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Clinical and anamnestic indicators for the risk assessment of airway remodeling in children with asthma

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RESEARCH ARTICLE

General Note

Article is recommended to print as color digital version in recycled paper.

ABSTRACT

The aim of the research was to analyse the diagnostic value of anamnestic and clinical indices for the risk assessment of bronchial remodeling to improve asthma management in children. The study involved 116 children with persistent bronchial asthma who have been subjected to a comprehensive clinical and paraclinical examination. At the beginning of the study patients with high levels of VEGF and MMP-9 in sputum were characterized by higher incidence of a birth weight of less than 2500 g (8.1% vs. 2.6%), history of maternal and paternal atopic diseases (13.5% vs. 2.6%), history of drug allergy (10.8% vs. 2.6%), and maternal smoking as a source of long-time exposure to second-hand tobacco smoke (27.0% vs. 13.2%) compared to children with low levels of bronchial remodeling markers. Children with high levels of airway remodeling markers in sputum were characterized by an increase in the incidence of severe asthma (from 13.5% to 26.8% vs. a decrease from 23.7% to 14.2%), as well as uncontrolled asthma (from 38.2% to 42.6% vs. decrease from 39.3% to 25.0%) compared to patients with lower levels of markers.

Keywords: Asthma, Airway remodeling, Risk assessment

1. INTRODUCTION

Persistent obstructive changes of bronchi in bronchial asthma patients are accompanied by a number of pathophysiological consequences that impose an imprint on clinical manifestations of the disease (James, 2007). Thus, inflammation of the bronchi – the main pathological change while the progression of asthma, becomes persistent during the development of the airway remodeling (Elliot, 2015; James, 2017). To some extent, the persistence of inflammation may be explained by the fact of its primary initiation as a reaction to a trigger stimulus, with the further progression and formation of the pathogenic self-supporting mechanisms involving conjunction of cellular and humoral factors. In its turn, chronic inflammation forms and amplifies the alteration of bronchial structures, which serves as a distinctive but not unique feature of asthma in some patients, who are likely prone to this, and leads to the development of sustained structural changes in bronchi, which are defined as airway remodeling (Jeffery, 2001; Woodruff, 2001). Remodeling is characterized by the modifications of tissue and cellular composition, affecting bronchial epithelium, smooth muscle, blood vessels, and extracellular matrix (Hirota, 2013, Parameswaran, 2006). However, in some cases, the development of bronchial remodeling precedes the appearance of the clinical manifestations of asthma or is present at the onset of the disease, which calls into question the exclusive role of inflammation in the alteration of bronchial structures (Fehrenbach, 2017; James, 2017). Neovascularization of the bronchi, which can occur not only due to the secretion of the vascular endothelial growth factor (VEGF) but also in response to increased vascular permeability, leads to bronchial edema, edema of the mucous membranes, penetration of blood proteins in the bronchial lumen, an increase in inflammation. It results in the persistent obstruction of the bronchi, especially in the lower parts of the bronchial tree (Matsuda, 2008; Postma, 2006; Wagner, 1998; Wagner, 2008).

Airway remodeling not only determines the persistent nature of the bronchial obstruction but also contributes to the development of the disease exacerbations and its more severe course (Bai, 2007; James, 2012). As a result, increased sensitivity to acute viral infection occurs, which increases further structural changes, and, in its turn, leads to the recurrent infection, which serves as a leading trigger stimulus in children with asthma (Jackson, 2010; Leigh, 2008; Naveed, 2016; Wark, 2005). It should also be noted that long-term exposure to tobacco smoke undoubtedly contributes to the development of airway remodeling and their increased sensitivity to viral infections (Boulet, 2006; Tsoumakidou, 2007; St-Laurent, 2008).

Thus, the development of airway remodeling usually associates with the severity of persistent asthma, which is characterized by low efficiency or resistance to anti-inflammatory therapy and a progressive decrease in the ventilation function of bronchi by the obstruction type. Consequently, determination and practical use of additional markers to predict the risk of bronchial remodeling and asthma progression could increase the quality of asthma management in children.

The aim of the research was to analyse the diagnostic value of anamnestic and clinical indices for the risk assessment of bronchial remodeling to improve asthma management in children.

2. MATERIAL AND METHODS

The research was conducted at the Pulmonology and Allergology Department of the Municipal Medical Establishment "Chernivtsi Regional Children's Clinical Hospital" (Ukraine). One hundred and sixteen children with persistent bronchial asthma (BA) were examined by the method of "trial-control" in parallel groups using a simple random sample. Based on the informed consent obtained from parents, patients have been subjected to a comprehensive clinical and paraclinical examination.

Diagnosis and management of asthma were performed in accordance with the national guideline "Unified Clinical Protocol for primary, secondary (specialized), tertiary (highly specialized) medical care Bronchial Asthma in Children", approved by the Order of the Ministry of Health of Ukraine dated 08.10.2013 No. 868; the recommendations of the international coordination guidelines (GINA). Complex laboratory and instrumental examination of patients was carried out during the non-exacerbation period. Biochemical studies were carried out in the accredited laboratory of the Chernivtsi Regional Children's Clinical Hospital.

The research design included determination of the next biomarkers in the sputum supernatant of patients: vascular endothelial growth factor (VEGF), matrix metalloproteinase 9 (MMP-9), cationic proteins, γ-interferon, IL-6, and IL-13. Based on obtained results, VEGF and MMP-9 were chosen for further analysis as two most indicative for the airway remodeling markers (Koloskova, 2017; 2018). The levels of VEGF and MMP-9 were determined by a solid-phase sandwich ELISA method using the commercial Kits (VEGF Human ELISA Kit A-8784 from Vector-Best, RF; and Human MMP-9 ELISA Kit BMS2016/2/BMS2016/2TEN from eBioscience, Austria).

The test sensitivity, test specificity, test accuracy and prevalence**,** positive predictive value, negative predictive value of the results, likelihood ratio, and post-test probability for the positive and negative results were analyzed to assess the informative significance of the results of a comprehensive examination. The risk difference, relative risk, absolute risk, and the odds ratio were estimated to conduct the population analysis. In all cases, a 95% confidence interval was determined (95% CI).

The statistical analysis of the obtained results was performed using the Statistica 6.0 software (StatSoft Inc., USA). The Student t-test was used to determine the significance of the difference between the means (P), and Fisher's exact test was used in the analysis of contingency tables (Pφ). P(Pφ)<0.05 was accepted as statistically significant.

3. RESULTS

Clinical observation groups were formed based on the determination of the level of VEGF and MMP-9 in the sputum supernatant of the examined patients. The mean value of the VEGF level in sputum supernatant was 122.3±9.72 (95% CI 102.9-141.6) ng/ml, median – 80.0 ng/ml (min 24.0 max 400.0). The mean value of the MMP-9 level in sputum supernatant was 5.37±0.43 (95% CI 4.52-6.22) ng/ml, median – 5.2 ng/ml (min 0 max 19.0). The first (I) clinical group, which was designated as a "high-risk group" on the development of airway remodeling, consisted of 37 patients with VEGF level in sputum supernatant exceeding 80.0 ng/ml, and MMP-9 level higher than 5.2 ng/ml. The second (II) clinical group – an "average-risk group" on the development of airway remodeling, included 41 patients with VEGF level in the sputum supernatant liquid higher than 80 ng/ml and MMP-9 level lower than 5.2 ng/ml, or VEGF level lower than 80 ng/ml and MMP-9 higher than 5.2 ng/ml. The third (III) clinical group consisted of 38 children with asthma and was a "low-risk group" on the development of airway remodeling. In the sputum supernatant of these patients, VEGF level did not reach 80 ng/ml and MMP-9 level did not exceed 5.2 ng/ml.

The general clinical characteristics of patients at the start of the monitoring period are given in Table 1. Differences in the places of residence between the patients from I and III groups did not affect the statistical significance of the comparative analysis of results of the complex examination in these groups but were taken into consideration in further analysis.

Table 1 General characteristics of children from the comparison groups

Clinical group	Number of patients	Frequency, %			Age (years)
		Sex		Villagers	
		Male	Female		
I (high-risk)	37	67.6	32.4	67.6	12.0±0.46
II (average-risk)	41	61.0	39.0	61.0	11.5±0.54
III (low-risk)	38	67.8	32.2	44.7	11.2±0.52
Pφ, t		>0,05	>0.05	I:III<0.05	>0.05

Duration of the asthma disease in children from the I group at the start of monitoring period was 5.8±0.68 years, in the II group – 4.4±0.68 years, and in the group with low-risk of airway remodeling – 4.4±0.63 years (Pφ>0.05 in all cases). The debut of asthma

before the age of 4 (early-onset asthma phenotype) in patients from the I clinical group occurred in 40.54±8.07% of cases, in the average-risk group – in 24.4±6.7%, and in the low-risk group – in 42.1±8.0% of observations (Pφ I:II:III>0.05).

The severity of asthma in children from the I clinical group was distributed as follows: severe in 13.5% of patients, moderate – in 62.2% of children, and mild persistent – in 24.3% of patients. In the II clinical group, the part of patients with severe asthma was 19.5%, moderate asthma – 41.5%, and with mild asthma – 39.0% of observations (in all cases Pφ>0.05). In the group of children with low risk for airway remodeling, patients with severe persistent asthma amounted 23.7%, with moderate asthma – 34.3%, and mild asthma – 42.0% (Pφ>0.05 in all cases). The absence of significant differences in the severity of asthma between the patients of the comparison groups could be explained by the fact that the latter is determined solely by the clinical manifestations of the disease and, accordingly, by the amount of therapy which is used to control the disease, and, consequently has a retrospective nature. Asthma severity is the characteristic of the disease, which is corrected by the anti-inflammatory therapy regardless of the degree of its other characteristics, in particular, reversible obstruction, bronchial inflammation and their remodeling. Thus, clinical management of all patients including severe and uncontrolled asthma cases was in line with the approved national guideline.

By the clinical subtype of asthma, the distribution of patients was as follows: atopic asthma observed in 67.6% of patients from the I group, in 56.1% of children in the average-risk group, and in 63.2% of representatives of the III group of comparison (Pφ>0.05 in all cases), the rest of the children had the mixed subtype of the disease. Thus, the comparison groups were comparable according to the basic clinical characteristics.

4. DISCUSSION

Based on the history of patients, the average birth weight of children from the comparison groups was 3283.0±65.4 g in the I group, 3475.6±96.0 g in the II group, and 3385.1±72.1 g in patients from the group of low risk for airway remodeling. At the same time, the proportion of children born with bodyweight less than 2500 g was significantly higher in the I and II groups. Thus, in the high-risk group for airway remodeling, such patients amounted 8.1% of cases, in the II clinical group – 7.3%, and in the III group of comparison – only 2.6% of observations (Pφ I,II:III<0,05). The percentage of children with a birth weight of more than 4000 g was significantly lower among representatives of the I clinical group. Thus, in the I group, children with high birth weight amounted 2.7% of cases, in the II group – 14.6%, and in the III group – 5.3% of the observations (Pφ I:II:III<0.05).

An indication of the birth of a child weighing less than 2500 g testified about the probability of airway remodeling with high specificity of 97.4 (95% CI: 92.0-99.6)% and moderate positive predictive value (75.7%: 95% CI: 41.1-95.7)%, but low sensitivity (8.1%: 95% CI: 3.5-15.3)% and negative predictive value (51.5%: 95% CI: 44.1-58.8)%. This test had low accuracy (52.8%: 95% CI 45.6-59.0) % and prevalence (50.0%: 95% CI 42.9-57.1) %. Birth of a child with the above-mentioned body weight indices increased the post-test probability of the possible airway remodeling by 24.3%, while the higher birth weight was associated with a decrease in the probability of this event by 1.5%. The risk difference for the positive test result was 3.3 (95% CI 0.79-13.7), the relative risk was 1.56 (95% CI 0.4-6.1) with an absolute risk of 0.27.

During the actual examination, BMI of children from the comparison groups did not differ significantly. Thus, in the I group BMI lower than normal values was found in 16.2% of cases, and BMI exceeding normal – in 21.6% of observations. In the II clinical group such indices were found in 17.1% and 21.9% of cases, respectively, and in the low-risk group of airway remodelling – in 13.2% and 26.3% of cases, respectively (Pφ I, II, III>0.05 in all cases).

Feeding of children from the comparison groups during the first year of their life did not differ significantly. Thus, 48.6% of children from the I group, 46.3% of children from the II group, and 47.4% of children from the III group were breastfed up to 6 months of age (Pφ I,II,III>0.05).

Passive smoking of children is considered as one of the causes of oxidative stress in respiratory organs, leading to airway remodeling. However, on average, the frequency of passive smoking among children from the comparison groups did not differ significantly. Thus, in the I clinical group, this situation was recorded in 34.0% of cases, with the same frequency in the II clinical group, and in 34.2% of the observations in the group of children with the low risk of airway remodeling. At the same time, the percentage of smoking mothers prevailed in the high-risk group compared to the group of children with a low risk of airway remodeling. Thus, in the I group it was observed in 27.0% of cases, in the II group – in 26.8%, and in the III group – only in 13.2% of the observations (Pφ I,II:III<0.05). An indication of the passive smoking of children had moderate test specificity (65.8%: 95% CI 55.6-75.0) %, but low test sensitivity (54.0%: 95% CI 43.7-64.1) %, positive predictive value (61.2%: 95% CI 50.2-71.4)% and negative predictive value (58.9%: 95% CI 49.2-68.1)%. The post-test probability of this test was +11.2% and -8.8%. The risk difference of bronchial remodeling for positive test result was 2.26 (95% CI 1.3-4.0) with the relative risk of 1.5 (95% CI 1.1-2.1) and absolute risk – 0.2. In case of the maternal smoking the test had a high test specificity (86.8%: 95% CI 78.5-92.8)%, but low test sensitivity (27.0%:

95% CI 18.6-36.8)%, negative predictive value (54.3%: 95% CI 46.3-62.2)% and moderate positive predictive value (67.2%: 95% CI 55.0-81.2)%. Test accuracy for identifying airway remodeling was 56.9% (95% CI 49.7-69.4) %, positive likelihood ratio – 2.05, and negative likelihood ratio – 0.8. Post-test probability for positive result increased by 17.2%, and for the negative test – decreased by 4.3%. Maternal smoking was associated with a risk of development of the structural changes in bronchi: the risk difference – 2.4 (95% CI 1.17-5.04) with absolute risk – 0.2, and relative risk – 1.5 (95% CI 0.8-2.7).

The incidence of factors associated with the formation of airway remodeling such as manifestations of exudative-catarrhal diathesis, the birth of a child during the plant flowering period, and the birth score did not differ significantly in the comparison groups. There were also no significant differences between the comparison groups in the frequency of infectious diseases in children. Thus, the part of children with the infection index of 2 and more was 16.2% in the I clinical group, 7.3% in the II clinical group, and 10.5% - in the III group of comparison (Pφ I,II,III>0.05).

Characteristics of the family history of allergy are shown in Table 2.

Table 2 Family history of atopic diseases in children from the comparison groups (%)

Clinical group	Number of patients	Negative history	Positive history		
			maternal	paternal	both parents
I (high-risk)	37	48.6	21.6	16.2	13.5
II (average-risk)	41	56.1	21.9	17.1	4.9
III (low-risk)	38	50.0	34.2	13.1	2.6
Pφ		>0.05	>0.05	>0.05	I:III<0.05

Accordingly, the incidence of positive family history of atopic diseases was significantly higher in the I clinical group. At the same time, the personal history of allergy in children from the comparison groups did not differ significantly in general (Table 3), however, patients from the I group had more frequent allergic drug reactions.

Table 3 Personal history of allergy in children from the comparison groups (%)

Clinical group	Number of patients	Hypersensitivity to:			
		food allergens	home allergens	food and home allergens	drugs
I (high-risk)	37	2.7	29.7	27.0	10.8
II (average-risk)	41	2.4	39.2	21.9	7.3
III (low-risk)	38	7.9	34.2	21.0	2.6
Pφ		>0.05	>0.05	>0.05	I:III<0.05

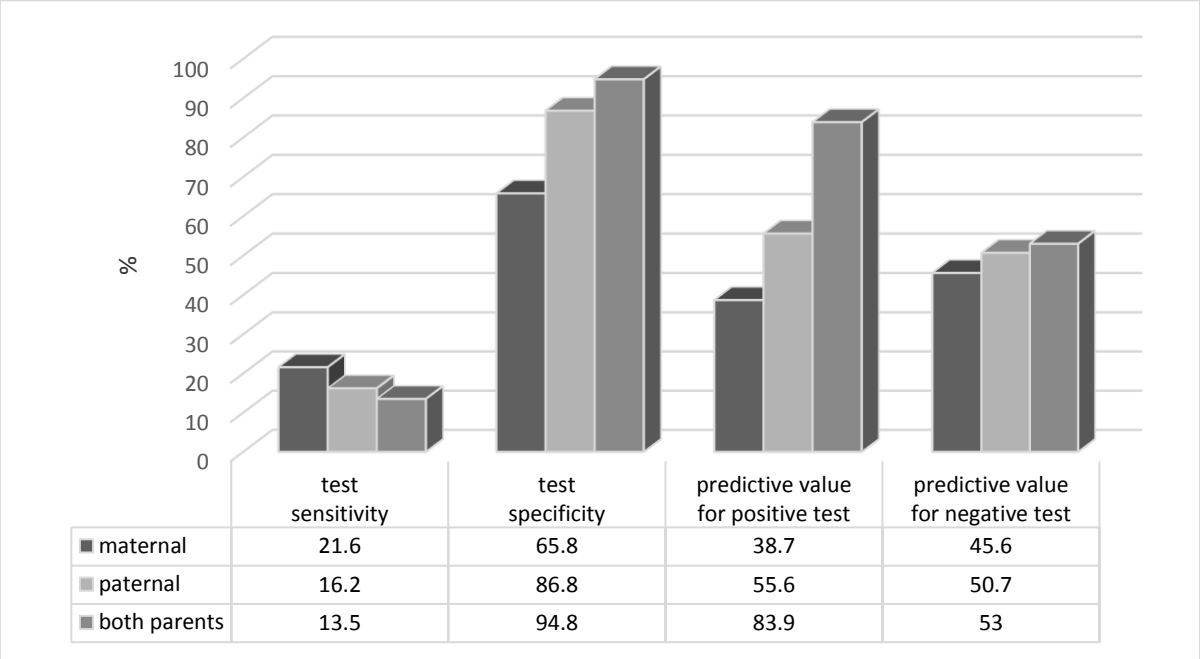
The incidence of comorbidities was similar in all of the comparison groups (Table 4).

Table 4 Incidence of comorbidities in children from the comparison groups (%)

Clinical group	Number of patients	Comorbidity		
		atopic dermatitis	allergic rhinitis	atopic dermatitis + allergic rhinitis
I (high-risk)	37	5.4	43.2	13.5
II (average-risk)	41	4.9	46.3	7.3
III (low-risk)	38	5.3	42.1	13.2
Pφ		>0.05	>0.05	>0.05

The obtained data give reason to suggest that comorbidity in children with asthma is an epiphenomenon, but not a determinative factor for the airway remodeling.

Diagnostic value of the positive family history of atopic diseases is given in Figure 1.

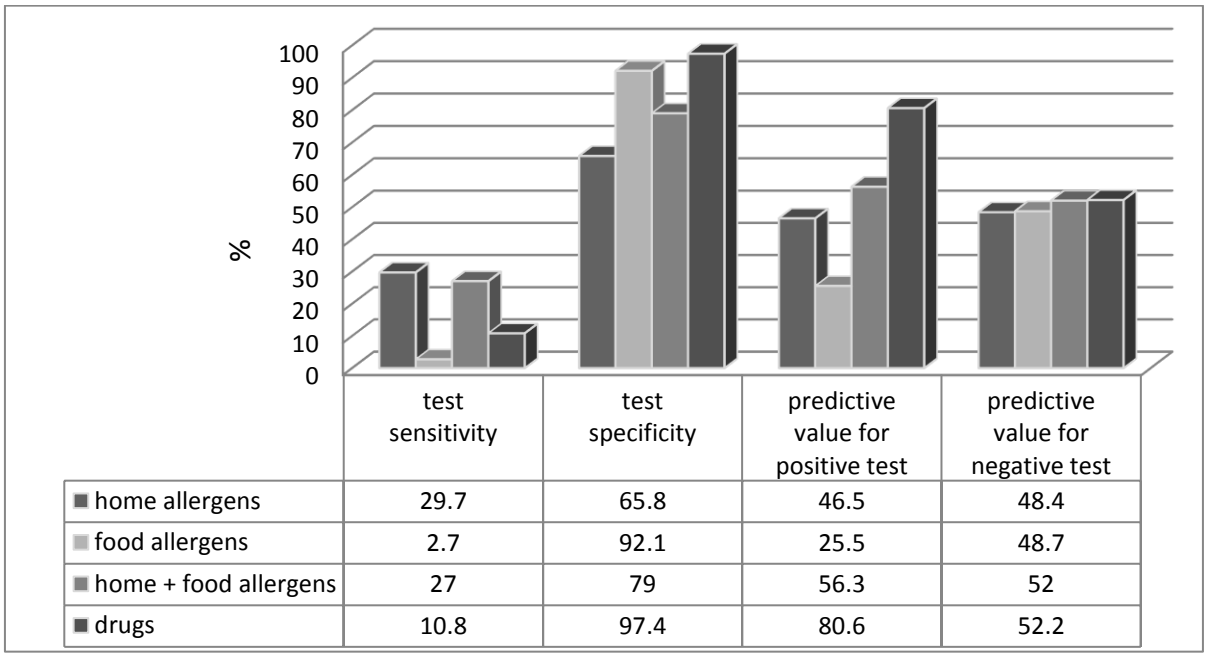


	test sensitivity	test specificity	predictive value for positive test	predictive value for negative test
maternal	21.6	65.8	38.7	45.6
paternal	16.2	86.8	55.6	50.7
both parents	13.5	94.8	83.9	53

Figure 1 Diagnostic value of the positive family history of atopic diseases

It should be noted that an increase in rating of the positive family history of allergy was associated with an increased test specificity and positive predictive value, while the test sensitivity and post-test probability for negative result respectively decreased. The positive likelihood ratio according to the given rating was 0.63, 1.23, and 5.2, while the negative likelihood ratio was 0.91, 0.97, and 0.9. The post-test probability of the airway remodeling for the positive result of the given rating was 11.3%, 4.9%, and 33.9%, while for the negative result it was reduced by 4.6%, 0.9%, and 3.0%, respectively. The risk difference of the airway remodeling in case of prior allergy history in both parents was 5.9 (95% CI 1.5-22.8), with a relative risk of 1.8 (95% CI 0.5-6.5) and absolute risk – 0.37. With decreasing rating, the risk indices tended to decrease.

Figure 2 shows the diagnostic value of indices of the personal allergy history in the form of increased sensitivity to home allergens, trophallergens, a combination of home and food hypersensitivity, and a drug allergy.



	test sensitivity	test specificity	predictive value for positive test	predictive value for negative test
home allergens	29.7	65.8	46.5	48.4
food allergens	2.7	92.1	25.5	48.7
home + food allergens	27	79	56.3	52
drugs	10.8	97.4	80.6	52.2

Figure 2 Diagnostic value of the increased hypersensitivity to standard allergens in children (according to history and prick tests)

Despite the high specificity of these tests, only an indication of the increased sensitivity to drugs had a significant positive likelihood ratio (4.15) with a negative likelihood ratio of 0.9. Use of this index as a diagnostic test increased the post-test probability for positive result by 29.4% and decreased the post-test probability for negative result only by 2.2%. At a positive result, the risk difference was 4.5 (95% CI 1.14-18.1) with a relative risk of 1.7 (95% CI 0.95-6.5), and absolute risk – 0.33. An indication of the high sensitivity of children to other allergens had a low diagnostic value, as evidenced by the positive likelihood ratio of about 1.0 and increase in post-test probability for the positive result to no more than 5.0%.

A dynamic analysis of the annual hospitalization frequency (Fig. 3) shows no significant differences for this parameter between the children from the clinical comparison groups. It can be explained by the positive effect of the anti-inflammatory maintenance therapy on the clinical symptoms of the disease, which mainly determine the frequency of hospitalization for asthma patients, but not a degree of the structural changes in bronchi. This fact also explains the absence of significant differences in the length of hospital stay of these patients. Thus, at the beginning of the study, the average length of hospital stay of the patients from the I group was 13.03±0.72 days, of the II group – 13.8±0.37 days, and of the III group – 13.3±0.64 days (P>0.05). At the end of the study, the average length of hospital stay of these groups was of 11.6±0.41, 11.2±0.83, and 12.6±1.0 days, respectively (P>0.05).

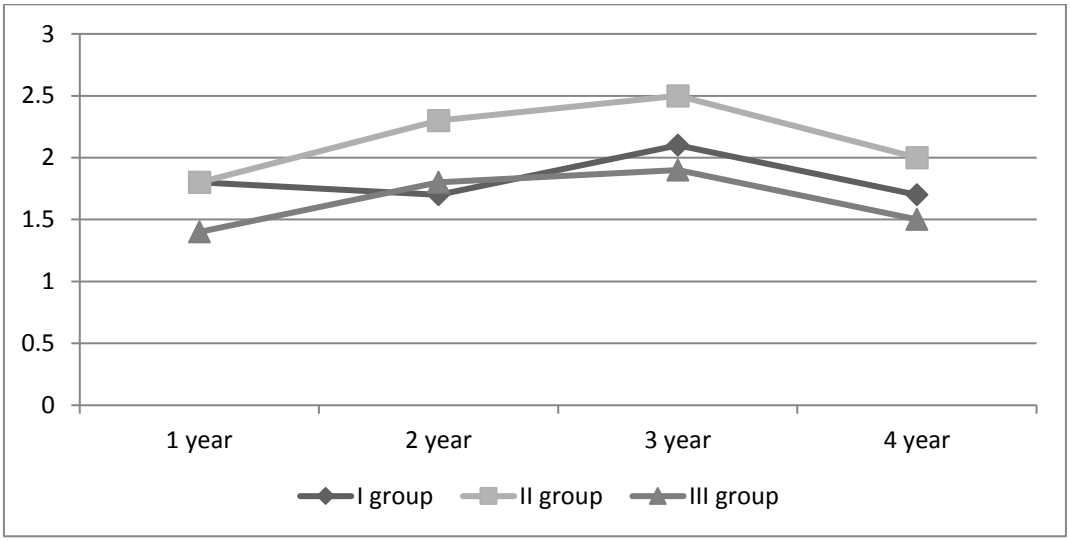


Figure 3 The frequency of annual hospitalizations of the children from the clinical comparison groups during the observation period

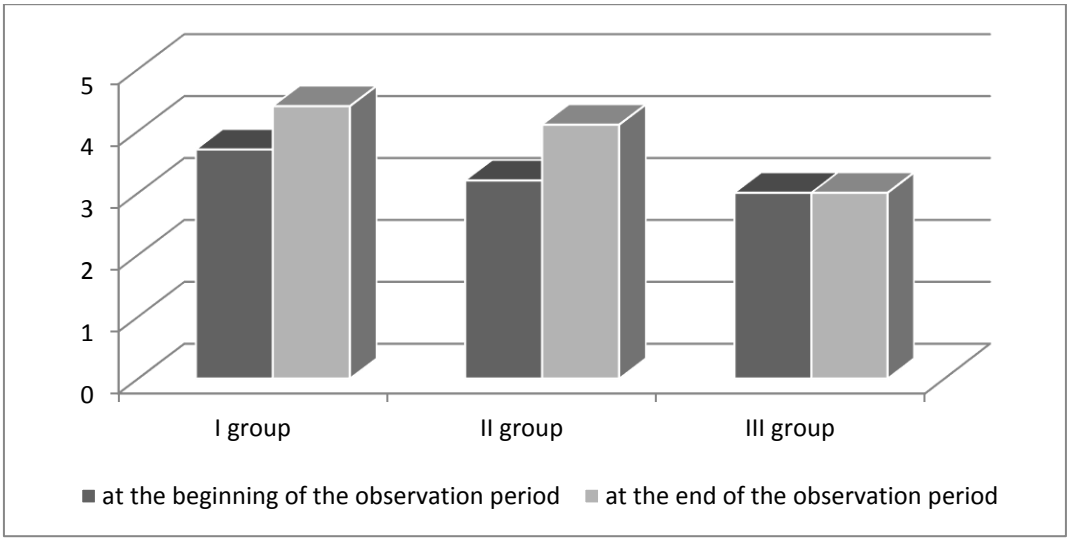


Figure 4 Indices of the bronchial desobstruction on the 3rd day of the in-hospital treatment of children from the clinical comparison groups (score)

The structural changes in bronchi, defined as remodeling, have the numerous negative effects on the functional state of the respiratory organs, except for one positive protective effect – a decrease in the severity of the asthma attacks due to the increased rigidity of the bronchial wall. Considering this fact, we analysed the reversibility of bronchial obstruction on the 3rd day of treatment (when the maximum desobstructive effect occurs in most cases) under the influence of fast-acting reliever medications during the management of asthma attacks at the beginning and at the end of the clinical dynamic monitoring of the children from the comparison groups (Fig. 4). The obtained results give grounds to consider that airway remodeling is not the main factor determining the bronchial obstruction in the process of treatment. In particular, among these factors is the bronchial hyper responsiveness to direct triggers of bronchospasm, caused by the spasm of bronchial smooth muscles.

Figure 5 shows the score of the asthma control in children from the comparison groups based on clinical and spirometry data using clinical-instrumental assessment scale (CIA scale).

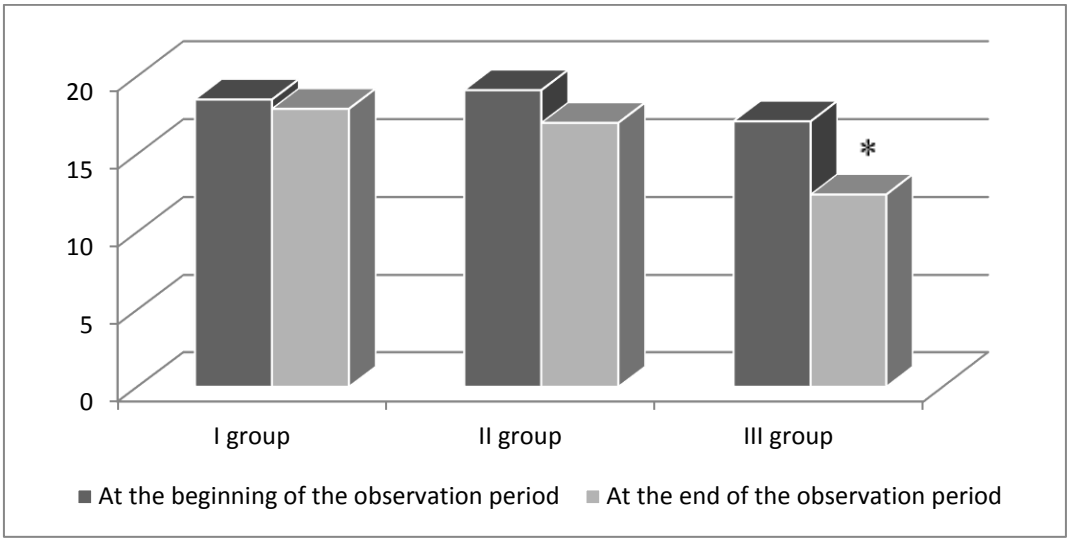


Figure 5 The scores of the asthma control (by CIA scale) at the beginning and at the end of the dynamic observation of children from the comparison groups (* – P<0.05)

The obtained data show a significant improvement in the control of asthma achieved only in the III clinical observation group, while in groups with an increased level of airway remodeling biomarkers this improvement was not statistically significant. It should be noted that at the beginning of the study, uncontrolled asthma (above 20 scores on CIA scale) occurred in 38.2% of cases in the I clinical group, in 45.0% of cases in the II group, and in 39.3% of the observations in the III group of comparison (P>0.05). In the middle of the observation period, the incidence of uncontrolled asthma in children from the clinical groups was of 42.6%, 57.1%, and 25.0% of cases, respectively (P I,II:III<0.05). Thus, maintenance anti-inflammatory therapy of asthma in patients with the low risk of airway remodeling was significantly more effective than in patients from the comparison groups.

An indication of the inadequate degree of asthma control (above 17 scores on CIA scale) evidenced the development of airway remodeling with moderate test specificity (75.0%: 95% CI 63.0-83.1)%, but low test sensitivity (42.6%: 95% CI 32.7-52.9)%, with positive predictive value of 68.0% (95% CI 50.3-74.5)% and negative predictive value of 56.7% (95% CI 47.8-65.8)%. The accuracy of this test was low (58.8%: 95% CI 51.6-65.7) %, as well as the positive likelihood ratio (1.7) and negative likelihood ratio (0.8) of the results. At the same time, it should be noted that an indication of the poor asthma control testified about the significant risk of the development of changes in bronchi with the risk difference of 2.23 (95% CI 1.2-4.1), the relative risk of 1.5 (95% CI 1.0-2.2) and absolute risk – 0.2. This conclusion is consistent with the results of the analysis of the asthma severity in children from the comparison groups in the dynamics of observation (Table 5).

It was established during the period of observation, that in spite of the adequate controller therapy, there was a significant increase in the proportion of severe asthma among children from the I clinical group. In patients with low risk of airway remodeling, use of controller therapy led to a statistically significant reduction in the number of patients with severe asthma at the end of the 4th year of observation.

Table 5 Dynamic analysis of the asthma severity in children from the comparison groups (%)

Clinical groups (number of patients)	Period of observation								
	at the beginning			after 2 years			after 4 years		
	Severity of asthma								
	mild	moderate	severe	mild	moderate	severe	mild	moderate	severe
I (37)	24.3	62.2	13.5	24.3	48.7	27.0	19.9	53.3	26.8
II (41)	39.0	41.5	19.5	36.6	39.0	24.4	28.1	46.9	25.0
III (38)	42.0	34.3	23.7	33.2	50.0	15.8	32.3	53.5	14.2
P	>0.05	I:III <0.05	I:III <0.05	>0.05	>0.05	>0.05	I:III <0.05	>0.05	I:III <0.05

5. CONCLUSIONS

At the beginning of the study patients with high levels of VEGF and MMP-9 in sputum were characterized by higher incidence of a birth weight of less than 2500 g (8.1% vs. 2.6%), history of maternal and paternal atopic diseases (13.5% vs. 2.6%), history of drug allergy (10.8% vs. 2.6%), and maternal smoking as a source of long-time exposure to second-hand tobacco smoke (27.0% vs. 13.2%) compared to children with low levels of bronchial remodeling markers.

Children with high levels of airway remodeling markers in sputum were characterized by an increase in the incidence of severe asthma (from 13.5% to 26.8% vs. a decrease from 23.7% to 14.2%), as well as uncontrolled asthma (from 38.2% to 42.6% vs. decrease from 39.3% to 25.0%) compared to patients with lower levels of markers.

Conflict of Interest

The authors declare no conflict of interest or financial support. All authors contributed to the research and/or preparation of the manuscript.

Ethical approval

The research protocol and informed consent form were approved by the Commission on Biomedical ethics in biomedical scientific research of the Higher State Educational Establishment of Ukraine, Bukovinian State Medical University (Protocol No. 36 dated 17.11.2016).

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