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The importance of biodiversity of human microbiota and environment in the susceptibility to the development of bronchial asthma in children

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ABSTRACT

Bronchial asthma (BA) remains one of the most common chronic respiratory diseases in childhood. BA develops with a combination of genetic predisposition and environmental factors. Epidemiological data on the development of BA emphasize the role of early-life microbiota in the formation of immune responses and susceptibility to the development of BA. In recent years, enough data has been accumulated to suggest that an imbalance in intestinal and airway microbiota during early life may predispose a child to the development of BA. In turn, the biodiversity of the environment influences the colonization of various biotopes in the human body by microorganisms. The study of the mechanisms of interaction between microbiota communities of the environment and humans will pave the way for the development of new strategies for the prevention of BA.

The aim of this review was to analyze current research aimed at assessing the importance of biodiversity of human microbiota and environment in the susceptibility to the development of BA in children.

Keywords: bronchial asthma, children, intestinal microbiota, airway microbiota, environmental microbiota

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Значение биоразнообразия микробиоты человека и окружающей среды в подверженности развитию бронхиальной астмы у детей

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РЕЗЮМЕ

Бронхиальная астма (БА) остается одним из наиболее распространенных хронических заболеваний дыхательных путей в детском возрасте. Развитие БА реализуется при сочетании генетической

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предрасположенности и воздействия факторов внешней среды. Эпидемиологические данные, касающиеся развития БА, подчеркивают важность воздействия микробиоты в раннем возрасте в формировании иммунных реакций и подверженности развитию БА. В последние годы накоплено достаточно данных, позволяющих предположить, что дисбаланс микробиоты кишечника и дыхательных путей в раннем возрасте может предрасполагать ребенка к развитию астмы. В свою очередь, биоразнообразие окружающей среды оказывает влияние на колонизацию микроорганизмами различных биотопов организма человека. Исследование механизмов взаимодействия микробиотических сообществ окружающей среды и человека откроет перспективу для разработки новых стратегий профилактики астмы.

Цель настоящего обзора – провести анализ современных исследований, направленных на оценку значения биоразнообразия микробиоты человека и окружающей среды в подверженности развитию бронхиальной астмы у детей.

Ключевые слова: бронхиальная астма, дети, кишечная микробиота, микробиота дыхательных путей, микробиота окружающей среды

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INTRODUCTION

Asthma is one of the most common chronic respiratory diseases, affecting up to 10% of children and adolescents [1]. Asthma develops through a combination of genetic predisposition to atopy and bronchial hyperreactivity and exposure to environmental factors[1]. Recent data suggest a possible link between the high prevalence of asthma and a decrease in exposure to microbes as a result of changes in dietary habits. This includes a decrease in dietary fiber intake and an increase in fat intake, improved hygiene, irrational use of antibacterial drugs, and other factors [2, 3]. Currently, there is more and more information on changes in the composition of human microbiota in various diseases and its role in the pathogenesis of various disorders, including asthma [4]. Epidemiological and experimental data demonstrate the importance of exposure to microbial factors at an early age in the formation of immune responses [5–7].

According to modern research, there are several hypotheses that explain the relationship between the prevalence of allergic diseases and environmental changes that have occurred in recent decades (such as urbanization, improved housing conditions, and changes in the diet) and a decrease in environmental biodiversity [3, 8, 9] Epidemiological studies show that reduced exposure to environmental bacteria in early life (e.g., cesarean birth, infant formula feeding, living in an urban environment, in small families, and with limited contact with various animals) is associated with an increased risk of developing allergies and asthma later in life [3, 8–10]. Conversely, a reduced risk of developing asthma is observed in children living in rural areas, as well as in large families with older children. This is probably due to the child’s exposure to a wide range of microorganisms and their metabolites [11]

Experimental and clinical studies aimed at studying the characteristics of the microbiota in asthma described the intestinal and airway microbiota. The formation of the microbiota is affected by many internal and external factors. One of the striking examples of the environment affecting the development of asthma is the “farm effect” [12]. Many epidemiological studies have shown that living on a farm in early life is associated with a reduced risk of asthma in children [12–15].

The aim of this review was to analyze current research focused on assessing the importance of biodiversity of human microbiota and the environment in the susceptibility to the development of bronchial asthma in children.

MATERIALS AND METHODS

We analyzed scientific publications of clinical studies aimed at assessing the biodiversity of the microbiota of airway, intestine, and environment in the development of asthma in children.

The search was conducted using the PubMed search engine (https://pubmed.ncbi.nlm.nih.gov/) and the Elibrary scientific electronic library (https://www.elibrary.ru/). The review presents original articles published from April 1, 2014 to April 1, 2024.

Initially, we searched for publications devoted to the study of the intestinal and/or airway and/or environmental microbiota in asthma in children from birth to 18 years of age. The search was conducted with the following keywords in English and Russian: asthma microbiota gut or microbiota airway or microbiota environment or microbiota household, asthma, children, intestinal microbiota, airway microbiota, environmental microbiota. We examined the summaries of 7,708 articles selected in the initial search.

Then we analyzed the summaries of 907 publications, excluding reviews, case-control studies, and works that did not contain data on the intestinal and/or airway and/or environmental microbiota in asthma in children.

The analysis included 19 publications that met the following inclusion criteria: a study of the intestinal and/or airway and/or environmental microbiota (microbiota of household dust samples) using sequencing in children without asthma symptoms at the time of inclusion in the study, followed by an assessment of the association with the development of asthma, and a complete description of the study design.

THE IMPORTANCE OF AIRWAY MICROBIOTA IN THE DEVELOPMENT OF ASTHMA IN CHILDREN

It is currently known that the respiratory mucosa in healthy individuals is colonized by bacterial communities specific to this biotope [16]. Studies have shown that the composition of the airway microbiota differs in healthy children and patients with asthma, and differences in the microbiota in different asthma phenotypes have been established [17].

Multiple studies have demonstrated that changes in the microbiota in early childhood are crucial for the development of asthma later in life [18–23]. However, the results of the studies are contradictory due to differences in the techniques for collecting the studied biospecimens, methods, and time points, which makes it difficult to generalize the results. As a result of the analysis of publications, we selected 6 prospective studies that analyzed the association of the airway microbiota in infants with the development of asthma later in life [18–23]. Most studies used samples taken from the nasopharynx to study the microbiota, and two studies reported airway aspirates as the studied biospecimens [18, 19]. Three studies reported on the assessment of alpha and beta diversity of the microbiota [18, 20, 21].

However, only one study found an association with the development of asthma of a higher alpha diversity index and a difference in beta diversity compared to children who did not have asthma symptoms at the age of 6 [18]. This study also demonstrated an increase in Veillonella and Prevotella in infants aged 1 month who later developed asthma [18].

Two studies have shown that higher relative abundance of Streptococcus in the nasal microbiota of infants is associated with the development of asthma [22, 23].

Another study showed that the abundance of Staphylococcus bacteria in the nasopharynx in the first 6 months of life is associated with recurrent wheezing in the first 3 years of life and the development of asthma at an older age [19]. Also, two studies demonstrated the association of Haemophilus with the risk of developing asthma [19,21]. Several studies have noted changes in the number of bacteria belonging to the Moraxella genus, but the data are contradictory [19, 21]. A prospective cohort study also confirmed the association of Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis with the development of asthma [20].

It should be noted that in children suffering from asthma, an increase in the Moraxella and Streptococcus w genera was noted in samples of the lower airway microbiota (analysis of sputum and exhaled air condensate) [24, 25].

THE IMPORTANCE OF INTESTINAL MICROBIOTA IN THE DEVELOPMENT OF ASTHMA IN CHILDREN

The intestinal microbiota is one of the most important factors determining human health and is currently considered as a system responsible for regulating the metabolic and immune homeostasis of the body [26]. Intestinal microbiota and its metabolites play an important role in the development of local and systemic immune responses [27]. Changes in the intestinal microbial composition can have a significant impact on respiratory diseases, such as asthma, by shaping microbial communities and modulating the metabolic and immune response. This concept is called the gut – lung axis [4, 28].

The development of the intestinal microbiome in early life is influenced by many environmental factors, such as living in a microbial-rich environment (e.g., on a farm or with frequent contact with livestock and pets) or dietary diversity, the preventive value of which in relation to the development of asthma in childhood has been shown in studies [29, 30]. Early life exposure and colonization by certain microbes are thought to be important for intestine development, immune cell maturation, and resistance to pathogens [31].

The taxonomic richness of the intestinal microbiota is thought to determine its resistance to various effects, including pathogen colonization, while low diversity of bacterial communities is associated with pathological conditions [32. The studies included in the review noted a decrease in alpha diversity in stool samples of infants who later developed asthma compared to healthy children [32, 33].

In a prospective study, G. Galazzo et al. showed that the *Lachnobacterium, Lachnospira*, and *Dialister* genera were significantly decreased in the intestinal microbiome of infants who developed asthma by school age compared to healthy children [34]. The analysis of the taxonomic composition of the microbiota showed that a high risk of developing asthma is associated with a decrease in genera such as *Faecalibacterium, Bifidobacterium, Roseburia, Alistipes, Ruminococcus,* and *Dialister* and a higher content of Veillonella [35, 36]. Similar results were obtained by scientists from the USA: the abundance of Veillonella in the intestine was associated with episodes of wheezing, while no association was found between wheezing and beta diversity [37].

However, in a cohort study conducted in Canada involving more than 300 children, the risk of developing asthma was associated with a decrease in the relative abundance of bacteria of the *Veillonella* genus [38]. Another study also showed an association of a decrease in the Bifidobacterium, Faecalibacterium, and Akkermansia genera with a high risk of developing asthma [39]. Several studies have described an association between a decrease in the relative abundance of the *Roseburia*, *Ruminococcus, Faecalibacterium*, and *Lachnospira* genera with an increased risk of developing this pathology [12, 33–35].

Despite the multifaceted and heterogeneous nature of the studies, taken together, these data confirm the importance of the composition of the intestinal microbiota in early life with susceptibility to the development of asthma in children.

THE IMPORTANCE OF ENVIRONMENTAL MICROBIOTA IN THE DEVELOPMENT OF ASTHMA IN CHILDREN

The microbiota of different biotopes is formed mainly during the first year of life and continues to develop until adulthood. The types of delivery and feeding affect the colonization with microorganisms in early life [22, 38]. Studies have shown that the type of delivery (vaginal or cesarean birth) and the environment in the first 6 months of life are of great importance for the formation of a stable microbiota of the respiratory and intestinal organs, which determines the state of health in older age [22, 38].

According to the meta-analysis, children delivered by cesarean section have a higher risk of developing bronchial asthma and allergic rhinitis compared to children born vaginally [40]. However, another study showed that the microbiota of infants is determined to a greater extent by maternal factors and does not depend on the mode of delivery [41]. Probably, the risk of developing allergic diseases is also associated with the influence of conditions that determine the mode of delivery in favor of cesarean section. Epidemiological studies have shown that contact with older siblings or attending preschool in the first two years of life prevents developing allergies, which is associated with an increase in the taxonomic diversity of the microbiota [11, 42].

It has also been shown that children living on farms are less susceptible to allergic diseases [2, 13, 14, 43, 44]. The results of a cohort study in Denmark showed that an increased risk of developing asthma was recorded in adolescents who lived in moldy and damp houses at an early age. In contrast, adolescents who lived in farmhouses and had contact with domestic animals were less likely to suffer from asthma by the age of 18 [45].

These factors are thought to affect the development of the immune system in childhood by shaping a taxonomically rich microbiota of diverse biotopes [14, 32]. Experimental and clinical studies have shown that inhaled dust particles can carry a complex mixture of microbes and their metabolites that influence susceptibility to asthma development through their effects on airway immune responses [14, 46]. The study also demonstrated the relationship between fungal and bacterial communities at home and the airway microbiota in early life [47]. The review of publications over the past 10 years identified six studies assessing indoor microbiota using molecular genetic methods and its association with asthma development [14, 43, 48–51]

A prospective cohort study showed that microorganisms associated with the rural environment in infant crib dust samples were associated with a lower risk of developing asthma and allergic rhinitis at the age of 6 years [48]. Low bacterial diversity was found in the microbiota collected from crib dust samples from children who later developed asthma [48]. Another study showed differences in beta diversity, increased *Lactococcus* and *Streptococcus*, and decreased *Sphingomonas* in house dust samples from homes of patients with asthma compared to homes of participants without asthma [49]. Among high-risk urban children, higher levels of indoor allergens in infancy were associated with a lower risk of developing asthma at age 7 [50]. In addition, studies of the farm environment and asthma risk have shown that the number of *Streptococcaceae* in the dust microbiota is higher in homes not located in rural areas, which is associated with the risk of developing asthma [43].

However, studies of dust microbiota in the homes of patients diagnosed with asthma demonstrate an association of high microbial biodiversity with uncontrolled asthma. Thus, a study conducted in the USA reported a positive association between bacterial abundance at home and asthma severity in children [52].

Diverse composition of indoor microbiota affects the colonization of the intestine and airways by microorganisms, promoting the development of immune tolerance [13, 53]. Exposure to environmental microbial communities in early life is associated with the risk of developing asthma in children, and these results can serve as guidelines for the development of asthma prevention strategies.

CONCLUSION

Thus, the analysis of modern studies demonstrates the important role of diversity and composition of human microbiota and the environment in the development of asthma in children. Summarizing the research results, we can conclude that the period from birth to 12 months is the ideal time for epigenetic changes associated with environmental exposure and susceptibility to asthma. Further research is needed to study the pathogenetic mechanisms of interaction between microbial communities and the human immune system. New studies will provide the basis for the development of new technologies for asthma management.

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