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COMPARATIVE CLINICAL AND IMMUNOLOGICAL CHARACTERISTICS OF THE MAIN PHENOTYPES OF WHEEZING SYNDROME IN PRESCHOOL CHILDREN

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Abstract
The aim of the study was to conduct a comparative clinical and immunological assessment of the main phenotypes of wheezing syndrome in preschool children. The results of the study showed that the phenotype of multifactorial wheezing is characterized by more pronounced nocturnal symptoms, persistent nature of the course of the disease, the onset of obstructive syndrome at the age of over three years, a higher level of total IgE, IL-8, IL-4, TNFα, a higher indicator of respiratory resistance. pathways and bronchial hyperreactivity. The phenotype of episodic wheezing is characterized by more pronounced daytime symptoms, an intermittent nature of the course of the disease, the onset of obstructive syndrome at the age of less than three years, lower than with multifactorial wheezing, the level of total IgE, IL-8, IL-4, TNFα, a lower indicator airway resistance and bronchial hyperreactivity.
Keywords: pediatrics, syndrome, ELISA, hyperreactivity, wheezing syndrome

Introduction

Diseases of the respiratory tract, accompanied by the onset of wheezing, are very common at an early age and are one of the main reasons for hospitalization of young children. Population studies have shown that by the age of 6, at least one episode of bronchial obstruction is tolerated by almost 50% of children [1,2]. In Uzbekistan, the prevalence of obstructive respiratory diseases is also high and amounts to 12.2-16.4 per 1000 children. In preschool age, broncho-obstructive syndrome is recorded in 20-25% of cases [3,4]. Moreover, in more than half (57.5%) of children, episodes of obstruction are repeated 2 times or more. The results of epidemiological studies using modern diagnostic criteria suggest that

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recurrent bronchitis in children, especially obstructive forms, is often a manifestation of bronchial asthma [5,6]. Currently, there is a classification in which two phenotypes of wheezing are distinguished, depending on trigger factors, and which allows one to study the effectiveness of various therapeutic approaches: may occur in other age periods (the frequency of occurrence of these wheezing decreases with age, by the age of 6 they usually pass, although sometimes they continue at school age and are transformed into a different phenotype); 2-Multiple-trigger (multifactorial wheezing), the cause of which, in addition to infectious diseases, are other triggers: allergens, tobacco smoke, laughter, crying, cold air. Many scientists believe that chronic allergic airway inflammation is observed with this phenotype, but there is still insufficient evidence for this [7,8]. Immunological parameters in children with wheezing syndrome can be very different, which is primarily associated with the cause of wheezing, therefore, wheezing syndrome in children can be a manifestation of both viral infections of the respiratory tract and bronchial asthma, that is, conditions in which are based on various pathogenetic mechanisms. Therefore, the identification of immunological features for differential diagnosis is very promising [9].

Purpose of the study. To carry out a comparative clinical and immunological assessment of the main phenotypes of wheezing syndrome in preschool children.

Materials And Methods

The study was conducted in 40 patients aged 3 to 5 years with persistent symptoms of wheezing syndrome (wheezing syndrome) for the period 2020-2021, who were inpatient treatment in the department of pulmonology. All patients met the study inclusion criteria.

The inclusion criteria for patients in the study were:

1. Age from 3 to 5 years;
2. Three or more episodes of bronchial obstruction during the year in the history, recorded by the doctor in the outpatient card or medical history.

Evaluation of immunological parameters included the study of IL-4, IL-8, IFNγ, TNFα. The concentration of IL-4, IL-8, IFNγ in the blood was determined by the enzyme-linked immunosorbent assay using monoclonal antibodies (ELISA).

Results

Clinical signs of broncho-obstructive conditions in children are the elongation of expiration, the appearance of expiratory noise, asthma attacks, the participation of auxiliary muscles in the act of breathing, and an unproductive paroxysmal cough. With a pronounced narrowing of the bronchi, a noisy exhalation, an increase in the respiratory rate, the development of respiratory muscle fatigue and a decrease in PaO2 may appear. This clinical symptom complex in the foreign literature is called wheezing-syndrome, since whistling sounds - distant or heard during auscultation - are its main manifestations [1,2,10]. Parents are not always able to objectively assess the appearance of signs of airway obstruction in a child, therefore, a prerequisite for the inclusion of patients in our study was the presence of at least three episodes of bronchial obstruction during the year, recorded by a doctor. We examined 40 children; in 65.0% (26) children, the only trigger provoking obstruction was respiratory tract infections (group I with episodic wheezing). In 25.0% (14) of the studied obstructions occurred with other allergens (group II - multifactorial wheezing). In group I, the allergic history was

aggravated in 34.6% of children (for bronchial asthma - in 33.3%, for allergic rhinitis - in 22.2%, for atopic dermatitis - 22.2%, for urticaria - 11.1% , for drug allergy - in 11.1%). In children of group II, hereditary burden was observed in 57.1%, than in I - 17.74% of the total number of children in this group. In the structure of concomitant allergic diseases in group II, allergic rhinitis was 64.2%, atopic dermatitis was 57.1%, allergic conjunctivitis was 7.14%, drug allergy was 14.2%. Pronounced bronchial hyperreactivity was detected in 64.2% of cases, moderate - in 28.5%, weak - in 11.1%. In group I, pronounced bronchial hyperreactivity was recorded in 26.9% of children, moderate - in 38.4%, weak - in 34.6%.

When analyzing clinical symptoms in children with multifactorial wheezing during the "introductory period" of the study, which lasted for 3 months, it was found that in this group 85.0% (n = 34) of the studied had attacks of typical expiratory dyspnea. The attacks lasted from 5 minutes to several hours and resolved with short-acting inhaled β2-agonists. The average need for short-acting bronchodilators was 0.47 doses. In 20.0% of children (n = 8), other manifestations of obstruction were also noted (episodes of wheezing without signs of shortness of breath, paroxysmal cough). Of these, 40% had both typical and atypical obstructive seizures within a month. Nocturnal symptoms (attacks of shortness of breath, coughing, shortness of breath) were observed in 87.5% of the subjects (n = 35), and 15.0% of children (n = 5) led to the awakening of the child. The average number of asymptomatic days was 18.26 ± 1.3. In patients with episodic wheezing, the clinical picture had a number of differences from the manifestations of broncho-obstructive syndrome in children with multifactorial wheezing. First, the symptoms were observed only against the background of viral infections. During the "introductory study period", 7.5% of children (n = 3) had no episodes of bronchial obstruction, the remaining 92.5% of the subjects (n = 37) suffered from 1 to 5 cases of acute respiratory infection accompanied by wheezing. In 27.5% of patients (n = 11), symptoms of bronchial obstruction appeared in the first three days of illness, which is more typical for bronchial asthma than for obstructive bronchitis (National Program "Bronchial Asthma in Children. Prevention and Treatment", 2020). It is interesting that with episodic wheezing, the manifestation of broncho-obstructive syndrome usually occurred at the age of 3 years (the average age of onset of symptoms was 2.49 ± 0.55, and with multifactorial ones later than 3 years - 3.68 ± 0.72; (P <0.01) .There were statistically significant differences between the groups in the following parameters: mean score for daytime symptoms (P <0.001), mean score for nighttime symptoms (P <0.05), number of asymptomatic days (P <0.001) and need for bronchodilators (P <0.001) (table 1).

Table 1. The severity of clinical symptoms and the need for bronchodilators in the main phenotypes of wheezing (M ± m)

Symptoms	I group (with multifactorial wheezing), n = 14	II group (with occasional wheezing), n = 26
Daytime symptoms	1,18±0,025	3,06±0,09***
Nightime symptoms	1,49 ±0,051	0,86±0,05*

Asymptomatic days	18,26±0,33	22,67±0,22***
Bronchodilators requirement	0,47±0,014	0,61±0,015***

*Note: the significance of differences when comparing between groups: * -P <0.05; ** - P <0.01; *** - P <0.001.*

The need for bronchodilators was higher in the group with episodic wheezing, despite the greater number of symptom-free days. This is probably due to a more severe course of broncho-obstructive syndrome, as well as a different dosage regimen.

Unfortunately, there are still no specific laboratory tests that would allow to determine what causes the inflammation of the airways - bronchial asthma or another cause [7,11,12]. This is probably due to the fact that the pathogenesis of the disease is not fully understood. At the same time, according to the current understanding, the Th2-variant of the immune response leads to the development of allergic reactions, including bronchial asthma. The produced Th2 cytokines include IL-4 and IL-8. IL-4 plays an important role in the switch in B-lymphocytes of IgG and IgM synthesis to IgE. IL-8 is essential for the differentiation and lifespan of eosinophils. It was also found that in patients with bronchial asthma, in addition to an increase in the production of IL-4 and IL-8, there are changes in the interferon system: a decrease in the level of IFNγ, which is produced by Th1 lymphocytes, promotes the activation of macrophages, increases the production of TNFα and IL-1, and enhances bactericidal activity serum, and is also an antagonist of IL-4. All of the above immunological parameters (biomarkers of inflammation) were studied in 14 children with multifactorial wheezing and a negative test with a bronchodilator and 26 children with an episodic and negative test with a bronchodilator (Table 2).

Table 2. Immunological parameters in the main phenotypes of wheezing (M ± m)

Indicator	I group (with multifactorial wheezing), n = 14	II group (with occasional wheezing), n = 26	P_1
IL-4 (pg / ml)	26,88±0,59	21,3±0,34	<0,05
IL-8 (pg / ml)	100,9±7,7	89,54±2,45	<0,01
INF-γ (pg / ml)	14,31±0,37	21,64±0,63	<0,01
TNFα (pg / ml)	98,7±2,04	62,5±1,16	<0,001

At baseline, in all patients with multifactorial wheezing, the level of IL-4, IL-8 was significantly higher than in patients with episodic wheezing (P <0.001). The IFNγ content was characterized by significant diversity; there were no statistically significant differences between the study groups. To assess mediator disorders, the TNFα ratio was used, which shows a change in the balance in the system of cytokines that regulate the functional activity of Th2 and Th1 lymphocytes. This indicator allows you to more accurately understand the changes in the immune system that occur in patients. In children with multifactorial wheezing, it was significantly higher than in patients with episodic wheezing (P <0.001).

Conclusion

1. The wheezing syndrome was more common in boys. The aggravation of the hereditary allergic history in children of group II was noted more often than in I. In group II, wheezing was often associated with other allergic diseases, pronounced bronchial hyperreactivity was more often observed than in children of group I.
2. The phenotype of multifactorial wheezing is characterized by the following differential - diagnostic features: more pronounced nocturnal symptoms, persistent nature of the course of the disease, the onset of obstructive syndrome at the age of over 3 years, a higher level of total IgE, IL-8, IL-4, TNFα higher an indicator of airway resistance and bronchial hyperreactivity.
3. The phenotype of episodic wheezing is characterized by the following differential - diagnostic features: more pronounced daytime symptoms, intermittent nature of the course of the disease, the onset of obstructive syndrome at the age of less than 3 years, lower than with multifactorial wheezing, the level of total IgE, IL-8, IL -4, TNFα, lower airway resistance and bronchial hyperreactivity.

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