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Peculiarities of Bronchial Hyperactivity in Children with the Phenotype of Late Onset Asthma Depending On Acetylation Status

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Abstract

Goal: To assess the indices of non-specific reactivity of the bronchi in children suffering from asthma of a late onset considering acetylated status of patients.

Material and methods: 72 children suffering from BA of late onset (after six years of age) were examined on the basis of the Pulmonological Department of the Regional Pediatric Clinical Hospital (Chernivtsi). The patients were distributed into two clinical groups depending on acetylation status. The first clinical group (I) included 34 children with LOA phenotype and slow acetylation character, and the second group (II) included 38 children suffering from LOS and quick acetylation phenotype. An average age of the representatives from I clinical group was 11,3±0,6 years, children from the group of comparison – 11,1±3,4 years ($p>0,05$). The groups did not differ reliably by the main clinical signs.

The bronchi lability was assessed using graduated jogging with inhalation of 200 mkg of salbutamol test and further calculation of Bronchospasm Index (BSI, %), Bronchodilatation Index (BDI, %), and of Bronchus Lability Index (BLI, %). Investigation of hypersensitivity of the bronchi to direct spasmogenic factors was carried out by means of standardized inhalation spirometric test with histamine considering recommendations on standardization of the study. The indices of histamine threshold concentration (HTC_{20}) were used to determine hypersensitivity of the respiratory tract. In addition, genetic marker was determined – the character of acetylation by Prebsting-Gavrylov's method modified by Tymofeyeva, which characterized peculiarities of II phase of the xenobiotic biotransformation system.

Results and discussion: On the basis of the presented data a tendency to more pronounced bronchial lability was found (mainly at the expense of considerable bronchospasm in response to the dosed physical exercise) in children with LOA and low acetylation status as compared with the rapid acetylation. Thus, positive bronchospastic test was found in 44,2% of patients with slow acetylation and only in 26,0% of children with rapid

acetylation status (Pφ<0,05). The indices of the risk of bronchospasm in response to the dose physical exercise in patients with slow acetylation phenotype compared with rapid acetylation were the following: relative risk – 1,7 [95%CI: 1,04-2,6] in case of odds ratio – 2,2 [95%CI: 0,8-5,9]. At the same time, slow acetylation phenotype increased a relative risk of pronounced bronchial lability 2,9 times [95%CI: 1,9-4,6] in case of odds ratio – 4,7 [95%CI:1,6-14,2]. Pronounced bronchial hypersensitivity is determined (HTC_{20}<2,0 mg/ml) to occur in 25% representatives of II clinical group and 8% of children from the group of comparison. The indices of the risk promoting development of pronounced respiratory tract hypersensitivity in children suffering from LOA with rapid acetylation type compared with slow acetylation were the following: relative risk – 3,2 (95% CI: 2,0-5,2) with odds ratio 4,0 (95% CI: 0,7-21,6).

Conclusions: There was established, that the relative risk of a distinct hypersensitivity of the airways increased 3,2 times, the odds ratio of the event was equal to 4,0, in children with late-onset asthma late with rapid type of acetylation as compared to slow acetylators.

Key words: bronchial asthma, children, phenotypes, bronchial lability, hyperresponsiveness, hyperreactivity.

Introduction. Bronchial asthma (BA) still remains an important issue of pediatric allergology [1]. The following phenomena peculiar for the disease are formed and intensify each other in BA patients: bronchial inflammation, their remodeling and increased susceptibility to specific and non-specific bronchospasmogenic stimuli [2].

Non-specific hypersensitivity of the respiratory tract to direct and indirect stimuli can be treated as a key phenomenon of bronchial asthma (BA), which is the base to form clinical signs, frequency and severity of exacerbations, course, severity and control over the disease in general. Hypersensitivity of the bronchi is determined as excessive narrowing of their lumen due to excessive bronchospastic response to different bronchospastic stimuli [3], that can vary in time depending on the force, character and frequency of effects of trigger stimuli, pronunciation of respiratory tract inflammation, efficacy of treatment, BA severity and other factors able to change bronchial response to spasmogenic stimuli. Persisting inflammation of the respiratory tract and its remodeling promote chronic course of bronchial hypersensitivity (BHS) [4]. BHS can develop asymptomatically, but its value as a predictor of asthma in children remains insufficiently studied.

BA is a heterogenic disease and can differ by clinical variants depending on the phenotype of the disease and child's age [5,6]. Nowadays childhood asthma is considered as the whole set of certain phenotypes with determined mechanisms of development and progress [7-9]. The effect of age when the first symptoms of BA occurred on its course is characterized by disputable data that might be caused by "memory error" [10-11]. Thus, certain authors associate the risk of a long persistence of the disease with its onset at the early childhood, still others – at the age over six, so-called phenotype of late onset asthma (LOA) [12-13]. The phenotype of late onset asthma certain authors associate with clinical signs of atopy (eczema, allergic rhinitis, conjunctivitis, food allergy), eosinophilia and/or increased level of general IgE in the blood. Children with late onset of BA have worse prognosis concerning recovery, therefore more active therapeutic tactics should be recommended [14-15].

On the basis of evidential medicine the parameters reflecting a characteristic phenomenon of the disease should be analyzed – hyperactivity of the bronchi depending on its phenotype in order to improve individual therapeutic-preventive measures [16-17].

Objective: to assess the indices of non-specific reactivity of the bronchi in children suffering from asthma of a late onset considering acetylated status of patients.

Materials and methods: 72 children suffering from BA of late onset (after six years of age) were examined on the basis of the Pulmonological Department of the Regional Pediatric Clinical Hospital (Chernivtsi). The patients were distributed into two clinical groups depending on acetylation status. The first clinical group (I) included 34 children with LOA phenotype and slow acetylation character, and the second group (II) included 38 children suffering from LOS and quick acetylation phenotype. An average age of the representatives from I clinical group was 11,3±0,6 years, children from the group of comparison – 11,1±3,4 years ($p>0,05$). The groups did not differ reliably by the main clinical signs.

Bronchial lability was determined according to the recommendations by means of assessment of their response to the dosed physical exercise and inhalation of short action β_2-agonist (200 mcg of Salbutamol) followed by the calculation of bronchial lability index as a sum of its components – bronchospasm index (BSI): BSI=((FEV_1 initial– FEV_1 after dosed physical exercise)/ FEV_1 initial)x100%; and bronchodilation index (BDI): BDI=((FEV_1 after Salbutamol inhalation – FEV_1 initial)/FEV_1 initial)x100%.

Investigation of hypersensitivity of the bronchi to direct spasmogenic factors was carried out by means of standardized inhalation spirometric test with histamine considering recommendations on standardization of the study. The indices of histamine threshold concentration (HTC_{20}) were used to determine hypersensitivity of the respiratory tract.

In addition, genetic marker was determined – the character of acetylation by Prebsting-Gavrylov's method modified by Tymofeyeva, which characterized peculiarities of II phase of the xenobiotic biotransformation system.

Statistical analysis of the obtained data was made from the position of biostatistics. To assess diagnostic value of the tests their sensitivity, specificity, predicted value of positive and negative results, and likelihood ratio of the results were determined. Event instance risk was assessed considering the probability of the values of relative risk, odds ratio and post-testing probability, as well as determination of their confidence interval.

Results and discussion: The indices of bronchial sensitivity to indirect stimulus (running) in children from the groups of comparison were assessed depending on the acetylation rate, and mean values of integrative bronchial lability index (BLI) and its components were determined, Table 1.

Table 1

On the basis of the presented data a tendency to more pronounced bronchial lability was found (mainly at the expense of considerable bronchospasm in response to the dosed physical exercise) in children with LOA and low acetylation status as compared with the rapid acetylation. Thus, positive bronchospastic test was found in 44,2% of patients with slow acetylation and only in 26,0% of children with rapid acetylation status ($P\varphi<0,05$). The indices of the risk of bronchospasm in response to the dose physical exercise in patients with slow acetylation phenotype compared with rapid acetylation were the following: relative risk – 1,7 [95%CI: 1,04-2,6] in case of odds ratio – 2,2 [95%CI: 0,8-5,9]. At the same time, slow acetylation phenotype increased a relative risk of pronounced bronchial lability 2,9 times [95%CI: 1,9-4,6] in case of odds ratio – 4,7 [95%CI:1,6-14,2].

Since bronchial lability index is integral and reflects the total response of the bronchi to the dosed physical exercises and Salbutamol inhalation, it values become

more pronounced in children with slow acetylation status. In particular, pronounced bronchial lability (BLI more than 25%) is peculiar for practically every second patient from I group with slow acetylation status (47,0%) and only every fifth one (16,0%) with rapid acetylation phenotype (Pφ>0,05).

For more detailed analysis of respiratory tract sensitivity to the dosed physical exercise considering bronchodilating effect of β2-adrenomimetic, the indices of their lability on the level of bronchi with different size were assessed (Table 2).

Table 2

Therefore, a tendency to more pronounced lability on all the levels of bronchi was determined in children suffering from LOA with slow acetylation character at the expense of bronchospastic and dilation components.

Analysis of bronchial dilation response to inhalation of short action β_2-agonist on the level of small size respiratory tract determined that BDI was no higher than 15% than in very second patient (60%) with rapid acetylation status against 38% of patients from the group of comparison (Pφ>0,05). At the same time, excessive bronchial dilation (BDI more than 30%) is reliably more frequent registered in children with slow acetylation phenotype of LOA (32,0%), than that in patients with rapid acetylation character (25%, Pφ<0,05).

Table 3 presents the indices of bronchial hypersensitivity to direct bronchospasmogenic stimulus in children from the groups of comparison.

Table 3

The presented results give the basis to consider that analysis of the respiratory tract hypersensitivity indices of the patient from the groups of comparison determines a tendency to more pronounced bronchial hypersensitivity to histamine in children with rapid acetylation character concerning children from I clinical group. Pronounced bronchial hypersensitivity is determined (HTC_{20}<2,0 mg/ml) to occur in 25% representatives of II clinical group and 8% of children from the group of comparison. The indices of the risk promoting development of pronounced respiratory tract hypersensitivity in children suffering from LOA with rapid acetylation type compared with slow acetylation were the following: relative risk – 3,2 (95% CI: 2,0-5,2) with odds ratio 4,0 (95% CI: 0,7-21,6).

Therefore, the presented results of assessment of the risk promoting the development of non-specific respiratory tract hypersensitivity in patients suffering from LOA depending on the character of acetylation processes give the basis to consider that in the presented populations of children the risk of development of non-specific bronchial hypersensitivity to indirect bronchospastic stimuli increases in children with slow acetylation type at the expense of bronchial lability. Hypersensitivity of the respiratory tract to direct spamogenic stimuli when bronchoprovocative test with histamine is made appears to be higher in children suffering from LOA with rapid acetylation status, which can be used to solve a clinical task concerning optimization of controlling treatment.

Conclusions

1. Children suffering from late onset bronchial asthma with slow acetylation status are characterized by a tendency to more pronounced bronchial lability of different size at the expense of bronchospastic and dilation components.

2. Slow acetylation phenotype increased a relative risk of pronounced bronchial lability 2,9 times [95%CI: 1,9-4,6] with odds ratio – 4,7 [95%CI:1,6-14,2].

3. In children with the phenotype of late onset asthma with rapid acetylation status more pronounced hypersensitivity of the respiratory tract to histamine was observed.

4. The indices promoting the risk of development of pronounced hypersensitivity of the respiratory tract in children suffering from late onset asthma with rapid acetylation type compared with the slow acetylation were the following: relative risk – 3,2 (95% CI: 2,0-5,2) with odds ratio 4,0 (95% CI: 0,7-21,6).

Prospects of further studies include detection of paraclinical markers in children with the phenotype of exercise-induced asthma reflecting the main characteristics of the disease – inflammation and hypersensitivity of the bronchi.

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Table 1: **Bronchial lability indices in children from the groups of comparison depending on acetylation type (M±m)**

Acetylation type	Bronchospasm index, %	Bronchodilation index, %	Bronchial lability index, %
Slow (n=34)	16,0±2,9	12,0±2,4	28,0±4,2
Rapid (n=38)	7,3±2,6	11,0±2,3	18,5±2,4
P	<0,05	>0,05	>0,05

Note: P – probability Student criterion

Table 2: **Bronchial lability indices of different size in children from clinical groups (M±m)**

Bronchial size	Lability indices, %	I – group (n=34)	II – group (n=38)	P
Small size	BSI	13,4±4,6	9,1±3,9	>0,05
	BDI	25,3±3,8	22,4±5,3	>0,05
	BLT	42,1±5,3	31±4,7	>0,05
Moderate size	BSI	19,4±3,6	11,1±3,7	>0,05
	BDI	28,3±5,1	23,5±4,7	>0,05

	BLT	48,1±6,6	32,6±5,1	>0,05
Large size	BSI	17,7±3,7	14,1±3,4	>0,05
	BDI	29,3±7,7	20,6±4,5	>0,05
	BLT	47,4±7,9	34±5,1	>0,05

Note: P – probability by Student criterion

Table 3: Indices of bronchial hypersensitivity to series histamine dilutions in children from clinical groups (M±m)

Clinical groups	HTC20, mg/ml	HDC20, mg	Dose dependent curve, s.u.
Slow (n=34)	3,4±1,3	0,5±0,2	1,8±0,2
Rapid (n=38)	1,3±0,4	0,3±0,09	1,7±0,2
P	>0,05	>0,05	>0,05

Note: P – probability by Student criterion