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EXERCISE-INDUCED BRONCHIAL ASTHMA IN CHILDREN: PHENOTYPICAL POLYMORPHYSM

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Abstract

Cluster analysis of a comprehensive clinical-anamnestic and paraclinical examination with the phenotype of exercise-induced bronchial asthma in schoolchildren depending on the type of acetylation. Heterogeneity of this cohort of patients has been found which requires a differential approach to administration of therapeutic measures.

Key words: children, exercise-induced bronchial asthma, nature of acetylation, cluster analysis.

Introduction. Recognition of heterogeneity of bronchial asthma (BA) with different degree of severity of bronchial obstruction, frequency of exacerbations and various response to treatment induce more comprehensive study of BA phenotypes [1, 4]. In contemporary studies physiological, morphological and molecular-genetic mechanisms involved in pathogenesis of BA have been investigated, clinical phenotypes of its course have been determined, enabling clinicians to apply individualized approach to therapy [8]. During the recent years cluster analysis has been used to isolate phenotypes of BA [7].

Exercise-induced bronchial asthma (EIBA) is not a homogeneous phenotype of the disease, and the mechanism of its formation remains unclear. Increased scientific interest to the problem of exercise – induced bronchial asthma is connected with the formation of a convenient model to study reverse bronchial spasm and refractoriness of patients to physical exertion, especially in children with evidenced psycho-emotional stress factor under conditions of limited motor activity [5].

As acetylation rate is considered to be one of the genetic markers of metabolic processes, scientific studies investigate possibilities of estimation of BA risks on the basis of detection of the type of acetylation of patients [9]. The use of cluster analysis for diversion of clinical phenotype of BA is the most objective and enables to avoid many systematic and/or subjective mistakes [2,10,13], and it is rather promising concerning the aspect of its application to optimize individualized treatment.

Objective: to analyze clinical-paraclinical peculiarities of EIBA in schoolchildren depending on their acetylation status by means of making cluster analysis to study the tactics of an individualized treatment.

Materials and methods. Keeping to the principles of bioethics 23 children suffering from EIBA were examined on the basis of Regional Children Clinical Hospital (the town of Chenivtsi). The disease was diagnosed in case after spirography test with dosed physical exercise bronchial spasm index was higher than 15% [5]. The diagnosis and severity of the course were verified on the basis of current national and international [11] regulating documents. An average age of the children examined was 12,2±0,6 years. Boys (65,2%) and rural residents (56,5%) prevailed.

Phenotype peculiarities were studied discretely in the groups of children formed depending on acetylation status [6] with the use of cluster analysis. The components of a comprehensive examination were considered to be forming signs of cluster analysis in the groups of patients with EIBA, in particular: clinical-anamnestic characteristics (topical body mass index, severity of the first day of exacerbation, genealogical index by atopic diseases), indicators of efficacy of the basic treatment by ACT-test, markers of inflammatory process in the bronchi (the content of nitrogen monoxide metabolites and general protein in the expired air condensate, a relative content of eosinophil and neutrophil granulocytes in induced sputum), indicators of atopic reactivity (the content of general IgE and IL-4 in the blood and results of skin allergy tests with non-bacterial allergens), and non-specific hyperactivity of the bronchi (according to the values of bronchial lability index, provocative concentration, histamine dose and dose-depending curve).

Among patients with EIBA the I clinical group included 10 children with quick acetylation mechanisms, an average age of 11,6±0,9 years, prevailing number of boys (80,0%), and urban residents (50,5%). The II clinical group included 13 patients with EIBA and slow acetylation status, an average age of schoolchildren12,6±0,8 years, prevailing number of boys (53,8%), rural residents constituted 61,5%.

Cluster analysis of the results of examination of a cohort of patients with EIBA was conducted. The probability approach by means of K-means method was used according to which every analyzed object referred to one of k classes [12].

Results of the study and their discussion. On the basis of the cluster analysis results of clinical-paraclinical signs of the examined children suffering from EIBA with quick acetylation status a number of features were determined. Their consideration enabled to differentiate three cluster groups (Table 1).

Table 1

Cluster subgroups of children with exercise-induced bronchial asthma and quick acetylation status (M±m)

Clinical-paraclinical characteristics	Cluster 1	Cluster 2	Cluster 3	P
Body mass index (kg/m^2)	21,4±2,7	18,6±3,5	17,4±2,0	ND
Genetic index by atopic diseases, standard units	0,18±0,16	0,13±0,06	0,20±0,02	ND
ACT-test before initiation of basic therapy, points	14,9±0,6	15,4±3,5	15,9±0,9	ND
Severity of the 1st day of attack, points	9,7±7,5	18,6±3,5	17,2±5,0	ND
Eosinophils in induced sputum, %	12,7±8,8	4,3±3,2	5,3±3,0	ND
Neutrophils in induced sputum, %	53,7±26,9	53,4±7,5	42,4±23,5	ND
Content of nitrogen monoxide metabolites in expired air condensate, mcmol/L	51,8±3,9	44,8±6,8	48,8±1,1	ND
Content of total protein in expired air condensate, mcmol/L	3,4±0,1	3,4±0,1	3,4±0,1	ND
Bronchial spasm index, %	24,9±13,6	24,4±6,4	23,4±10,9	ND
Bronchial dilation index, %	5,6±7,0	27,2±22,1	17,8±12,9	ND
Bronchial lability indicator, %	30,6±12,7	51,7±18,6	29,2±21,1	ND
Threshold histamine concentration, mg/ml	1,00±0,9	0,44±0,26	0,36±0,31	ND
Threshold histamine dose, mg	0,21±0,20	0,08±0,06	0,07±0,06	ND
Dose-depending curve, standard units	2,13±0,90	1,59±0,53	1,90±0,1	ND
Content of total IgE in the blood, IU/ml	802,2±144,9	1364,1±73,4	151,3±49,0	ND
Content of interleukin-4 in the blood, pg/ml	19,1±11,6	12,8±4,7	12,7±4,5	ND

Note. ND – no distinction

On the basis of cluster analysis we have found that the I subgroup included patients suffering from EIBA prone to excessive body mass characterized by insufficient control of the course of the disease, probably at the expense of marked inflammation of the respiratory tract of eosinophilic character.

The II cluster subgroup included patients with quick acetylation mechanisms and susceptibility to atopic reactivity, whose course of the disease differed by severe exacerbation and insufficient control against the ground of basic therapy. It might be caused by pronounced bronchial lability bot in response of dosed physical exertion and inhalation of a short-term selective adrenergic agonist.

The III cluster subgroup included "quick acetylators" with EIB, severe exacerbations and insufficient control of which was explained by severe hypersensitivity of the bronchi to histamine and their expressed hyper-reactivity.

The discrete analysis of the II clinical group of children managed to determine its phenotype heterogeneity and isolate three cluster subgroups (Table 2).

On the basis of the data obtained the I cluster subgroup was found to include patients with EIBA with a slow acetylation status, susceptibility to excessive body weight and IgE-dependent reactions in the body, during whose examination a considerable bronchial lability was found.

The II cluster subgroup included patients with EIBA with a slow acetylation mechanisms characterized by severe exacerbations and insufficient control of the diseases at the expense of severe hyper-sensitivity of the respiratory tract to histamine and their expressed lability.

On the contrary, representatives of the III subgroup are prone to severe exacerbations and insufficient control at the expense of inflammatory components mainly. At the same time, relatively less indices of non-specific reactivity of the bronchi in those children can be explained by a formed rigidity of the bronchial wall.

Therefore, on the basis of the conducted cluster analysis of clinical-paraclinical indices considering the character of acetylation among schoolchildren with EIBA the subgroups of children with different control of symptoms of the disease and severity of attacks were detected, enabling to individualize both basic anti-inflammatory therapy and relieve desobstructive treatment of the attack.

Table 2

Cluster subgroups of children with exercise-induced bronchial asthma and slow acetylation status (M±m)

Clinical-paraclinical characteristics	Cluster 1	Cluster 2	Cluster 3	P
Body mass index (kg/m^2)	23,5±5,4	18,7±2,6	22,0±1,5	ND
Genetic index by atopic diseases, standard units	0,16±0,07	0,17±0,08	0,19±0,05	ND
ACT-test before initiation of basic therapy, points	15,6±2,9	14,6±1,3	13,4±2,1	ND
Severity of the 1st day of attack, points	12,2±4,5	16,0±4,9	18,1±2,4	ND
Eosinophils in induced sputum, %	9,0±7,5	9,2±1,5	5,5±4,8	ND
Neutrophils in induced sputum, %	51,1±12,9	54,8±6,8	41,0±16,4	ND
Content of nitrogen monoxide metabolites in expired air condensate, mcmol/L	43,9±17,8	42,3±1,6	43,1±0,2	ND
Content of total protein in expired air condensate, mcmol/L	3,5±0,4	3,6±0,2	4,3±0,8	ND
Bronchial spasm index, %	34,3±13,2	26,2±12,6	18,0±2,8	ND
Bronchial dilation index, %	30,6±19,2	22,3±12,2	4,3±5,7	ND
Bronchial lability indicator, %	65,0±9,7	48,6±22,4	22,3±8,5	ND
Threshold histamine concentration, mg/ml	0,58±0,07	0,16±0,02	0,42±0,32	ND
Threshold histamine dose, mg	0,12±0,03	0,03±0,01	0,09±0,06	ND
Dose-depending curve, standard units	2,1±0,3	2,1±0,5	2,2±0,1	ND
Content of total IgE in the blood, IU/ml	1166,4±159,3	715,6±148,1	120,1±89,6	ND
Content of interleukin-4 in the blood, pg/ml	9,3±7,1	9,0±2,5	12,5±4,4	ND

Note. ND – no distinction

Conclusions

1. The results of cluster analysis of a comprehensive clinical-anamnestic and paraclinical examination of schoolchildren with the phenotype of exercise-induced bronchial asthma demonstrated their heterogeneity associated with the character if acetylation processes, that should be considered while making the plan of basic anti-inflammatory treatment and during treatment of attacks of the disease.

2. The patients with quick type of acetylation with excessive body weight of eosinophilic character in the bronchi present insufficient efficacy of basic therapy which substantiate their implementation according to the “step upwards” recommendations at the expense of an increased dose of inhalation glucocorticosteroid. In “quick acetylators” with

susceptibility to atopic reactivity and severe exacerbations the treatment of attacks should include liberal administration of systemic glucocorticosteroids. In the basic therapy of "quick acetylators" whose severe exacerbations and insufficient control are explained by severe hyper-sensitivity of the bronchi to histamine and their marked hyper-reactivity "de-escalation" principle is reasonable to be indicated.

3. Patients with exercise-induced bronchial asthma with a slow acetylation status, prone to excessive body weight, IgE-dependent reaction and severe exacerbations with insufficient control, probably at the expense of neutrophil character of inflammation in the bronchi, in addition to inhalation glucocorticosteroids prolonged theophyllines should be indicated.

Prospects of further studies: to continue to study phenotype heterogeneity of bronchial asthma in children and determine the tactics of a controlled therapy.

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