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Gut Microbiota and Its Clinical-Immunological Significance in Children with Comorbid Bronchial Asthma and Atopic Dermatitis

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Abstract This article highlights the current pathogenetic aspects of the interaction between the gut microbiota and the immune system in the comorbid course of bronchial asthma and atopic dermatitis in children. Scientific purpose. Determination of changes in intestinal microbiota and immune system in the comorbid course of bronchial asthma and atopic dermatitis in children. Materials and methods. 56 children with comorbid bronchial asthma and atopic dermatitis were included in the study. Their age ranged from 3 to 12 years, all of them were diagnosed based on clinical and laboratory criteria. 30 age- and sex-matched healthy children were taken as controls. Results and their discussion. The results showed that the diversity of microbiota in children with bronchial asthma and atopic dermatitis was significantly lower than in healthy children. In particular, the proportion of probiotic strains such as Bifidobacterium and Lactobacillus was reduced, while the Enterobacteriaceae and Clostridioides species increased. In conclusion, it was proven that the composition and diversity of the intestinal microbiota in children with comorbidity of bronchial asthma and atopic dermatitis underwent significant changes.

Keywords Bronchial asthma, Atopic dermatitis, Comorbid course, Intestinal microbiota, Immune system, Dysbiosis, Th2-immune response, Allergic inflammation, Pathogenesis, Children

1. Introduction

In recent years, the incidence of allergic diseases in children, in particular bronchial asthma (BA) and atopic dermatitis (AD), has been increasing. According to the World Health Organization, at least one in ten children has allergic diseases, and a large proportion of them continue not only in childhood but also in adulthood. The co-occurrence of BA and AD with each other is a particular problem in clinical practice. When these two diseases coexist, the patient's quality of life deteriorates sharply, severe forms of the disease are more often observed, the effectiveness of treatment decreases, and numerous complications arise [1-3]. Currently, the role of the intestinal microbiota in the development of these diseases is of particular interest. The composition of the intestinal microbiota is of great importance for the normal functioning of the immune system, the limitation of inflammatory processes, and protection against allergic reactions [4,5]. Dysbiosis in the microbiota composition—especially in the early years of life—has been scientifically proven to be associated with impaired immune tolerance and the development of allergic diseases [6-8].

Scientists have been paying great attention to the intestinal microbiota in the last decade. Because at least 70% of the activity of the human immune system is closely related to the intestinal microbiota. The formation of the microbiota in children occurs in the first years of life, and various factors - nutritional characteristics, the use of antibiotics, perinatal complications, artificial feeding, etc. - have a significant impact on its composition. Imbalance (dysbiosis) in the composition of the intestinal microbiota disrupts immune homeostasis, disrupts the balance between Th1 and Th2 lymphocytes, and increases the secretion of inflammatory cytokines (IL-4, IL-5, IL-13) and IgE. This condition aggravates the clinical manifestations of AD and BA, reduces the response to treatment, and often causes recurrent relapses. Children with BA and AD often have a reduced intestinal microbiota of Faecalibacterium prausnitzii,

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Bifidobacterium, and Lactobacillus species, as well as an increase in opportunistic pathogens. This leads to a decrease in short-chain fatty acids (SCFA), especially butyrate, a decrease in epithelial barrier function, and an increase in the secretion of inflammatory mediators [9,10].

According to the gut–lung–skin axis concept, the microbiological balance in the gut shapes the immune response not only through the digestive system, but also through the respiratory and skin. Therefore, factors that affect the gut microbiota — antibiotics, diet, perinatal conditions, viral infections — can affect the clinical course of not only AD, but also BA. The comorbid course of BA and AD in children is accompanied by dysregulation not only in the respiratory tract, but also in the skin and general immune system. Often, such children have: frequent illnesses, aggravated allergen sensitivity, congenital or acquired immune imbalance, vitamin and microelement deficiencies, and a decrease in the number of bifidobacteria and lactobacilli in the intestinal microflora. These conditions combine to further complicate the pathogenesis of the disease. Studies conducted during the COVID-19 pandemic have provided additional evidence of the relationship between viral infections and the composition of the microbiota. After SARS-CoV-2 infection, some children have been found to have persistent gut microbiota dysbiosis and signs of immune dysregulation, which may increase the risk of developing or worsening allergic diseases.

In this regard, studying the interrelationship between the gut microbiota and the immune system in the comorbid course of BA and AD is an important step not only to understand the pathogenesis, but also to develop new diagnostic and therapeutic methods. Research in this direction will allow the implementation of individualized approaches aimed at probiotic and prebiotic therapy, nutritional correction, and microbiota modulation.

2. Purpose of the Research

Determination of changes in intestinal microbiota and immune system in the comorbid course of bronchial asthma and atopic dermatitis in children.

3. Materials and Methods

The study included 56 children with comorbid asthma and atopic dermatitis. Their ages ranged from 3 to 12 years, and all had a confirmed diagnosis based on clinical and laboratory criteria. Thirty healthy children matched for age and sex were used as controls. All participants had their airways assessed using spirometry and, where possible, body plethysmography. Atopic dermatitis severity was assessed using the SCORAD index, and asthma control was measured using the ACT/C-ACT tests.

For the composition of the intestinal microbiota, soil samples collected in the morning were taken, certain parts of the 16S rRNA gene were sequenced, and the taxon composition was determined by bioinformatic analysis. The microbiome α-diversity indices (Shannon, Chao1), the Firmicutes/Bacteroidetes ratio, and the proportion of probiotic and opportunistic pathogens were analyzed. Serum immunological markers, including IL-4, IL-10, TNF-α, total IgE, and peripheral eosinophil levels, were determined by ELISA and standard methods. The collected data were processed using statistical methods, and differences and correlations between groups were assessed.

4. Results and Discussion

The results showed that children with bronchial asthma and atopic dermatitis had significantly lower microbiota diversity than healthy children. In particular, the proportion of probiotic strains such as Bifidobacterium and Lactobacillus decreased, while Enterobacteriaceae and Clostridioides species increased. These changes were consistent with data reported in the scientific literature that could lead to impaired barrier function and increased inflammatory mediators.

The results of the study showed that children with bronchial asthma and atopic dermatitis had a sharp decrease in microbiota diversity. In the main group, the Shannon index was on average 3.1±0.6, compared to 3.7±0.5 in the control group ($p<0.01$), and the Chao1 index was 145 and 172, respectively ($p<0.05$). These indicators indicate a loss of microbiome stability. The proportion of Bifidobacterium, a probiotic, was about 12.4%, compared to 19.6% in the control group ($p<0.01$), while the amount of Lactobacillus decreased to 6.1%, compared to 10.5% in the control group ($p<0.01$). Among opportunistic pathogens, the proportion of Enterobacteriaceae in the comorbid group was 14.8% and did not exceed 6.3% in the control group ($p<0.001$), while Clostridioides spp. were observed at 8.2% and 3.9%, respectively ($p<0.01$).

Immunological analyses also showed a close correlation with changes in the microbiome. In the comorbid group, IL-4, IL-5, and IL-13 levels were significantly increased, while IL-10 and IFN-γ were decreased. This indicates a lack of compensatory resources of the immune system and an increase in Th2 dominance. It was found that children with higher levels of total IgE and eosinophils had worse asthma control, and skin lesions were more severe, as expressed by the SCORAD index.

Immunological analyses revealed a sharp increase in Th2 mediators: IL-4 level was 12.8 pg/ml, compared to 5.1 pg/ml in the control ($p<0.001$), IL-5 level was 8.4 pg/ml, compared to 3.7 pg/ml in the control ($p<0.001$), IL-13 level was 15.6 pg/ml, compared to 7.3 pg/ml in the control ($p<0.001$). At the same time, a decrease in regulatory markers was detected: IL-10 level was 3.9 pg/ml, compared to 6.5 pg/ml in the control ($p<0.01$), and IFN-γ level was 4.8 pg/ml, compared to 9.7 pg/ml in the control ($p<0.001$). Total IgE was 328 IU/mL (range 240–450) in the comorbid group and 105 IU/mL (80–140) in the control group ($p<0.001$). The proportion of eosinophils in peripheral blood was 8.5%, compared to 2.1% in the control group ($p<0.001$). Clinical parameters also corresponded to immunological and microbiome changes. Asthma control C-ACT score was 18.2 on average in the comorbid group and 24.1 in the control group ($p<0.001$). The number of exacerbations per year was 3.6, compared to 0.7 in the control group ($p<0.001$). The median value of the SCORAD index for the severity of atopic dermatitis was 42.5, indicating a moderate-severe stage.

Significant differences were also observed in functional tests. Spirometry showed that FEV1 was 89.4% in the comorbid group compared to 96.2% in the control group ($p=0.04$). However, body plethysmography showed an increase in airway resistance: Raw value was 0.47 kPa s/l compared to 0.32 kPa s/l in the control group ($p<0.01$), and specific permeability decreased to 0.78 compared to 1.15 in the control group ($p<0.01$). Correlation analyses showed that the decrease in diversity was inversely associated with the increase in SCORAD ($\rho=-0.42$; $p<0.01$). A decrease in the proportion of Bifidobacterium was associated with an increase in total IgE levels ($\rho=-0.38$; $p<0.05$), and an increase in Enterobacteriaceae was associated with a decrease in the ACT/C-ACT score ($\rho=-0.35$; $p<0.05$).

According to the results of multivariate analysis, low α-diversity (OR=2.9), high Enterobacteriaceae (OR=2.4), and total IgE levels greater than 200 IU/ml (OR=3.6) were identified as independent predictors of comorbidity. In ROC analysis, the Shannon index, IgE and Enterobacteriaceae composite index, had a discriminatory power of AUC=0.82, indicating that it can be used in future clinical practice.

Functional testing also confirmed microbiome and immune changes. Although spirometry often showed values close to normal, body plethysmography revealed increased airway resistance and decreased specific permeability. These “hidden” obstructive changes can be explained by a disturbance in the balance of the microbiota and the immune system. The analysis showed that the lower the diversity of the intestinal microbiota, the greater the severity of atopic dermatitis and the worse the control of bronchial asthma. It was found that a decrease in Bifidobacteria was inversely associated with total IgE, and an increase in the proportion of Enterobacteriaceae was associated with a decrease in asthma control. Multivariate analyses showed that microbiome diversity, dysbiosis, and high IgE were independent predictors of comorbid conditions in children.

5. Conclusions

In conclusion, it has been proven that children with bronchial asthma and atopic dermatitis have significant changes in the structure and diversity of the intestinal microbiota. A significant decrease in probiotic strains of Bifidobacterium and Lactobacillus, an increase in opportunistic pathogens such as Enterobacteriaceae and Clostridioides, and a decrease in α-diversity negatively affect the barrier function and compensatory mechanisms of the immune system, contributing to Th2-dominance and increased allergic reactivity mediated by IgE. From an immunological point of view, an increase in the levels of IL-4, IL-5, IL-13 in the comorbid condition and, conversely, a decrease in IL-10 and IFN-γ are consistent with an imbalance in the microbiome, leading to chronic persistence of inflammation and aggravation of clinical symptoms. These changes were also confirmed by clinical indicators: increased SCORAD scores and poor asthma control were noted. Bodyplethysmographic “hidden” airway obstruction is also associated with microbial-immune changes.

Multivariate analyses showed that reduced diversity, increased Enterobacteriaceae, and increased total IgE were clinically significant as independent predictors of comorbidity. These findings further support the central role of the gut–immune axis in the pathogenesis of allergic diseases in children.

Scientifically, the obtained data reveal a number of directions for future clinical practice: the dynamic assessment of intestinal microbiota can be used as a reliable biomarker in predicting the severity of allergic diseases and the effectiveness of treatment; individual corrective therapies based on probiotics and prebiotics can be an optimal direction in restoring the immune balance and strengthening the barrier function; and integration of nutritional, microbiome and immune components in the comprehensive management of the comorbid course of bronchial asthma and atopic dermatitis.

Thus, the joint analysis of microbiota diversity and immune indicators can be considered as a scientifically based modern direction in improving clinical control of atopic diseases in children, personalizing treatment algorithms and improving long-term prognosis.

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