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Mechanisms Of Cytokine Balance Disturbance And Immune Response In Children With Bronchial Asthma After Covid-19

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Abstract. *The interplay between COVID-19 infection and pre-existing bronchial asthma in children necessitates a thorough understanding of the resulting immune dysregulation. This study investigated the immunological alterations in children with bronchial asthma following COVID-19 infection, comparing them to a control group of asthmatic children without a history of COVID-19.* ***Objective:*** *To evaluate the mechanism of the immune response and cytokine balance features in children with bronchial asthma after COVID-19.*

Materials and methods. *The study involved 125 children aged 7-15 years, divided into two groups: Group 1 (n=60) comprised children with bronchial asthma and confirmed COVID-19; Group 2 (n=65) consisted of asthmatic children without COVID-19. Both groups exhibited varying asthma severities. Immunological analysis revealed significant differences between the groups.*

Results and discussion: *Children in Group 1 (COVID-19 positive) demonstrated a marked reduction ($p<0.01$) in CD3+ lymphocytes (46.57 ± 0.67%), representing total T lymphocytes, compared to the control group (Group 2). This decrease highlights a compromised cellular immune response, potentially impacting the body's ability to effectively fight off future infections. Further analysis showed significant deviations from normal ranges in CD4+ (helper T cells) and CD8+ (cytotoxic T cells) lymphocyte populations in the COVID-19 group, suggesting an imbalance in T-cell mediated immunity. Intriguingly, CD20+ lymphocytes (B cells) were significantly elevated ($p<0.001$) in the COVID-19 group (40.7 ± 1.01%), indicating a possible over-activation of the humoral immune response, possibly contributing to the overall inflammatory state. This might be linked to increased antibody production, potentially including autoantibodies, which could worsen asthma symptoms. The observed decrease in T-lymphocytes might be explained by several factors. Viral infection can directly deplete T-cells, or indirectly through cytokine storm, where an overproduction of pro-inflammatory cytokines like IL-6 and TNF-α leads to immune cell exhaustion and apoptosis. The elevation in CD20+ lymphocytes could also be a consequence of the cytokine storm, as B-cell activation is influenced by these cytokines. Additionally, the prolonged inflammatory environment in asthma could further exacerbate the impact of COVID-19, creating a synergistic effect on immune dysregulation.* ***Conclusion.*** *These findings underscore the importance of individualized immunotherapy approaches tailored to the specific immunological profiles of children with bronchial asthma post-COVID-19. Further research should focus on the long-term effects of COVID-19 on the immune system of asthmatic children and the development of targeted interventions to mitigate these effects. Studies exploring the efficacy of various immunomodulatory therapies, such as biologics targeting specific cytokines or pathways, are warranted. Longitudinal studies monitoring immune function and respiratory health outcomes would be crucial in assessing the long-term impact of COVID-19 on this vulnerable population.*

Keywords: *COVID-19, bronchial asthma, children, immunity, cytokines, lymphocytes.*

INTRODUCTION

Bronchial asthma (BA), a prevalent chronic respiratory illness in children, is characterized by persistent inflammation and heightened bronchial sensitivity. This leads to recurring episodes of wheezing,

breathlessness, chest tightness, and coughing, significantly impacting quality of life. The underlying mechanisms involve complex interactions between genetic predisposition, environmental triggers (like allergens, pollutants, and respiratory infections), and immune dysregulation. Specifically, mast cells, eosinophils, and T helper 2 (Th2) lymphocytes play key roles in the inflammatory cascade, releasing mediators like histamine and leukotrienes that constrict airways and increase mucus production. Importantly, prior infection with the SARS-CoV-2 virus (COVID-19) can exert a considerable influence on the course of asthma. Studies have shown that COVID-19 can trigger or exacerbate asthma symptoms in several ways. Firstly, the virus itself can directly damage the airways, leading to increased inflammation. Secondly, the subsequent immune response, including a cytokine storm characterized by an imbalance of pro- and anti-inflammatory cytokines (like IL-6, TNF-α, and IFN-γ), can further contribute to airway hyperresponsiveness and exacerbations. Long COVID, a condition with lingering symptoms following acute COVID-19 infection, has also been linked to the development or worsening of asthma-like symptoms in some individuals, even those without a prior asthma diagnosis. This suggests a potential long-term impact of COVID-19 on respiratory health and emphasizes the need for close monitoring of asthmatic children following COVID-19 infection. Further research is crucial to understand the long-term consequences and develop tailored management strategies for this growing population [1, 3, 5]. The emergence of COVID-19 triggers an immune response, marked by shifts in the balance of inflammatory and regulatory signaling molecules. This alteration can intensify inflammation within a child's airways who already has bronchial asthma. Conversely, inadequate immune defenses and a disrupted immune response may worsen the illness's progression and elevate the likelihood of long-term health issues following the infection [1, 6].

A person's predisposition to allergies may significantly influence how COVID-19 unfolds in individuals with asthma. ACE2, a receptor involved in viral entry, is boosted by interferon (IFN), resulting in increased levels when the body encounters a virus [10]. Considering that bronchial cells in asthma often exhibit a weak IFN-β reaction to viral infections [9], this could limit the usual rise in ACE2 during SARS-CoV-2 infection, potentially lessening the severity of the illness. Studies have revealed fewer ACE2 receptors in the nasal and bronchial cells of both adults and children experiencing allergies or allergic asthma, particularly those with elevated IgE and sensitivity to allergens. This reduction wasn't observed in those with non-allergic asthma [4, 8]. A type 2 immune response, common in conditions like allergies, asthma, atopic dermatitis, and parasitic infections, prompts the release of interleukins (IL)-4, -5, -9, and -13. Research by C. Huang et al. suggests that cytokines associated with this response, alongside eosinophilia, may offer some protection against COVID-19 [5, 9, 10]. Work by H. Kimura et al. and D.J. Jackson et al. has shown diminished ACE-2 expression in nasal epithelial cells of individuals with bronchial asthma and allergic rhinitis, compared to healthy controls. Furthermore, it's been demonstrated that IL-13—a cytokine linked to allergic asthma type 2 and allergic rhinitis—suppresses ACE-2 while increasing TMPRSS2 in nasal and airway epithelial cells [3, 4, 8]. D.J. Jackson et al. also verified that individuals with allergic asthma, allergic rhinitis, and high IgE levels exhibit reduced ACE-2 expression in the nasal and bronchial epithelium [7, 8].

To gain a deeper understanding of the interaction between viral infection and chronic inflammation of the respiratory tract, it is necessary to study the immune response and cytokine balance in children with bronchial asthma who have had COVID-19 [2, 4, 5]. The data obtained can contribute to the development of more effective approaches to the treatment and rehabilitation of such patients, which makes this problem relevant for modern pediatrics and immunology.

Purpose Of The Study: Study of the mechanisms of immune response and cytokine balance in children with bronchial asthma after COVID-19.

MATERIALS AND METHODS OF RESEARCH.

Materials and methods of the study. To study the immune status of children who had coronavirus infection against the background of bronchial asthma, a study was conducted on 125 children with bronchial asthma aged 7 to 15 years. The examined children were divided into 2 groups: Group 1 - 60 patients with a diagnosis of bronchial asthma of varying severity, with a diagnosis of COVID-19 confirmed by the anamnesis, Group 2 - 65 children diagnosed with bronchial asthma of varying severity, without COVID-19. The control group consisted of 30 practically healthy children of the same age. Clinical, laboratory and functional methods were used in the work. The clinical examination included collecting anamnesis, analyzing the frequency and severity of exacerbations of bronchial asthma, as well as assessing the symptoms associated with post-COVID syndrome. Laboratory studies were conducted to assess the immune status of patients. Hematological analysis included determining the level of leukocytes, lymphocytes, neutrophils, eosinophils and the erythrocyte sedimentation rate (ESR). The subpopulation composition of lymphocytes was determined by flow cytometry

($CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, $CD16^+/CD56^+$). To assess humoral immunity, the levels of immunoglobulins of classes A, M and G were determined using enzyme-linked immunosorbent assay (ELISA). The cytokine profile was assessed by determining the concentration of pro-inflammatory and anti-inflammatory cytokines (IL-4, IL-6, IL-10, TNF-α, IFN-γ) in the blood serum using ELISA.
To process the obtained data, methods of variation statistics, correlation and regression analysis were used, which made it possible to identify significant differences and patterns in immune changes in children with bronchial asthma after COVID-19.

RESULTS AND DISCUSSION

The results of the analysis of the immune status of the children we examined are presented in Table 1. The data in Table 1 show that children with BA have a significant ($p<0.01$) decrease in the CD3+ lymphocyte level to 46.57±0.67% compared to the CG.
The CD4+ and CD8+ lymphocyte levels also differed significantly from normal values, amounting to 29.52±0.5% and 15.6±0.47%, respectively. The CD3+ and CD4+ levels were lower than in the control group by 1.3 and 1.4 times, respectively. In addition, the CD20+ lymphocyte content was significantly ($p<0.001$) higher than in the CG and amounted to 28.7±0.61%.
Cellular resistance factors such as natural killers with cytopathic activity play an important role in the performance of immune functions. Activation of natural killers occurs when they interact with an antigen, which leads to cytotoxic damage to infected cells.

Table 1. Parameters of cellular immunity in children in the studied groups, (M±m)

Indicators	Practically healthy children (n=20)	I group BA+COVID-19 (n=65)	II group of BA (n=60)	P	P_1
Leukocytes, abs.	6598,7±165,4	5815,1±39,93	6069,33±41,7	<0,001	<0,001
Lymphocytes, %	33,5±0,5	45,18±1,03	37,47±0,89	<0,01	<0,01
CD3+ lymph.,%	61,5±2,2	31,34±0,77	46,57±0,67	<0,05	<0,001
CD4+ lymph.,%	39,1±2,1	15,25±0,61	29,52±0,5	<0,05	<0,001
CD8+ lymph.,%	19,5±1,8	10,4±0,32	15,6±0,47	>0,05	<0,05
(CD4+/CD8+)	2,0±0,2	1,6±0,11	1,8±0,08	<0,05	<0,05
CD16+ lymph.,%	10,2±1,3	18,2±0,37	15,75±0,58	>0,05	<0,05
CD20+ lymph.,%	16,4±0,5	40,69±1,01	28,7±0,61	<0,05	<0,001
FAN, %	58,5±2,3	24,32±0,79	43,3±0,78	<0,01	<0,001

Note: *P - reliability of differences in indicators between groups I and II of patients; P1 - reliability of differences in indicators between group II and the control group.*

The results of immunological studies of children who had COVID-19 against the background of bronchial asthma indicate the presence of profound disorders: a significant decrease in the content of CD3+ lymphocytes by 1.65 times (31.34±0.77%) ($p<0.001$), including immunoregulatory subpopulations, CD4+ lymphocytes by 2.3 times (15.2±0.67%) ($p<0.001$) and CD8+ lymphocytes by 1.7 times (10.42±0.32%) ($p<0.001$) compared to the indicators of children with bronchial asthma without COVID-19. The content of CD20+ lymphocytes in patients with bronchial asthma+COVID-19 was significantly ($p<0.001$) higher than in children with bronchial asthma and amounted to 40.7±1.01%.
In the group of patients with BA without COVID-19, a significant increase in the relative number of CD16+ lymphocytes was recorded compared to and was 15.75±0.58% ($p<0.01$). The analysis of FAN in patients with BA, regardless of whether they had COVID-19, compared to the control was 43.3±0.78% ($p<0.01$).
A gradual decrease in the activity of T-suppressors contributes to the activation of the B-immune system, which is a key stage in the development of allergic reactions. Analysis of phagocytosis indicators characterizing

the non-specific link of immunity in the group of patients who had COVID-19 against the background of bronchial asthma revealed a significant decrease in FAN to 24.32±0.79 mg/%, which is 2 times lower than in children with bronchial asthma without COVID-19 ($p<0.001$).

The results of the study of humoral immunity in children with bronchial asthma are presented in Figure 1. In children with bronchial asthma without COVID-19, the concentration of IgA was reduced to 94.4±1.89 mg/% and IgG to 792.23±9.02 mg/%, and the content of IgM increased to 120.43±2.39 mg/% (in the C=107.9±3.6 mg/%; 938.3±17.6 mg/% and 90.7±2.8 mg/%, respectively) ($p<0.001$).

In children who had COVID-19 against the background of bronchial asthma, the most pronounced changes in the studied parameters were revealed, namely: a decrease in the level of IgA to 72.7±1.85 mg/% and IgG to 613.63±4.74 mg/%, and an increase in the content of IgM to 150.37±2.3 mg/%.

The results of the analysis of the cytokine status in children with bronchial asthma without COVID-19 showed that the level of IL-4 production was significantly increased ($p<0.01$) and amounted to 21.3±0.34 ng/ml compared to the control group. In patients with bronchial asthma+COVID-19, the level of IL-4 reached 38.62±1.07 ng/ml. There was a natural increase in the anti-inflammatory cytokine IL-4 in all children with bronchial asthma, but the most pronounced increase was in patients with bronchial asthma+COVID-19, exceeding the norm by 8.4 times.

Under the influence of bacterial endotoxins and cytokines, especially tumor necrosis factor (TNF), IL-8 is synthesized. This cytokine plays an important role in creating the gradient necessary for chemotaxis of phagocytic cells. IL-8 is a significant mediator of inflammatory processes in the lungs. During the study of the IL-8 level, its increase was revealed compared to the CG data, regardless of the coronavirus infection and amounted to 89.54±2.45 ng/ml and 112.5±2.77 ng/ml, respectively.

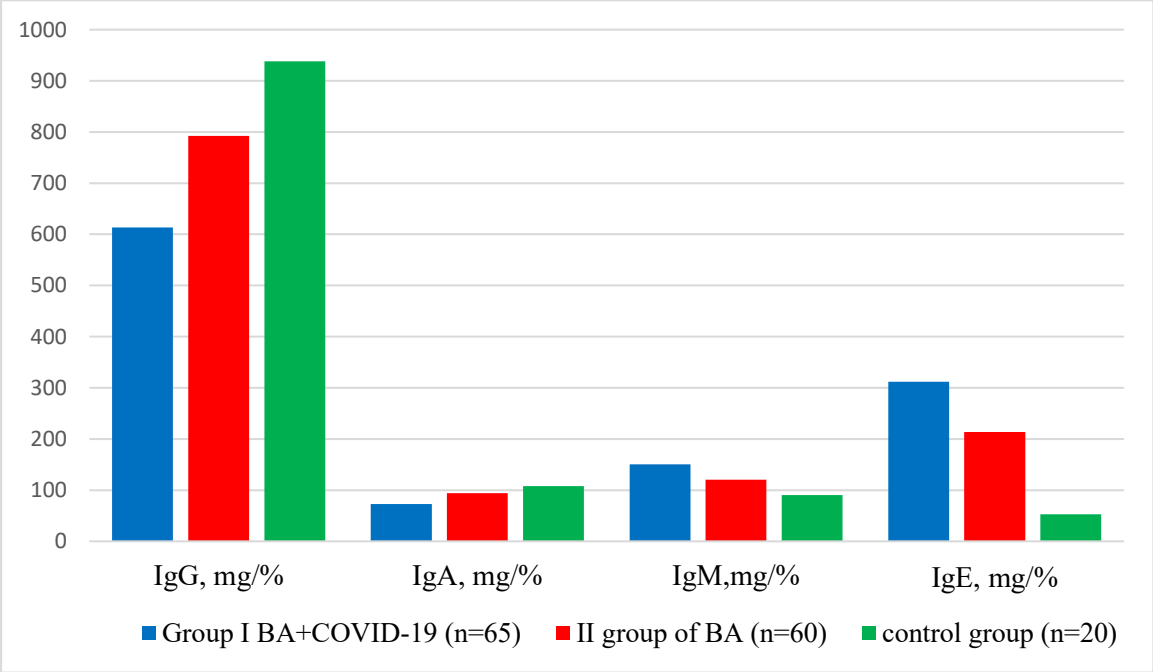

Figure 1. Characteristics of humoral immunity in children in the studied groups (M±m)

In the course of our studies aimed at studying the level of interferon-γ in the examined patients, its significant deficiency revealed in all children with bronchial asthma. In children with bronchial asthma without COVID-19, the average level of serum IFN-γ was 21.64±0.63 ng/ml ($p<0.05$), while in children with bronchial asthma+COVID-19, this figure was 10.5±0.53 ng/ml. These values were 1.6-1.8-2.2 times lower than in children in the control group (p from <0.01 to <0.001). The most pronounced decrease observed in patients

who had COVID-19 against the background of bronchial asthma. A decrease in IFN-γ production probably contributes to a long-term relapsing course of the disease.

An increase in IL-4 concentration against the background of a steady decrease in IFN-γ levels indicates the dominance of the Th2-type immune response. This may indirectly indicate the presence of immunopathological changes that lead to impaired differentiation of T-helpers and the development of immunosuppression.

According to our study, the level of TNF-α in children with BA + COVID-19 was significantly increased and amounted to 104.7 ± 2.04 ng / ml, which is 3.8 times higher than in the CG ($p < 0.001$). In patients with BA without COVID-19, the level of TNF-α was 62.5 ± 1.16 ng / ml compared to the CG ($P < 0.001$), indicating an increase in the activity of macrophages involved in maintaining the inflammatory process.

CONCLUSION:

Thus, the analysis of immunological parameters in children with bronchial asthma after a SARS-CoV-2 infection revealed an imbalance in cellular and humoral immunity. This imbalance was characterized by a decrease in T-killer subpopulations, lymphocyte functional activity, neutrophil levels, serum IgA, and induced IFN-γ production, alongside an increase in total serum IgE, IL-4 levels, and spontaneous IFN-γ production. The appointment of adequate immunotherapy taking into account the indicators of the immunological examination and the principles of differentiated treatment will help to increase the effectiveness of therapy, reduce the frequency of exacerbations of bronchial asthma, and optimize the recovery period in children after coronavirus infection. An individualized approach to the correction of immune disorders will minimize the risk of complications and improve disease control.

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