.).



Pic.5. Level of IL-4, INFγ and IgE in examined patients (ng/ml)with BA, COPD, ACO

The earlier study to determine the level of pro- and anti-inflammatory cytokines (IL-4, IFNγ) revealed a clear relationship with the synthesis of IgE in the examined groups, which was more pronounced in the group with bronchial asthma. This may be an evidence factor of the leading role of bronchial asthma in the development of ACO. (Pic.5.)

Interleukin-4 (IL-4) is leading in the formation CD4+ type of immunoreactivity, thus defining a completely different nature of inflammation. Despite the fact that this cytokine is determined to play a leading role in the formation of respiratory tract inflammation in bronchial asthma, it can also contribute to the pathogenesis of the inflammatory response in COPD. The formation of the CD4+ type of immune response is important in the development of the eosinophilic type of inflammation in the tissue of the respiratory tract, forming the eosinophilic phenotype of COPD. In addition, IL-4 activates the production of growth factors that contribute to the formation of airway remodeling. [18, 22]

This once again proves that the violation of the mechanisms of immunological reactivity leads to the development of chronicity and aggravation of pathological processes in the bronchial tree.

Next, we carried outcorrelation analysis (Table 1) of clinical and immunological parameters in those examined in the BA group. 16 connections were revealed, of which 10 (r=0-0.3) are positive and 6 are negative. (Table 2.)

Table 2

Correlation indicators of patients with bronchial asthma

	IL-4	IL-8	TNF-α	IFN-γ	IgE	CRP	LN	Vit D	fibrin	Eoz
IL-4	1									
IL-8	0.04	1								
TNF-α	0.031	0.184	1							
IFN-γ	-0.038	-0.31	-0.0406	1						
IgE	0.11	0.004	0.1151	-0.039	1					
CRP	0.09	0.074	0.2012	-0.041	0.18	1				
LN	-0.27	-0.127	-0.0505	0.111	-0.01	-0.01	1			
Vit D	0.05	0.179	0.1352	-0.029	0.18	0.06	-0.011	1		
fibrin	0.066	0.17	0.1419	-0.051	0.01	0.02	-0.113	0.046	1	
Eoz	0.274	0.143	0.0465	-0.091	-0	0.14	-0.102	0.075	0.1779	1

Thus, IL-4 has 1 direct (r=0.27) relationship with eosinophils and 1 inverse relationship (r=-0.27) with lactoferrin. IL-8 has 2 direct links with TNFα (r=0.18), vitamin D (r=0.17) and 2 reverse links with IFNγ (r=-0.31), lactoferrin (r=-0.12) . TNFα has 4 direct relationships with such indicators as IgE, CRP, vitamin D and fibrinogen (from r = 0.11 to r = 0.2), in turn, interferon gamma has one direct relationship with lactoferrin. The obtained values of immunoglobulin E were also in direct relationship with CRP and vitamin D (r=0.18). CRP also had a direct relationship with eosinophils (r=0.13). Lactoferrin has 3 relationships, all of which are negative with vitamin D, fibrinogen and eosinophils (r=-0.11). And the latter, in turn, have a direct relationship with each other (r=0.17).

In the group of patients with COPD, 22 correlation relationships were identified, of which 11 were positive (r=0-0.5) and 10 were negative values. (Table 3)

Table 3

Correlation indicators of patients with COPD

	IL-4	IL-8	TNF-α	IFN-γ	IgE	CRP	LN	Vit D	fibrin	Eoz
IL-4	1									
IL-8	0.078	1								
TNF-α	0.05	0.1	1							
IFN-γ	-0.221	-0.33	-0.0956	1						
IgE	0.073	0.03	0.173	-0.016	1					
CRP	0.03	0.12	0.0079	-0.16	0.02	1				
LN	-0.129	-0.15	-0.052	0.129	-0.01	-0.12	1			
Vit D	0.13	0.16	0.096	-0.008	0.09	0.02	-0.10	1		
fibrin	0.045	0.03	0.0524	-0.199	0.12	0.21	-0.01	0.0494	1	
Eoz	0.073	0.01	0.1524	-0.297	0.13	0.23	-0.15	0.064	0.027	1

Direct correlations were found between the following indicators: 1) IL-4 with vitamin D (r=0.13); 2) IL-8 with TNFα, CRP and vitamin D (r=0.1-0.16); 3) TNFα with IgE and eosinophils (r=0.15-0.17); 4) IFNγ with lactoferrin (r=0.13); 5) IgE with fibrinogen and eosinophils (r=0.12-0.13); 6) CRP with fibrinogen and eosinophils (r=0.21-0.23). It should be noted that the obtained inverse correlations were not in all indicators and ranged from r=-0.11 to r=-0.33. So, IL-4 with IFNγ and lactoferrin, IL-8 also with IFNγ and lactoferrin, IFNγ has 3 relationships with CRP, fibrinogen and eosonophylls. The C reactive protein has one bond with lactoferrin. And vitamin D and eosinophils have one inverse relationship with lactoferrin, respectively.

Next, a correlation analysis of clinical and immunological parameters was carried out in the group with ACO.

In the course of studying the correlation values between indicators in the ACO group, 33 relationships were identified, of which 22 were positive and 11 were negative. (Table 4)

Table 4

Correlation parameters of patients with ACO

	IL-4	IL-8	TNF-α	IFN-γ	IgE	CRP	LN	Vit D	fibrin	Eoz
IL-4	1									
IL-8	0.33	1								
TNF-α	0.26	0.01	1							
IFN-γ	-0.13	-0.41	-0.281	1						
IgE	0.24	0.42	0.334	-0.129	1					
CRP	0.24	0.19	0.408	-0.13	0.32	1				
LN	-0.17	-0.21	-0.2026	0.08	-0.02	-0.09	1			
Vit D	0.031	0.16	0.052	-0.08	0.2	0.03	-0.09	1		
fibrin	0.34	0.44	0.1602	-0.19	0.3	0.09	-0.24	0.236	1	
Eoz	0.21	0.19	0.1028	-0.14	0.1	0.21	-0.07	0.22	0.3047	1

A direct correlation relationship was observed within r=0-0.3 for 14 links and r=0.3-0.5 for 8 links. The r=0-0.3 value was between relationships; IL-4 and TNFα, IgE, CRP, eosinophils; IL-8 and CRP, vitamin D, eosinophils; TNFα and fibrinogen, eosinophils; IgE with vitamin D, fibrinogen CRP and eosinophils; vitamin D and fibrinogen, eosinophils. And the value of r=0.3-0.5 was in IL-4 and IL-8, fibrinogen; IL-8 with IgE and fibrinogen; TNFα with IgE, CRP; IgE with CRP; fibrinogen with eosinophil.

In contrast to the groups with bronchial asthma or COPD, in this group the number of inverse correlations is greater and ranges from r=-0.12 to r=-0.41. Of the 11 relationship values r=-0.3 to 0 occurs in 10 relationships between IL-4 with IFNγ, lactoferrin; IL-8 with lactoferrin; TNFα with IFNγ, lactoferrin; IFNγ with IgE, CRP, fibrinogen and eosinophils; lactoferrin with fibrinogen. And the values of r=-0.5 to -0.3 are found in only one relationship - between IL-8 and IFNγ (r=-0.41).

Thus, the analysis of correlation relationships between 10 clinical and immunological indicators revealed that in all groups of the studied (BA, COPD and ACO) 71 weakly significant correlation relationships were recorded. In particular, 16 relationships were found in the bronchial asthma group, 22 in the COPD group, while 33 relationships were identified in the ACO group, and IL-8 and IFNγ were subject to the greatest changes. This may indicate complex immunological mechanisms for the development of these pathologies, which leads to deeper changes in the bronchopulmonary tree and a severe course of the disease.

Our studies have revealed that in patients with ACO, the levels of pro-inflammatory cytokines - IL-8 and IFNγ - undergo a sharp change, mainly. In this regard, we considered it appropriate to calculate an index that combines these indicators using the following formula:

$$IL\text{-}8/IPCD = \frac{\qquad}{IFN\gamma},$$

where IPCD is the index of the prognosis of the course of the disease.

Previously, this ratio was used to predict the course of cystic fibrosis in children (N.Ya. Fayzullaeva 2017).

Calculations showed that in practically healthy people (control group) the IPTI was less than 1 and amounted to 0.6±0.15 (Table 4.4).

This indicator increased in patients with BA, which amounted to 2.96±0.3, in patients with COPD = 1.61±0.12, and in ACO = 3.19±0.17. (Table 5)

Table 5

The content of IL-8 and IFNγ in the peripheral blood serum of the examined

Indicators	Examined patients			
	K.gr.	BA	COPD	PBAH
IL-8	11.6	34.7	27.8	39.6
IFNγ	19.1	11.7	14.3	12.4
IPCD	0.60	2.96	1.94	3.19
	(0.45-0.75)	(2.66-3.26)	(1.89-1.99)	(3.02-3.36)

Ratio IL-8 and IFNγ can serve as a reliable prognostic and diagnostic criterion for the course of this disease.

Conclusion

Analysis of the result of the index of the prognosis of the course of the disease (IPCD) showed that among the examined, an increased index corresponded to a more severe clinical condition. So, for example, in patients with ACO with IPCD equal to 3.19 and higher, a higher percentage of complications, a severe protracted course, combined with symptoms of intoxication, were observed.

Our studies have shown that immunological parameters make it possible to predict the course of the disease with a fairly high accuracy.

Thus the ratio IL-8 and IFNγ provide important information about the state of the immune system not only at the time of the examination, but also allows predicting the further course of the disease. The study of these cytokines will help the doctor in determining the choice and duration of the necessary therapy.

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