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CLINICAL-ALLERGOLOGICAL AND IMMUNOLOGICAL ASPECTS OF CHILDREN WITH BRONCHIAL ASTHMA IN THE REPUBLIC OF UZBEKISTAN

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Bronchial asthma (BA) is the most common chronic allergic respiratory disease, the onset of which more often occurs in childhood [1, 2]. The urgency of the problem of bronchial asthma is explained by the steady growth in all countries of the world, including Uzbekistan, of cases with a more severe clinical course, often ending in death [1-7].

Among the reasons that often determine the implementation of the disease, its subsequent course, and sometimes the outcome, an important role in the pathogenesis of bronchial asthma is given to infection. Infections can be both a trigger mechanism for the development of the disease, especially in young children, and a trigger mechanism for exacerbations of bronchial asthma [6]. Infectious viral diseases of the respiratory tract most often lead to exacerbation of bronchial asthma [7],

The generally accepted theory is that allergic diseases are caused by disorders in the immune system, dysregulation of cytokine mechanisms, and activation of allergen-specific clones of T-lymphocytes.

Analysis of the dynamics of cytokine production, the ratio of oppositional cytokines and a complex of regulatory coefficients illustrates the mechanisms of realization and prognosis of multifactorial allergic diseases [5, 11, 12].

The aim is to determine the features of the clinical course and the state of the cytokine status in children with bronchial asthma.

Materials and methods. A comprehensive examination of 60 sick children with asthma aged 5-14 years in the period of exacerbation was carried out. Of these, there were 29 boys and 31 girls. The duration of the disease ranged from 6 months to 3 years. Children, depending on the allergen - infectious and non-infectious - were divided into 2 groups: 25 children with BA on the background of a non-infectious allergen and 35 children with BA and an infectious allergen. The main and concomitant diseases were diagnosed on the basis of a carefully collected allergological history and on the basis of the results of complex clinical and allergic, functional, laboratory and radiological studies. The power of forced expiration with a pneumotachometer, the threshold of sensitivity of the receptor apparatus of the bronchi to histamine and acetylcholine, the number of eosinophils in the peripheral blood and nasal secretions, the cause of sensitization according to the results of skin allergic tests were determined.

The serum level of cytokines (IL-4, IL-8 and IFNγ) was determined by ELISA, according to the attached instructions, test system - LLC "Vector Best", Russia.

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30 practically healthy children of the same age made up the control group.

Numerical values were processed by methods of variation statistics. The significance of the differences was assessed by the Student's test (t) and the level of significance (p). Correlation analysis was carried out using the Pearson correlation coefficient.

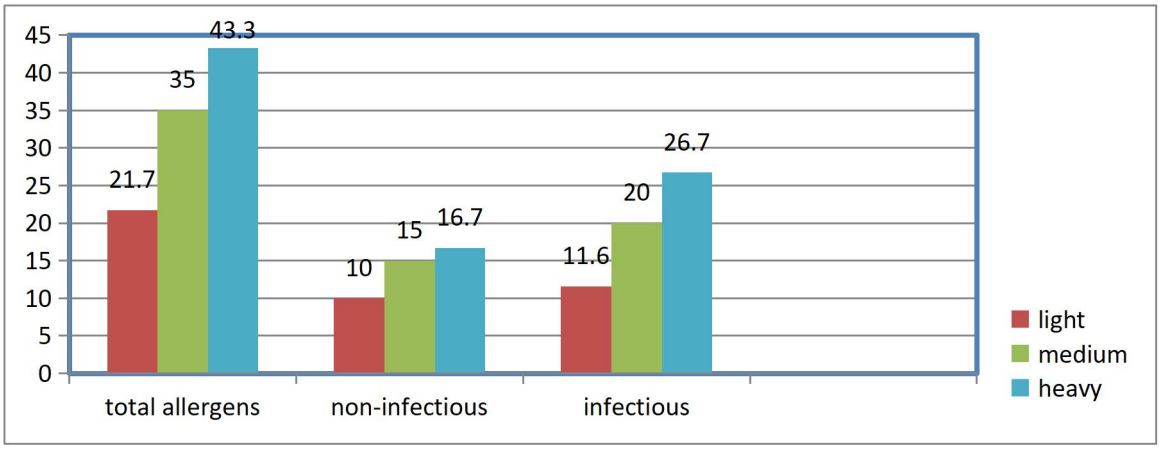
Results and discussion

The majority (66.7%) of the examined patients had a burdened heredity of allergic diseases. There was an increased frequency of allergic rhinitis (AR) in relatives of patients with AD ($P < 0.05$). Differences in the frequency of occurrence of drug (34.3%) and food (31.8%) allergies were statistically significant ($P < 0.05$).

The tests revealed that pollen allergens were the most significant in patients with asthma (the frequency of occurrence of pollen sensitization was 45.5%). Sensitization to household and epidermal allergens was observed in 90.9% and 60.6% of cases. The incidence of pathology of the upper respiratory tract in the form of adenoids, curvature of the nasal septum, polyps in patients with BA was 3.0%.

It was found that in the group of BA patients in 42.9% of cases the onset of asthma symptoms was preceded by the symptoms of rhinitis. However, the timely diagnosis of AR was made only in 18.1% of patients, in 53.3% of cases it was made simultaneously with the diagnosis of asthma, in 28.6% of cases - later.

When analyzing the severity of the disease, it was revealed that 13 children had a mild form (21.7%), a moderate form was observed in 21 (35%) children and a severe form was observed in 26 children (43.3%).



Picture . 1. Distribution of children with bronchial asthma depending on its course and causes of sensitization, (%)

Among the causes of sensitization of the body, non-infectious in 25 (41.7 ± 6.3%) children and in 35 children, infectious (58.3 ± 6.3%) allergens, such as herpes simplex virus

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types I – II, cytomegalovirus, virus Epstein-Barr, Chlamydophilapneumoniae, Mycoplasmapneumonia (Fig. 1).

Combined infection with various pathogens was noted in 17 (48.6%) patients, which confirms the assumption that persistent infection of the respiratory tract in bronchial asthma supports chronic inflammation and aggravates the course of the pathological process, causing a more severe course of bronchial asthma in children.

The development of sensitization and allergies is facilitated by toxicosis during pregnancy, artificial feeding of children. These factors are important in the formation and development of the disease in 57.7-71.5% of cases.

We analyzed the differences in the duration of the current exacerbation of bronchial asthma in groups of children, which was recorded from the moment of the first symptoms of bronchial obstruction, including the period of not always effective outpatient treatment. When comparing these indicators, it was found that in the group of children with BA infected with a viral allergen, the duration of an exacerbation was 1.4 times longer than in the group with a non-infectious allergen. Thus, in the group of children with an infectious allergen, the duration of the current exacerbation was 24.9 ± 2.3 days, and in the group with a non-infectious allergen, 17.6 ± 1.5 days ($P < 0.05$). With mild persistent BA, the duration of exacerbation in group I was 23.7 ± 2.5 days, in group II - 16.3 ± 1.7 days, with moderate persistent course - 25.1 ± 2.3 and 18.2, respectively. ± 1.6 days, with severe persistent course - 27.3 ± 2.4 and 19.1 ± 1.8 days, respectively ($P < 0.05$). Long duration of BA exacerbation in the group of children infected with intracellular pathogens may be associated with the absence of typical exacerbation attacks and the absence of pathogenetic treatment, which entails a longer time stage of ineffective outpatient treatment.

In order to assess the degree of sensitization of children with bronchial asthma, infected and not infected with intracellular pathogens, the levels of immunoglobulin E (IgE) in blood serum were determined. In the group of patients infected with intracellular infections, the IgE level was 1.3 times higher than in patients without infection, and amounted to 219.61 ± 38.17 and 164.26 ± 25.46 ng / ml, respectively ($P < 0.05$). A high level of IgE indicates the development of IgE-mediated allergic reactions due to a violation of the Th1 / Th2 ratio due to the switching of reactions from Th1-type to Th2-type [8-11].

The choice of the studied cytokines in the blood serum, in particular the proinflammatory - IL-1β, IL-6, IL-8 and IFN-γ and the anti-inflammatory - IL-4, was based on the spectrum of their mediated capabilities. Conditions associated with hyper- or hypoproduction of cytokines were of diagnostic value in this monitoring (Table 1).

Table 1

Serum cytokine level in children with ALS, an infectious and non-infectious allergen, (M ± m), pg / ml

Cytokines	control group, n=30	1-group, n=25	2-group, n=35

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IFN-α	115,8± 6,7	68,7 ± 5,2*	79,5 ± 4,9*
IFN-γ	28,6 ± 2,1	58,4 ± 3,3*	73,5 ±3,6*
IL-1β	24,8 ± 2,0	39,7 ± 2,1*	94,7±5,8* **
IL-4	4,7 ± 0,9	16,8 ± 1,9 *	28,5 ±3,1 * **
IL-6	19,6 ± 1,7	31,4 ± 2,2*	62,8 ± 2,7 * **
IL-8	18,5 ± 1,6	38,9 2 ± 2,3*	32,6 ± 2,2* **

Note: * Values are reliable relative to the control group

** Values are reliable in relation to the 1st group

(P <0.05 - 0.001)

We have obtained data on a significant decrease in the level of IFN-α in the blood serum of children with bronchial asthma, both infected and not infected with intracellular pathogens. Thus, in the 2nd group of patients, the level of IFN-α was slightly higher than in the comparison group, and, accordingly, amounted to 79.5 ± 4.9 and 71.7 ± 5.2 pg / ml. There was no statistical difference between these indicators (p = 0.999), however, there were statistically significant differences between the indicators of children infected and not infected with intracellular infections with bronchial asthma and practically healthy children - 115.8 ± 6.7 pg / ml (p <0.001).

A decrease in the level of IFN-α indicates a violation of antiviral immunity, a violation of stimulation of cells with cytotoxic activity. The low level of IFN-α, as in the 2nd group of patients, contributes to the chronization of the infection and increases the likelihood of recurrence of bronchial obstruction.

The content of the IFN-γ level in the blood serum of children with bronchial asthma proceeding against the background of infection with intracellular pathogens averaged 73.5 ± 2.6 pg / ml, which was almost 3 times higher than that of practically healthy children (P <0.001) ... In the 1st group of patients, the level of IFN-γ was 58.4 ± 2.3 pg / ml and was higher than in the children of the control group (P <0.01), however, there was no statistically significant difference between the groups of sick children (P = 0.741).

Hypersecretion of IFN-γ indicates the activation of the T-cell link of immunity in favor of the Th1-type cells, especially in the group of children with bronchial asthma infected with intracellular pathogens. Patients suffering from bronchial asthma occurring against the background of intracellular infection are exposed to both pathogens and IFN-γ. A high level of IFN-γ production is usually associated with the immune response to the persistence of intracellular pathogens, as well as with immune-mediated and autoimmune pathology associated with delayed-type hypersensitivity reactions, contributes to the chronization of the infectious and inflammatory process and increases the risk of developing systemic chronic, including autoimmune pathology.

The consequence of constant antigenic load and chronic inflammation explains the increased serum IL-1β level in the observed patients. However, if in children with bronchial

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asthma not infected with intracellular pathogens, there was a twofold increase in the indicator, which was 59.7 ± 3.1 pg / ml compared to 24.8 ± 2.0 pg / ml in healthy children (P <0 01), then in the group of patients infected with intracellular agents, its increase was 3.8 times - 94.7 ± 5.8 pg / ml (P <0.001). Therefore, the identified deviations of this cytokine confirm the dependence of its hyperproduction on the antigenic load in children with bronchial asthma, which is aggravated in patients infected with intracellular pathogens.

IL-1β has the ability to influence the synthesis of other cytokines, which leads to an increase in the activity of representatives of the "pro-inflammatory" group, in particular IL-2-6-8, TNF-α, INF, GM-CSF, G-CSF, M-CSF [13]. Therefore, it was natural to increase the activity of IL-6 in the blood serum of the observed children with bronchial asthma.

Analysis of the serum IL-6 level showed an increase in it in all sick children. However, the increase in this cytokine was not as high as in IL-1β. If in practically healthy children the level of IL-6 averaged 19.6 ± 1.7 pg / ml, then in children with bronchial asthma not infected with intracellular pathogens, it was increased to 31.4 ± 2.2 pg / ml (P < 0.05). The level of IL-6 in children with bronchial asthma and infected with intracellular infections was higher and already amounted to 67.14 ± 12.24 pg / ml (p <0.001). The difference in IL-6 indices in children with bronchial asthma, infected and not infected with intracellular infections, was statistically significant, P <0.05. Its long-term high level is an indicator of the development of complications or chronization of the pathological inflammatory process [14].

The level of IL-8 in the blood serum of the examined children with bronchial asthma of the 1st and 2nd groups was statistically significantly higher than that of practically healthy children, (P <0.01). In the group of those infected with bronchial asthma, it was 28.5 ± 3.1 pg / ml, and in the group of uninfected patients, the average cytokine indicator was as high as 38.9 ± 2.3 pg / ml, which did not have a statistically significant difference (P = 0.274). IL-8 stimulates the stimulation of the release of TGF-α, which has profibrotic effects, which leads to remodeling of the airway membrane [15].

Significant immunoregulatory cytokines with suppressive effects aimed at suppressing the inflammatory proliferative response are the anti-inflammatory cytokine IL-4, a key cytokine that determines the formation of chronic allergic inflammation in patients with bronchial asthma [16]. The level of IL-4 in the blood serum in bronchial asthma in the observed children, infected and not infected with intracellular pathogens, statistically significantly exceeded the indicators of healthy children (P <0.001), which is characteristic of allergic diseases, and amounted to 16.8 ± 1.9 and 21.5 ± 2.1 pg / ml.

In the 2nd group of patients, the level of IL-4 was 1.7 times higher than in the children of the comparison group, the difference was statistically significant (p = 0.016). Determination of a higher level of IL-4 in children with bronchial asthma infected with intracellular pathogens, compared with uninfected patients, suggests that the formation of this anti-inflammatory cytokine is stimulated by persistent intracellular pathogens.

Thus, the combination of decreased production of pro-inflammatory cytokines with an increase in the levels of pro- and anti-inflammatory cytokines contributes to the maintenance of the inflammatory process, provoking its chronicity, the formation of a deep

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immune imbalance and the occurrence of irreversible changes in the airways, leading to their remodeling. As a result of such changes, allergic inflammation of the mucous membrane of the respiratory tract increases, which ultimately leads to the formation of a higher hyperreactivity of the bronchi in children with bronchial asthma infected with intracellular pathogens, the processes of remodeling of the respiratory tract and the difficulty of controlling the course of the disease.

Conclusion

Based on the results of the study and a comprehensive statistical analysis, the following conclusions were made:

1. Bronchial asthma often develops against the background of an infectious allergen.

2. In AD, an imbalance in the content of interferons was revealed - the level of IFNα was decreased, and IFNγ-increased relative to the values of the control group.

3. The level of proinflammatory cytokines (IL-1β, IL-6 and IL-8) in AD is increased in children, but the depth of changes depends on the allergen.

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