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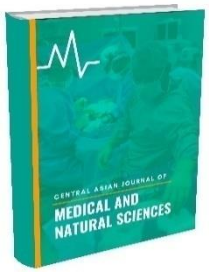

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Features of Cytokine Imbalance in Bronchial Asthma, Chronic Obstructive Pulmonary Disease and Their Comorbidity

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Abstract: Nowadays respiratory diseases represent not only medical but also social and economic problem, which is the most widespread according to the World Health Organization, "the number of people suffering from bronchial asthma (BA) is 300 million, and chronic obstructive pulmonary disease (COPD) is the fourth most important cause of death". In clinical practice there are often patients with characteristic symptoms of both nosological forms, which leads to certain difficulties in diagnosis and treatment. The aim of the study is to assess the role of cytokines IL-4, IL-8, IgE and TNF-α in the blood and in the exhaled air condensate of patients with bronchial asthma, chronic obstructive pulmonary disease and their combination. The subjects of the study were 101 patients diagnosed with bronchial asthma and chronic obstructive pulmonary disease. The results showed that while comparing indices of interleukin - 8 (IL-8) in blood and in PBV among 3 comparable groups in acute stage it was revealed that in patients with COPD unlike BA patients (P<0,05), BA+COPD had statistically significant high indices (P<0,001). When comparing BA+COPD and BA, high IL-8 values were found among BA patients, this index was also statistically significant in blood (P<0.05) and statistically insignificantly high in the study of IL-8 in CVB (P<0.02).

Key words: bronchial asthma, cytokines, interleukins, COPD, immunoglobulins.

Introduction. Nowadays respiratory diseases are not only a medical but also a socio-economic problem, which is the most common according to the World Health Organization, "the number of people suffering from bronchial asthma (BA) is 300 million, and chronic obstructive pulmonary disease (COPD) is the fourth most important cause of death [2]. In clinical practice, there are often patients with characteristic symptoms of both nosological forms, which leads to certain difficulties in diagnosis and treatment. Despite the similarity of symptoms, these diseases differ histologically, are characterized by different physiological disorders, and have different clinical manifestations.

Currently, the main task of specialists is to slow down the progression of AD and COPD and their combinations, taking into account the specific pathogenetic pathways of the diseases, improving the quality of life of patients and preventing the development of complications. Despite the study of mechanisms of bronchial asthma and COPD in the world, a number of scientific studies to analyze the pathogenetic mechanisms in the principles of prevention and treatment, measures to prevent the disease and create a fundamental basis for early diagnosis are conducted. The diseases are progressive in their course, with clear systemic manifestations, especially in severe and extremely severe forms, despite differences in etiology, pathophysiology and clinical manifestations, which is explained by the presence of COPD and bronchial asthma symptoms in 10-20% of cases[6,7]. In AD and COPD, assessment of endothelial state, immunological status, functional state of respiratory system and functional lung reserve is of particular importance. Our country has set a number of tasks for the development of the medical industry, adaptation of medicine to the requirements of world standards, development of diagnostics, prevention and treatment of various somatic diseases. "Improving the efficiency, quality and accessibility of medical care, as well as the introduction of high-tech methods, support for healthy lifestyles and disease prevention...". These objectives serve to reduce the level of disability in the population as a result of prediction by assessing the age and recovery of patients with BA and COPD, assessment of immunological status, the functional state of the respiratory system and functional lung reserves.

The aim of the study is to assess the role of cytokines IL-4, IL-8, IgE and TNF-α in blood and in exhaled air condensate in patients with bronchial asthma, chronic obstructive pulmonary disease and their combination.

Materials and methods of the study. The objects of the study were 101 patients diagnosed with bronchial asthma and chronic obstructive pulmonary disease in the Department of Pulmonology and Allergology of Samarkand City Medical Association in 2017-2020 and 20 relatively healthy control subjects.

The diagnoses of bronchial asthma and chronic obstructive pulmonary disease were based on GINA 2019 and GOLD 2019[10].

Exclusion criteria for patients from the study were: severe and decompensated diseases of other organs and systems; tuberculosis of any localization in an active stage;

The control group consisted of 20 virtually healthy people (11 men and 9 women) aged 59.1 ± 3.7 years. All the patients included in the control group were without chronic diseases and without any harmful habits.

Bronchial asthma severity criteria were given according to GINA, and the main signs of moderate severity were considered: daily symptoms, nocturnal attacks > once a week, GEF1 and PSR 60-80% of the reference parameters, PSR> 30%, daily inhaled beta2 agonists;

15 patients were a group of persons with simultaneous BA + COPD pathology (interrelatedness syndrome). In 9 patients, BA was combined with moderate to severe COPD, in the remaining 5 patients who had BA first, then COPD was added to it, and in another 1 the diagnosis of combined pathology was made for the first time.

For immunological testing in exhaled air condensate (EAC), EAC was collected in the exacerbation and remission stages, and the obtained samples were stored at -80°C in the freezer. Quantification using R&D Systems equipment (USA) and 3 nitrotyrosine (3NT) using Hycult biotech reagent kit (Netherlands) was performed using enzyme immunoassay.

Results of the study. The state of immune reactivity plays an important role in pathogenesis of respiratory tract inflammation in chronic diseases. Airway inflammation is one of the main

pathogenetic links of AD, COPD, carried out with the help of cytokines and other immunocompetent cells [18,20]. In this regard, we studied the indices of proinflammatory (TNFα, IL-8) and anti-inflammatory (IL-4) cytokines and immunoglobulin (IgE) in blood and in CVB in patients with BA, COPD and at their combination in the acute stage of the disease.

When comparing the indices of interleukin - 8 (IL-8) in blood and in CVV among 3 comparable groups in the acute stage, it was found that among COPD patients, unlike BA patients ($P<0.05$), BA+COPD had statistically significant high indices ($P<0.001$). When comparing BA+COPD and AD, IL-8 was found to be high among BA patients, this index was also statistically significant in blood ($P<0.05$) and statistically not significantly high in the study of IL-8 in CVB ($P<0.02$). The study of interleukin-4 (IL-4) revealed a slightly different picture. Patients with BA and BA+COPD had.

A study of cytokine levels in BA and COPD patients (Fig.1) revealed a virtually lopsided pattern of changes. The levels of IL-4 production in BA patients were significantly higher both in blood - 69.1±4.1 pg/ml, and in exhaled air condensate - 4.0±0.2 pg/ml, compared to 31.5±1.8 pg/ml in blood and 2.5±0.1 pg/ml in exhaled air condensate in COPD, where significant differences ($P>0.001$) were found.

In a comparative evaluation of IL-4 in the serum of AD + COPD patients, cytokine production levels were higher ($P<0.001$) (42.1±2.4 pg/ml) than in COPD patients (31.5±1.8 pg/ml).

The insignificant change in cytokine production of IL-4 in patients with COPD compared to patients with BA is probably due to the fact that these types of cytokines do not play a leading role in the pathogenesis of COPD inflammation.

However, a comparative analysis of IL-4 cytokine levels in BA and BA+COPD patients in the acute stage revealed a multidirectional pattern, so while IL-4 content in blood had a significant difference with predominance in BA, cytokine production in exhaled air condensate in this group did not have such a significant difference ($P>0.1$).

IL-4 is a Th2 immune mediator that leads to allergic inflammation and disease pathogenesis responses specific to AD, COPD, and their combination.

However, the increased production of IL-4 in each group of patients can be explained by the activation of inflammatory processes by nonspecific factors and allows to confirm that IL-4 is the main cytokine in the development of allergic inflammation and this is confirmed by studies.

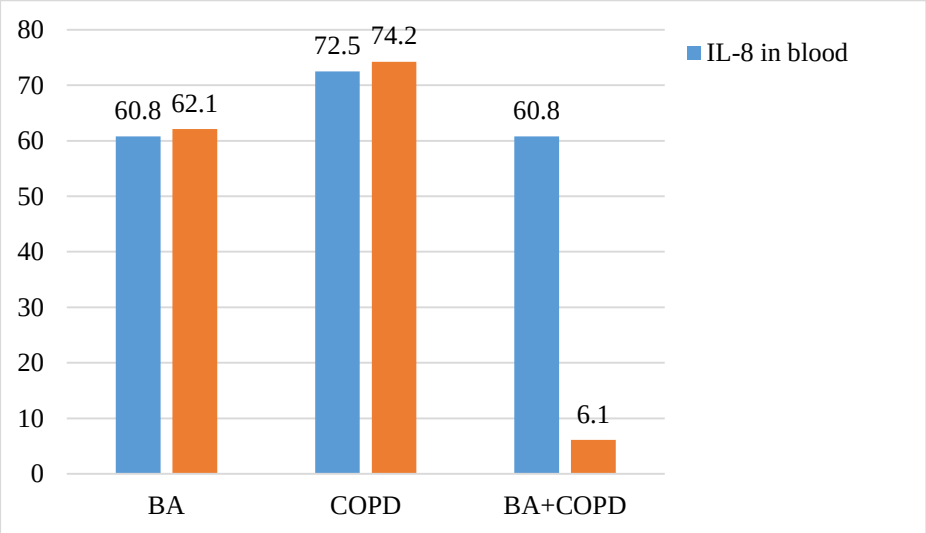

Figure 1: IL-8 production levels in BA, COPD, and BA+COPD patients at the acute stage.

When studying IL-8 production, there was a statistically significant difference in patients with AD compared to the COPD patient group (Figure1). This activation of IL-8 is primarily a product that has been associated with granulocytes and neutrophils as a response to toxic and bacterial pathogens[18,20]. IL-8 is known to be produced by neutrophils, and the predominance of its production in patients with COPD helps maintain neutrophilic inflammation in the airways. This conclusion was confirmed by the result of comparing the levels of cytokine IL-8 production in blood and in exhaled air condensate in the groups of patients with COPD (72.5±4.7 pg/ml and 74.2±4.8 pg/ml) and BA+COPD (52.2±2.5 pg/ml and 31.2±1.7 pg/ml) in which the significance of high degree ($P<0.001$) was determined.

In summary, cytokines play a major role in the pathogenesis of inflammation in the respiratory tract in the course of concomitant diseases, with a leading neutrophilic type of inflammation [18,20] leading to increased production of IL-8 and prolonged course of various types of airway lesions. No significant difference in the levels of IL-8 in the blood of patients with BA and COPD was revealed ($P>0.5$). However, when comparing the results obtained in exhaled air condensate in patients with BA, IL-8 production was significantly higher than in patients with BA + COPD ($P<0.02$).

Differences in IL-8 were also found in the COPD patient groups, in which blood cytokine levels (72.5 ± 4.7 pg/ml) and in exhaled air condensate (74.2 ± 4.8 pg/ml) were statistically significant, which is high compared with BA + COPD patients (60.4 ± 2.8pg/ml and 52.2 ± 2.5 pg/ml) ($P<0.001$). IL-8 promotes the formation of bronchial tree fibrosis, which can lead to a more severe course of the disease, which is typical of the clinical course of COPD [15,17]. IL-8 is produced by neutrophils in response to an infectious agent. Elevated levels of these cytokines in these patients with COPD may be associated with the presence of foci of chronic infection, activation of infectious agents that are common in the course of the disease and thus persistence of neutrophilic inflammation.

By analyzing cytokine levels in patients with COPD, it can be concluded that the inflammatory process of the airways is caused by immunological abnormalities[16,17]. COPD patients are characterized by increased production of IL-8, which is involved in the development of neutrophilic types of airway inflammation.

A study of TNF-α index in the blood revealed significantly high values among patients with BA of 19.2±1.1pg/ml in contrast to COPD ($P<0.001$) (Fig. 3). When comparing COPD and BA+COPD, statistically significant high values were found among patients with comorbid course in both blood ($P<0.001$) and CVV ($P<0.01$). When comparing AD and AD+COPD patients, TNF-α indices in blood were higher among patients with comorbid pathology, 19.2±1.1; 31.2±1.7 ($P<0.001$), respectively.

Comparison of immunoglobulin E indices among the above mentioned 3 groups in the acute stage revealed that BA patients, in contrast to COPD and BA+COPD patients, had significantly high indices in the blood, when comparing patients with COPD and BA+COPD, high indices were revealed among patients with combined pathology ($P<0.001$), which corresponds to the data of literature sources we studied.

Thus, the study of immunological parameters among the above groups (BA, COPD, BA+COPD) revealed a significant increase of immunoglobulin E and patients with combined pathology had prevailing levels of tumor necrosis factor TNF-α.

The results show that immunopathogenesis of the disease reflects the type of airway inflammation, while the development of AD is characterized by Th2 immune response, which is manifested by increased induced production of IL-4. Increased production of IL-8 indicates the predominance of a non Th2 immune response specific to patients with COPD. Cytokine production in AD + COPD has properties similar to those of COPD, characterized by respiratory tract inflammation to a greater extent than in isolated COPD [11,12,13].

Thus, IL-4, IL-8 play an important role in the immunopathogenesis of diseases and significantly differ in the distribution of cytokine production in the development of AD, COPD and their combination. In AD cytokines IL-4 prevail, which belong to Th2-type immunity, which is typical for the formation of allergic (eosinophilic) airway inflammation. In COPD, the level of cytokines IL-8 increases, the release of which occurs under the influence of the activation of infectious agents (microbes, viruses) and toxins [18,20].

We also studied the indices of proinflammatory (TNFα, IL-8) and anti-inflammatory (IL-4) cytokines and immunoglobulin (IgE) in blood and in CVD in patients with BA, COPD and with their combination in remission stage of the disease.

When comparing the indices of interleukin - 8 (IL-8) in blood and in CVV among 3 comparable groups in the acute stage, it was found that among COPD patients, unlike BA patients ($P<0.05$), BA+COPD had statistically significant high indices ($P<0.001$). When comparing BA+COPD and AD, there was a high value of IL-8 among BA patients, this index was also statistically significant in blood ($P<0.05$) and statistically not significant high in the study of IL-8 in CVB ($P<0.02$). The study of interleukin-4 (IL-4) revealed a slightly different picture. BA and BA+COPD patients had statistically significant high data in contrast to COPD patients in both blood and CVV ($P<0.001$). When comparing BA and BA+COPD patients, there was a high rate of anti-inflammatory interleukin-4 among patients with comorbid pathology in blood and in CVB ($P<0.001$). Thus, patients with comorbid pathology in the acute stage, unlike BA and COPD patients, had statistically high indices. The level of interleukin-4 in BA patients exceeded 6.5±3.7 pg/ml in blood and 4.0±0.2 pg/ml in exhaled air condensate, compared to 13.2±0.6 pg/ml in blood and 2.4±0.1 pg/ml in exhaled air condensate in COPD, at which we found significant differences ($P>0.001$.

At comparative estimation of IL-4 in serum of patients with BA + COPD we marked significant increase ($P<0,001$) of interleukin level (20,7±1,2 pg/ml) in comparison with COPD (13,2± pg/ml).

At comparison of analyses of IL-4 cytokine level in BA and BA+COPD patients, a multidirectional character was revealed, so while IL-4 content in blood had a reliable difference with prevalence in BA, production of cytokine in exhaled air condensate in this group had no such a significant difference ($P>0,1$).

The mediator of Th2-type, namely IL-4, plays an important role in pathogenesis of AD, COPD and their combination. At the same time, IL-4 production increase in patients of all groups can be connected with activation of inflammatory processes through nonspecific factors, and it enables to prove that IL-4 is a key cytokine in development of allergic inflammation, which was confirmed by the research [18,20].

When IL-8 production was examined, there was also a statistically important difference in patients with AD compared to the COPD patient group

It is clear that IL-8 is produced by neutrophils and its dominance in COPD supports the neutrophilic type of inflammation in the airways [14,16]. This conclusion was confirmed by the result of comparing the levels of IL-8 cytokine production in blood and in exhaled air condensate in the groups of patients with COPD (69.0±3.7 pg/ml and 6.5±0.3 pg/ml) and BA+COPD (54.4±3.1 pg/ml and 6.2±0.3 pg/ml) in which significant high significance ($P<0.001$) was determined.

Significant differences in IL-8 values between the groups of BA patients and the BA+COPD group were not detected in the blood in the acute stage ($P>0.5$). At the same time, when comparing acquired outcomes in exhaled air condensate in patients with BA, IL-8 production was higher in comparison with BA+COPD patients, which was significant ($P<0.02$).

Besides, in the acute stage differences in IL-8 level were established in the groups of COPD patients in blood cytokine level was (72,5±4,7 pg/ml) and in exhaled air condensate (74,2±4,8 pg/ml) and was statistically higher in comparison with patients from COPD+BA group (50,8±2,8 pg/ml and 52,2±2,5 pg/ml) respectively (P<0,001).

IL-8 promotes the formation of bronchial tree fibrosis, which may lead to a more severe course of the disease, which is typical of the clinical course of COPD[14,16].

IL-8 is a product of the immune system as a response to an etiological factor. In COPD, increased levels of these cytokines, when compared with patients from the BA group, can be justified by the presence of chronic foci of infection, activation of infectious agents often occurring in the disease and thus persistence of neutrophilic inflammation[18,20].

Referring to the results of research work on cytokine levels in patients with COPD, it can be concluded that the inflammatory process of the airways is substantiated by immunological disorders.

The results of the study showed that at the heart of the immunopathogenesis of disease is the presence of the nature of inflammation of the airways, with the formation of AD is characterized by a pronounced immune response. Increased production of IL-8 indicates the prevalence of

Consequently, IL-4, IL-8 play the necessary significance in the immunopathogenesis of diseases and differ significantly in the predominance of cytokine production in the development of AD, COPD and in their combination. In AD, IL4 cytokines dominate, participating in Th2 type of immune response, which took place in the formation of allergic (eosinophilic) type of inflammation of the respiratory tract. In COPD, cytokine IL-8 indices are increased, which are formed under the influence of infectious (bacteria, viruses) and toxins [18,20].

A study of TNF-α index in the blood revealed significantly high values among patients with BA of 19.2±1.1pg/ml in contrast to COPD (P<0.001) (Fig. 7). When comparing COPD and BA+COPD, statistically significant high values were found among patients with comorbid course in both blood (P<0.001) and CVV (P<0.01). When comparing AD and AD+COPD patients, TNF-α indices in blood were higher among patients with comorbid pathology, 19.2±1.1; 30.8±1.6 (P<0.001), respectively.

When comparing immunoglobulin E indices among the above 3 groups in the acute stage, it was found that BA patients, unlike COPD and BA+COPD patients, had significantly high indices in blood, when comparing COPD and BA+COPD patients, there were high indices among patients with comorbid pathology (P<0.001) (Fig. 8), which corresponds to our studied literature sources.

Conclusions: Thus, the study of immunological indicators among the above groups (BA, COPD, BA+COPD) revealed a significant increase of immunoglobulin E and patients with co-morbidities had a prevailing level of tumor necrosis factor TNF-α. The study of cytokine status showed that patients with BA had high blood levels of IL-4 compared to COPD and BA+COPD, patients with COPD had elevated blood levels of IL-8 compared to BA and BA+COPD, patients with BA+COPD showed elevated levels of TNF-α compared to the isolated disease course.

Literature

1. Bazarova SA, Nasirova AA, Shodikulova GZ Evaluation of medical tactics in the treatment of bronchial asthma and chronic obstructive pulmonary disease // Theoretical and applied problems of modern science and education. - 2019. - C. 43-47.
2. Botalenkova O.S. Evaluation of the effectiveness of bronchial asthma therapy at the therapeutic area [Text]/ O.S. Botalenkova, N.A. Kurashina // Smolensk medical almanac.-2017.-¹.2.P.2-5

3. Brodskaya ON Berodual - a universal drug for the treatment of exacerbations of bronchial asthma and COPD. Asthma and allergy. 2014; (4): 21-23.
4. Brodskaya O.N. Bronchial asthma with frequent exacerbations: risk factors and preventive measures [Text]/ O.N. Brodskaya // Practical pulmonology.- 2016.- №3.- P. 11-18.
5. Brodskaya, O.N. Factors of achieving control of bronchial asthma: global and personalized approach [Text]/ O.N. Brodskaya, A.S. Belevsky // Practical Pulmonology.-2016.- № 4.- P. 3-8.
6. Budnevsky AV, Burlachuk VT, Olysheva IA, et al. Possibilities of bronchial asthma control: the role of small airways. Pulmonology. 2011; (2): 101-109.
7. Budnevsky A.V., Prozorova G.G., Burlachuk V.T. Opportunities of combination therapy in severe chronic obstructive pulmonary disease [Text] / A.V. Budnevsky, G.G., Burlachuk V.T. // Atmosphere. Pulmonology and allergology. - 2010. - № 4. - C. 34-38.
8. Viesel A.A. Viesel I.Yu. "Bronchial asthma and chronic lung disease". 2016r.
9. Wiesel A.A., Wiesel I.Yu. The GOLD Global Initiative and national guidelines for the management of chronic obstructive pulmonary disease (COPD) patients: the place of dual bronchodilation. Medical Board. 2019;(15):17-21.
10. Wiesel AA, Wiesel IY. Some aspects of the use of formoterol and budesonide combination: what has changed? Medical Advice. 2019; 15: 99-104.
11. Gavriziuk V.K. Four decades of innovation in the treatment of bronchoobstructive diseases. Asthma ta alergia. 2015; 4: 48-50.
12. Gereng E.A. Molecular markers of inflammation in the bronchial contents in different phenotypes of severe bronchial asthma [Text]/ E.A. Gereng, I.V. Sukhodolo, R.I. Pleshko et al. // Bulletin of Siberian medicine. - 2011. - № 3. - C.24-29.
13. Global strategy for diagnosis, treatment and prevention of chronic obstructive pulmonary disease (GOLD), revision 2014. Ed. by A.S. Belevsky. Moscow: Russian Respiratory Society. 2014.- 92 c
14. Global Strategy for the Treatment and Prevention of Bronchial Asthma (GINA), revision 2015. Ed. by A.S. Belevsky. Moscow: Russian Respiratory Society. 2015; 148 c.
15. Gnatyuk O. P. Organizational problems of providing quality medical care to patients with chronic bronchitis and chronic obstructive pulmonary disease [Electronic resource] / O. P. Gnatyuk, N. 2010.
16. Gnatiuk O. P. Epidemiology, diagnosis and prevention of chronic bronchitis and COPD: medico-social and organizational-methodical aspects : dissertation. D. in Medicine. Sciences : 14.02.06 [Text] / Gnatiuk Oleg Petrovich ; SEE HPE "Far Eastern State Medical University. Univ. - Khabarovsk, 2