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*M.N. Garas, H.V. Lekhkun, V.V. Lysenko, N.V. Basiuk***FEATURES OF SEVERE BRONCHIAL ASTHMA IN CHILDREN WITH EXERCISE-INDUCED BRONCHOSPASM**

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**Abstract.** Based on a complex examination 46 of schoolchildren suffering from severe asthma, we established that greater proportion of schoolchildren with exercise-induced asthma was with symptoms of mucospin hypereosinophilia (average content of eosinophilic granulocytes over 8 %) than children suffering from severe type of the disease, with no signs of exercise-induced bronchoconstriction. The bronchi of the schoolchildren with severe

exercise-induced bronchial asthma are hyperresponsive to histamine, significantly greater proportion of patients with severe airway hypersensitivity to histamine (PC20H<0,5 mg/ml) among the children exercise-induced asthma than those without phenomena of exercise-induced constriction.

**Key words:** children, exercise-induced bronchial asthma, bronchial inflammation, airway hyperresponsiveness.

**Introduction.** Bronchial asthma (BA) is one of the most common chronic multifactorial diseases of the lungs that is formed by the combination of genetic susceptibility and influence of environmental factors [1]. At least 10-12 % of patients with bronchial asthma (BA) are suffering from a severe form of the disease, which is uncontrollable, despite avoiding contact with trigger factors of the environment, performing an adequate therapy and optimal patient compliance. [2]. Severe asthma in children is characterized by persistent symptoms despite treatment with high doses of inhalation corticosteroids or use of oral corticosteroids [3]. Children suffering from severe asthma are at an increased risk of adverse effects, particularly related to the side effects of high-corticosteroid therapy, and also due to frequent life-threatening exacerbations, which impair their quality of life significantly [4]. Based on the features of controlled therapy from this cohort of children we single out patients with difficult-to-treat asthma and those with therapy-resistant asthma. It is recognized increasingly that severe asthma is a very heterogeneous disease associated with the presence of a number of clinical and inflammatory phenotypes [3], including neutrophil ones [4] and eosinophilic ones [5], the first of which can cause deterioration of control under the influence of a specific cytokine cascade [4], and the latter one provides for additional components of the basic therapy [5]. Exercise-induced bronchospasm, which occurs quite frequently in children with BA, can be considered a separate phenotype [6, 7]. The term "exercise-induced bronchoconstriction" describes a transient airway narrowing after exercise, it is one of the options of bronchial hyperreactivity, defined as the tendency of the airways to easier and faster narrowing in response to a large variety of bronchoconstriction stimuli. As hyperreactivity of airways is a characteristic feature of asthma, and the ratio of phenotypes of severe asthma and exercise-induced asthma in children, according to the literature, is disputable and poorly studied, it is appropriate to study the factors, characterizing the basic phenomena of the disease in children suffering from severe asthma with and without exercise-induced bronchoconstriction [8].

**The objective** of the paper was to analyze markers of inflammation and bronchial hyperresponsiveness in school-age children, having severe exercise-induced asthma.

**Material and methods.** Based on the pulmonary department of Regional Children's Clinical Hospital (Chernivtsi), we examined 46 children with severe persistent bronchial asthma. The diagnosis of the disease and its severity were verified on the basis of existing national [9] and international [10] regulatory documents. Signs of a provocative role of exercise for asthma attacks were exercise-induced asthma criteria, as well as reducing FEV<sub>1</sub> by 15 % or more after a graduated running [8]. The first clinical group included 15 schoolchildren suffering from severe asthma, which met the specified criteria, the second clinical group (comparison one) consisted of 31 children suffering from severe type of the disease, with no signs of exercise-induced bronchoconstriction. For the main clinical characteristics the groups were comparable. For instance, the average age of children in the first clinical group was 12,2±0,9 years, and in the second clinical group – 12,8±0,5 years ( $p>0,05$ ), more than half of the patients in both groups were boys (60,5 % and 58,1 % in the first and second groups, respectively,  $r_p>0,05$ ) and rural residents (60,5 % and 45,1 % in the first and second groups, respectively,  $r_p>0,05$ ). All the children received an amount of anti-inflammatory treatment equivalent to severity and control, defined by current standards of care [9].

Airway hyperresponsiveness was assessed according to the results of bronchoprovocation testing with histamine by determining bronchial hypersensitivity to stimuli while calculating the provocation concentration (PC20H) and dose (PD20H) [11-12].

Bronchial inflammation intensity was determined by the content of metabolites of nitrogen monoxide in the expiratory condensate by Yemchenko N.L. [13].

The type of bronchial inflammation was determined by the results of sputum cytology obtained by induction using serial dilution of hypertonic sodium chloride; after a previous inhalation of a short-acting bronchodilator (salbutamol 200 mcg) we received

Table

Indices of sputum cellular structure of the surveyed children (M±m)

Cytogram results, %	I clinical group	II clinical group	P
Eosinophils	10,0±2,8	6,2±2,3	>0,05
Neutrophils	55,1±5,2	53,5±5,1	>0,05
Macrophages	25,1±5,7	32,8±5,9	>0,05
Lymphocytes	10,1±3,8	8,6±2,3	>0,05
Epithelial cells	49,7±4,6	43,2±3,8	>0,05

Note. P – reliability criterion by Student's test

sputum. Eosinophilic inflammation in the bronchi was diagnosed with 3 % or more eosinophilic leukocytes in the sputum. In patients with lower content of eosinophils in sputum chronic airway inflammation was regarded as non-eosinophil one [14, 15].

For the results matching normal distribution, we determined the arithmetic mean of the sample (M), the value of the standard deviation (s) and standard error (m), maximum and minimum values. In assessing the reliability of difference between the rates, we did Student's t-test. As a reliable difference was taken that  $p < 0,05$ . The assessment of event implementation risk was conducted taking into account the reliability of relative risk (RR) index, and attribute risk (AR) and odds ratios (OR), as well as their confidence intervals [16].

**Results and discussion.** Inflammation figures reflected the type and intensity of bronchial inflammation. The type of the inflammatory process was established by the results of cytology of induced sputum (Table).

We have found a trend towards relative sputum eosinophilia in children with severe exercise-induced asthma, compared to the representatives of the second clinical group. In particular, eosinophilic inflammation occurred in the majority of schoolchildren, suffering from severe exercise-induced asthma (60,1 %) and in 47,2 % of those from the comparison group ( $r_p > 0,05$ ). Identified differences were confirmed by the analysis of discrete cellular composition of induced sputum in particular by reliably greater proportion of schoolchildren of the first clinical group (60,1 %) with symptoms of mucospin hypereosinophilia (average content of eosinophilic granulocytes over 8 %) than that of the comparison group (17,6 %,  $r_p < 0,05$ ). Thus, the relative risk of hypereosinophilia (>8 %) of the induced sputum against the background of severe exercise-induced asthma was 3,4 (95 % CI 1,2-9,0) at odds ratio 7,0 (95 % CI 1,2-41,3). Post-test reliability of detection of induced sputum hypereosinophilia in children with severe exercise-induced asthma, increased by 25 %.

There was a high activity of the bronchial inflammation process in children in the comparison clinical group, the markers of which were metabolites content of nitrogen monoxide in expiratory condensate. For instance, the nitrogen monoxide content of metabolites in expiratory condensate of children in both clinical groups, turned to be almost the same (46,5±5,1 mmol/l and 46,5±3,5 mmol/l in representa-

tives of the first and second groups respectively,  $p > 0,05$ ). Thus, indices of inflammation activity are likely to reflect the severity of the disease and do not depend on the response of the airways to exercise.

Unlike the inflammation markers, while analyzing bronchial hyperresponsiveness, we found more pronounced bronchial hypersensitivity of the airways to histamine in schoolchildren, suffering from severe exercise-induced bronchial asthma (0,33±0,13 mg/ml and 0,71±0,20 mg/ml in representatives of the first and second groups respectively,  $p < 0,05$ ).

The fact that the bronchi of the schoolchildren with severe exercise-induced bronchial asthma are hyperresponsive is confirmed by a significantly greater proportion of patients with severe airway hypersensitivity to histamine (PC20H<0,5 mg/ml) among the children of the first clinical group (87,5 %) than those without phenomena of exercise-induced constriction (54,5 %,  $r_p > 0,05$ ).

Therefore, exercise-induced bronchoconstriction is associated with an increased risk of severe bronchial hyperresponsiveness to histamine in the schoolchildren, suffering from with severe asthma. For instance, the relative risk of severe bronchial hyperresponsiveness to histamine in children with severe exercise-induced asthma was 1,6 (95 % CI 0,6-55,7), the odds ratio of 5,8 (95 % CI 0,6-55,7). Post-test probability of detecting severe bronchial hyperresponsiveness to histamine in children with symptoms of exercise-induced bronchoconstriction suffering from severe asthma, increased by 30,2 %.

### Conclusions

1. The indices of bronchial inflammation in children with severe exercise-induced asthma are characterized by a slightly higher proportion of patients with eosinophilic type of inflammation and by hypereosinophilia of induced sputum.

2. We have established reliably more pronounced airway hypersensitivity to histamine in the schoolchildren suffering from severe exercise-induced bronchial asthma.

**Prospects for further research** are to improve the effectiveness of treatment of children suffering from severe exercise-induced bronchial asthma.

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## ОСОБЕННОСТИ ТЯЖЕЛОЙ БРОНХИАЛЬНОЙ АСТМЫ У ДЕТЕЙ С БРОНХОСПАЗМОМ ФИЗИЧЕСКОГО НАПРЯЖЕНИЯ

*Н.Н. Гарас, Г.В. Лехкун, В.В. Лысенко, Н.В. Басюк*

**Резюме.** На основании комплексного обследования 46 школьников, страдающих тяжелой персистирующей бронхиальной астмой, установлено, что большинство детей с фенотипом астмы физического напряжения характеризовалась гиперэозинофилией мукоспина (среднее содержание эозинофилов индуцированной мокроты более 8 %), по сравнению с детьми, страдающими тяжелой бронхиальной астмой без признаков бронхоспазма физического напряжения. Также установлена выраженная гиперчувствительность дыхательных путей к гистамину у школьников, больных тяжелой бронхиальной астмой физического напряжения, что подтверждается достоверно большей долей пациентов с тяжелой гиперчувствительностью дыхательных путей к гистамину (ПК20Г < 0,5 мг/мл) среди школьников с признаками бронхоспазма физического напряжения, чем среди детей без явлений констрикции физического усилия.

**Ключевые слова:** дети, бронхиальная астма физического напряжения, воспаление бронхов, гипервосприимчивость дыхательных путей.

## ОСОБЛИВОСТІ ТЯЖКОЇ БРОНХІАЛЬНОЇ АСТМИ У ДІТЕЙ З БРОНХОСПАЗМОМ ФІЗИЧНОЇ НАПРУГИ

*М.Н. Гарас, Г.В. Лехкун, В.В. Лисенко, Н.В. Басюк*

**Резюме.** На підставі комплексного обстеження 46 школярів, які хворіють на тяжку персистувальну бронхіальну астму, встановлено, що більшість дітей із фенотипом астми фізичної напруги характеризувалася гіпереозинофілією мукоспину (середній вміст еозинофілів індукованого мокротиння більше 8 %), порівняно з пацієнтами, що хворіють на тяжку бронхіальну астму без ознак бронхоспазму фізичної напруги. Також встановлена виразніша гіперчутливість дихальних шляхів до гістаміну у школярів, хворих на тяжку бронхіальну астму фізичної напруги, що підтверджується вірогідно більшою часткою пацієнтів із тяжкою гіперчутливістю дихальних шляхів до гістаміну (ПК20Г < 0,5 мг/мл) серед школярів з ознаками бронхоспазму фізичної напруги, ніж серед дітей без явищ констрикції фізичного зусилля.

**Ключові слова:** діти, бронхіальна астма фізичної напруги, запалення бронхів, гіперсприйнятливості дихальних шляхів.

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