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Indicators of Nonspecific Bronchial Hyperresponsiveness in Children with Asthma Depending on Inflammatory Blood Patterns

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Abstract

Introduction. Achieving control over bronchial asthma (BA) in children is fundamental for treatment strategy for this socially significant disease. The need to monitor bronchitis in order to reduce frequency and severity of BA exacerbations is considered to be of an extreme importance.
Purpose. The aim of the study is to retrospectively investigate the indicators of nonspecific bronchial reactivity depending on the inflammatory bloodpatterns in order to optimize the comprehensive treatment of children with asthma.
Materials and methods. To achieve this goal, a comprehensive clinical and immunological examination of I-II level of 120 children with BA was conducted. Indicators of cellular and humoral immunity, the content of T-lymphocytes and their subpopulations in the peripheral blood, the level of immunoglobulins of classes A, M, G, E total and interleukin-4, -5, -8 in the blood serum were studied. All children were assessed for immediate skin sensitivity to household, food, epidermal, and pollen allergens. Studies of nonspecific bronchial hyperresponsiveness (NBHR) to direct bronchospasmogenic stimuli were performed using an inhalation spirometric test with serial dilutions of histamine, taking into account the recommendations for the study standardization. Depending on the content of granulocytes in the blood, four clinical groups were formed. The first (I) group consisted of 34 children with asthma with hypogranulocytic inflammatory pattern (countof eosinophils in blood <250 cells/mm3 and neutrophils <5000 cells/mm3) (average age – 13.7±2.6 years, the percentage of boys – 64.7%), group II included 60 children with asthma with a predominantly eosinophilic pattern of peripheral blood (eosinophil count ≥250 cells/mm3) (average age – 12.8±2.9 years, the percentage of boys – 70.0%), group III included 14 children with a neutrophilic pattern (neutrophil count ≥5000 cells/mm3) (average age – 12.6±2.7 years, the percentage of boys – 64.3%), group IV included 12 children with hypergranulocytic pattern of the inflammatory response (eosinophil count ≥250 cells/mm3 and neutrophil count ≥ 5000 cells/mm3) (average age – 14.9±1.9 years;

the percentage of boys – 58.3%). According to the main clinical characteristics the groups under observation were compared.
Results. The presence of hypergranulocytic inflammatory blood pattern increases the chances of developing severe nonspecific bronchial hyperresponsiveness and, consequently, the severe course of disease. In particular, the chances of severe asthma with probability of losing control over the disease in patients with hypergranulocytic inflammatory blood pattern in the presence of bronchial hyperresponsiveness to histamine (at a concentration rate of less than 1.2 mg/ml, which decreases FEV_1 by 20%) compared with hypogranulocytic inflammatory phenotype increased by 17.0.
Conclusions. Chances of severe asthma course with the probability of control loss over the disease control in patients with hypergranulocytic inflammatory blood pattern in the presence of bronchial hyperresponsiveness to histamine compared with hypogranulocytic inflammatory phenotype increased by 17,0.
Keywords: bronchial asthma, children, phenotype, inflammatory blood pattern, nonspecific bronchial hyperresponsiveness

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Показатели неспецифической гипервосприимчивости бронхов у детей с бронхиальной астмой в зависимости от воспалительных паттернов крови

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Этическое одобрение. Протокол исследования и форма информированного согласия одобрены Комиссией по биомедицинской этике в области биомедицинских научных исследований Черновицкой областной детской клинической больницы (протокол № 81 от 26.11.2020).

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Резюме

Введение. Достижение контроля над бронхиальной астмой у детей является основой стратегии лечения этого социально значимого заболевания. Чрезвычайно важной задачей является необходимость проведения мониторинга бронхиального воспаления для уменьшения частоты и степени тяжести обострений.
Цель. С целью оптимизации комплексного лечения детей, больных бронхиальной астмой, ретроспективно исследовать показатели неспецифической реактивности бронхов в зависимости от воспалительных паттернов крови.
Материалы и методы. Для достижения поставленных целей проведено комплексное клинико-иммунологическое обследование I–II уровня 120 детей, больных

бронхиальной астмой. Изучались показатели клеточного и гуморального иммунитета, содержание в периферической крови Т-лимфоцитов и их субпопуляций, а в сыворотке крови – уровень иммуноглобулинов классов A, M, G, E общего и интерлейкина-4, -5, -8. Всем детям проводили оценку кожной чувствительности немедленного типа к бытовым, пищевым, эпидермальным и пыльцевым аллергенам. Исследование неспецифической гипервосприимчивости бронхов к прямым бронхоспазмогенным стимулам проводили с помощью ингаляционного спирометрического теста с серийными разведениями гистамина с учетом рекомендаций по стандартизации исследования. В зависимости от содержания гранулоцитов крови сформированы четыре клинические группы. Первую (I) группу составляли 34 ребенка с бронхиальной астмой с гипогранулоцитарным паттерном воспаления (содержание эозинофилов крови <250 клеток/мм^3 и нейтрофилов <5000 клеток/мм^3) (средний возраст – 13,7±2,6 года, доля мальчиков 64,7%), во II группу вошли 60 детей с бронхиальной астмой с преимущественно эозинофильным паттерном периферической крови (содержание эозинофилов ≥250 клеток/мм^3) (средний возраст – 12,8±2,9 года, доля мальчиков – 70,0%), в III группу вошли 14 детей с нейтрофильным паттерном (содержание нейтрофилов ≥5000 клеток/мм^3) (средний возраст – 12,6±2,7 года, доля мальчиков – 64,3%), в IV группу вошли 12 детей с гипергранулоцитарным паттерном воспалительного ответа (содержание эозинофилов крови ≥250 клеток/мм^3 и нейтрофилов ≥5000 клеток/мм^3) (средний возраст – 14,9±1,9 года; доля мальчиков – 58,3%). По основным клиническим характеристикам группы наблюдения были сопоставимы.

Результаты. Показано, что наличие гипергранулоцитарного воспалительного паттерна крови повышает шансы развития выраженной неспецифической гипервосприимчивости бронхов и, соответственно, тяжелого течения заболевания. В частности, шансы тяжелого течения астмы с вероятностью потери контроля над заболеванием у пациентов с гипергранулоцитарным воспалительным паттерном крови при наличии гиперчувствительности бронхов к гистамину (при концентрации менее 1,2 мг/мл, что приводит к уменьшению ОФВ1 на 20%) по сравнению с гипогранулоцитарным воспалительным фенотипом увеличивались в 17,0 раза.

Выводы. Шансы тяжелого течения астмы с вероятностью потери контроля над заболеванием у пациентов с гипергранулоцитарным воспалительным паттерном крови при наличии гиперчувствительности бронхов к гистамину по сравнению с гипогранулоцитарным воспалительным паттерном увеличивались в 17,0 раза.

Ключевые слова: бронхиальная астма, дети, фенотип, воспалительный паттерн крови, неспецифическая гипервосприимчивость бронхов

■ INTRODUCTION

Achieving control over bronchial asthma (BA) in children is fundamental for the treatment strategy of this socially significant disease. The necessity to monitor bronchial inflammation in order to reduce frequency and severity of BA exacerbations is considered to be of an extreme importance [12, 13].

At the same time, the scientific literature data accumulated in recent years concerning association of the disease severity with a certain inflammatory phenotype of BA are mostly quite contradictory. Thus, some authors indicate a predominantly neutrophilic model of

asthma in a severe course of the disease [14], others state a severe hyperresponsiveness of the respiratory tract and, accordingly, more severe disease in the presence of eosinophilic model of asthma [2, 4, 15].

In clinical practice, the most accessible method is to determine inflammatory phenotypes by the content of circulating granulocytes in the peripheral blood. Thus, a number of authors [3] indicate the existence of four inflammatory phenotypes of bronchial asthma by the content of circulating eosinophils and neutrophils: hypogranulocytic or paucigranulocytic (with a normal content of these granulocytes), eosinophilic (with blood eosinophilia higher than 250 cells/mm3), neutrophilic (with blood neutrophils over 5000 cl/mm3) and hypergranulocytic (with an increased content of eosinophilic and neutrophilic blood granulocytes).

Certain researchers associate the increase in nocturnal symptoms of the disease and a severe course of the disease, which requires the use of high doses of inhaled glucocorticosteroids, mainly with the hypergranulocytic inflammatory pattern of blood in children with bronchial asthma [9,11]. On the one hand, administration of high doses of inhaled glucocorticosteroids to such patients leads to apoptosis of eosinophils, and on the other hand, prolongs life of neutrophilic granulocytes in the blood, causing a more severe course of the disease [5].

Eosinophilic inflammatory phenotype of asthma (according to the content of granulocytes in the peripheral blood) is characterized by positive skin tests with standard allergens, increased levels of specific IgE in the blood, eosinophilia and decreased forced exhaling volume in 1 second (FEV_1) [6, 7]. The neutrophilic model of BA is characterized by a more severe course of the disease which is difficult to control with anti-inflammatory therapy, less distinct allergic sensitization, moderate results of the skin tests with allergens, fixed obstruction of the respiratory tract, a predominant influence of environmental factors and the development of inflammation mediated through macrophages and epithelial cells rather than through activated Th2 cells [10]. Patients with a neutrophilic phenotype are characterized by a moderate response to broncholytic therapy and low FEV_1 levels after administration of bronchodilators.

All the above determines reasonability of the current study dealing with the indicators of nonspecific bronchial hyperresponsiveness in children depending on the inflammatory blood patterns, since fragmentary literature data are quite contradictory.

■ PURPOSE OF THE STUDY

The objective of the study is to retrospectively investigate the indicators of nonspecific bronchial reactivity depending on the inflammatory blood patterns in order to optimize the comprehensive treatment of children suffering from bronchial asthma.

■ MATERIALS AND METHODS

To achieve this purpose a comprehensive clinical and immunological examination of I–II level of 120 children with BA was conducted. Indicators of cellular and humoral immunity, the content of T-lymphocytes and their subpopulations in the peripheral blood, the level of immunoglobulins of classes A, M, G, E total and interleukin-4, -5, -8 in the blood serum were studied. All the children were assessed for immediate skin sensitivity to household, food, epidermal, and pollen allergens.

Depending on the content of granulocytes in the blood, four clinical groups were formed. The first (I) group consisted of 34 children suffering from BA with hypogranulocytic inflammatory pattern (count of eosinophils in the blood <250 cells/mm3 and neutrophils <5000 cells/mm3) (average age – 13.7±2.6 years, including 64.7% of boys), group II included 60 children suffering from BA with a predominantly eosinophilic pattern of the peripheral blood (eosinophil count ≥250 cells/mm3) (average age – 12.8±2.9 years, the percentage of boys – 70.0%), group III included 14 children with a neutrophilic pattern (neutrophil count ≥5000 cells/mm3) (average age – 12.6±2.7 years, the percentage of boys – 64.3%), group IV included 12 children with hypergranulocytic pattern of the inflammatory response (eosinophil count ≥250 cells/mm3 and neutrophil count ≥5000 cells/mm3) (average age – 14.9±1.9 years; the percentage of boys – 58.3%). According to the main clinical characteristics the groups under observation were comparable.

Nonspecific bronchial hyperresponsiveness (NBHR) to direct bronchospasmogenic stimuli was studied using an inhalation spirometric test with serial dilutions of histamine, taking into account the recommendations for the study standardization [1]. The concentration ($PC_{20}H$) and dose ($PD_{20}H$) of histamine, which caused a decrease in FEV_1 by 20% from baseline, were calculated. $PC_{20}H$ and $PD_{20}H$ indicators were used to determine airway hyperresponsiveness, considering the fact that the higher the bronchial hyperresponsiveness was the lower those values were. Bronchial hyperreactivity (BHR) reflects the dose-response curve (DRC), in particular, the slope of the 'flow-volume' curve during the histamine inhalation test. The rate of DRC was found to increase with the growth of BHR. Bronchial lability was determined according to the recommendations [8] by assessing their response to the dosed physical exercise (DPE) and inhalation of short-acting β2-adrenomimetics (Salbutamol 200 mcg), followed by calculation of bronchial lability indicator as the sum of components, i.e. index of bronchospasm (IBS) and index of bronchodilation (IBD).

The results of the study obtained were analyzed from the standpoint of biostatistics and clinical epidemiology with the help of computer software Statistica7 StatSoft Inc. and Excel XP for Windows, the indicator difference was considered statistically significant at $p<0.05$. From the clinical epidemiology standpoint the relative risk (RR) and the odds ratio (OR) of a certain event were determined. The selection and examination of patients complied with the biomedical ethics principles in pediatrics.

■ RESULTS AND DISCUSSION

Considering contradictory data concerning the features of nonspecific bronchial hyperresponsiveness in children with bronchial asthma and taking into account inflammatory blood patterns, these indicators were determined and the data are presented in Table 1.

The obtained results give grounds to believe that children with hypergranulocytic inflammatory blood pattern possess hyperresponsiveness to histamine, with probably higher bronchial lability rates both due to bronchospatic and bronchodilator reactions.

Bronchial hyperresponsiveness and, in particular, the slope of the 'flow-volume' curve in patients with hypergranulocytic inflammatory blood pattern probably correlated with the presence of atopic asthma ($r=0.8$, $p<0.05$), loss of disease control due to AST test results ($r=0.8$, $p<0.05$), an increase of interleukin-4 count in the blood ($r=0.9$, $p<0.05$), a decrease in the relative count of CD22 lymphocytes in the blood

Table 1
Indicators of nonspecific bronchial hyperresponsiveness in representatives of the comparison groups (95% CI)

Clinical groups	Indicators					
	$PD_{20}H$ (mg/ml)	$PC_{20}H$ (mg/ml)	DRC (standard units)	IBL (%)	IBS (%)	IBD (%)
Group I (hypogranulo-cytic)	1.3 (0.2–3.1)	5.8 (1.1–8.3)	0.9 (0.3–1.9)	15.9 (3.1–42.3)	6.1 (3.9–30.1)	9.7 (1.1–40.9)
Group II (eosinophilic)	0.3 (0.1–0.8)	1.6 (0.8–3.3)	1.7 (0.8–3.4)	24.3 (6.2–48.9)	13.4 (6.4–59.0)	11.0 (6.4–43.9)
Group III (neutrophilic)	0.4 (0.1–0.9)	1.8 (0.6–4.6)	1.6 (0.8–3.3)	25.3 (2.2–45.8)	16.4 (8.3–53.4)	11.5 (2.6–35.8)
Group IV (hypergranulo-cytic)	0.3 (0.1–0.8)	1.2 (0.6–3.3)	1.8 (0.6–4.6)	41.0 (2.2–53.5)	18.8 (2.9–44.5)	23.8 (2.2–52.5)
p	I : II, IV <0.05	I : II, IV <0.05	I : II, III, IV<0.05	I : II, III, IV<0.05	I : II, III, IV<0.05	I : IV<0.05

(r=–0.8, p<0.05) and a decrease in the ratio of herper-suppressor population of T-lymphocytes (r=–0.8, p<0.05).

The correlations study of the airway hyperresponsiveness in patients belonging to the clinical group IV also showed the presence of probable correlations with the atopic form of bronchial asthma (r=0.6, p<0.05), increased functional activity of eosinophils (r=0.9, p<0.05) and neutrophilic (r=0.9, p<0.05) blood granulocytes, inversely correlated with the relative count of the helper subpopulation of T-lymphocytes (r=–0.7, p<0.05) and indicators of skin hypersensitivity to household allergens (r=–0.9, p<0.05) and directly correlated with the relative count of T-lymphocytes – suppressors (r=0.8, p<0.05).

Based on the above data the following dividing points were selected to study the diagnostic value of NBHR indicators in detecting a probable severe course of bronchial asthma in patients with hypergranulocytic inflammatory blood pattern: for $PC_{20}H$ – less than 1.2 mg/ml; for DRC – more than 1.8 standard units; for IBL – more than 40%; for IBS – more than 18%; for IBD – more than 25%.

Table 2
Diagnostic value (%) of NBHR indicators in the probability of severe bronchial asthma in children with hypergranulocytic inflammatory blood pattern compared with hypogranulocytic inflammatory phenotype

Indicators	Diagnostic value				The probability of a positive result	The probability of a negative result
	Sensitivity of the test	Specificity of the test	Prognostic value (+)	Prognostic value (–)		
PC_{20H} <1.2mg/ml	75.2	85.3	83.3	77.3	5.0	0.3
DRC >1.8 st.un.	50.1	82.1	73.2	62.4	2.8	0.6
IBL >40%	42.2	93.0	85.4	61.6	6.0	0.6
IBD >25%	46.0	90.3	82.0	62.7	4.6	0.6
IIBS >18%	46.1	95.2	90.3	63.0	9.2	0.6

Taking into account the above dividing points, the diagnostic value of NBHR indicators in detecting severe BA is presented in Table 2.

The provided diagnostic value indicators of NBHS markers suggest that the NBHS markers to histamine, when the concentration is less than 1.2 mg/ml causes decrease of FEV_1 by 20% from baseline can be used to confirm the prognostically severe course of bronchial asthma with the likelihood of control loss over the disease in patients with hypergranulocytic inflammatory blood pattern. At the same time, this test, due to its low sensitivity and the expected value of its negative result, should not be used for this purpose for screening patients, which coincides with the data in scientific literature.

At the same time, due to a high specificity of these tests and indicators of prognostic value and the ratio of probability of a positive result, these tests can refute the likelihood of severe disease course in the absence of hypergranulocytic inflammatory blood pattern and, in particular, hypogranulocytic inflammatory phenotype.

This assumption is confirmed by assessing the risk of severe uncontrolled bronchial asthma course in patients using the above-mentioned diagnostic tests (Table 3).

Table3
Risk indicators for severe bronchial asthma course in children with hypergranulocytic inflammatory blood pattern compared to hypogranulocytic inflammatory phenotype

Indicators	Odds ratio (95% CI)	Relative risk (95% CI)	Absolute risk
PC_{20H} <1.2 mg/ml	17.0 (8.3–34.6)	3.6 (2.3–5.9)	0.58
DRC >1,8 st.un.	4.2 (1.7–8.4)	2.1 (1.1–2.8)	0.32
IBL >40%	9.6 (4.0–22.8)	2.2 (1.0–4.7)	0.47
IBS >18%	20.4 (6.9–59.8)	2.5 (0.9–6.8)	0.56
IBD >25%	7.6 (3.5–16.4)	2.2 (1.1–4.1)	0.44

The provided risk indicators of severe asthma course in children with hypergranulocytic inflammatory blood pattern suggest that the probable value is specific not only to indicators of bronchial sensitivity and hyperresponsiveness to histamine, but also indicators of bronchial lability, the distinguishing of which is easier in the practice of treatment and prevention facilities of different levels.

Thus, the above-mentioned results of assessing NBHR diagnostic value in children, taking into account inflammatory blood patterns, as well as the magnitude of clinical and epidemic risk of the event, suggest that they can be used to solve a clinical task concerning verification of the prognostic disease course in the presented populations of children with asthma, especially in the presence of hypergranulocytic inflammatory blood pattern. At the same time, none of these tests have a sufficient degree of sensitivity and the prognostic value of its negative result, which do not allow their use as a method of primary screening. However, the presence of hypergranulocytic inflammatory pattern of blood increases the chances of developing severe nonspecific bronchial hyperresponsiveness and, consequently, the severe course of the disease, which requires a higher level of control therapy.

■ CONCLUSIONS

1. Patients with hypergranulocytic inflammatory blood pattern showed significant indicators of bronchial hypersensitivity and hyperresponsiveness to histamine.

2. Chances of severe asthma course with the probability of control loss over the disease control in patients with hypergranulocytic inflammatory blood pattern in the presence of bronchial hyperresponsiveness to histamine (at a concentration rate of less than 1.2 mg/ml causes decrease of FEV_1 by 20% from baseline) compared with hypogranulocytic inflammatory phenotype increased by 17.0.
3. Inflammatory blood patterns should be determined in order to predict the probable severe disease course with the risk of developing nonspecific bronchial hyperresponsiveness. In the presence of a hypergranulocytic inflammatory blood pattern one should start with the highest step of basic anti-inflammatory therapy in order to achieve control over the disease.

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