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PROGNOSTIC CRITERIA FOR THE RISK OF BRONCHIAL ASTHMA IN CHILDREN WITH OBSTRUCTIVE BRONCHITIS

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The purpose of the study was to identify prognostic criteria for the formation of bronchial asthma in children with obstructive bronchitis. The material for the work included the data of a retrospective examination of 100 children with recurrent obstructive bronchitis aged from 1 to 7 years (the first group). The second group included 89 children diagnosed with bronchial asthma. All children underwent a comprehensive examination, including the copying of information from medical records, questioning of parents, analysis of risk factors, assessment of allergic history and examination of laboratory parameters. The diagnostic test for the absolute number of eosinophils showed high specificity of 84.9±4.9, and sensitivity of 63.6±14.5. The relative number of eosinophils showed high sensitivity and specificity: 81.8±5.2 and 84.1±4.0, respectively. Testing of immunoglobulin E showed absolute sensitivity of 100.0±0.0, specificity 72.2±7.5. Thus, high prognostic efficiency in the development of asthma in children with obstructive bronchitis has parental allergic diseases, urogenital infections and maternal preeclampsia during pregnancy, birth injury and asphyxia in the neonatal period, absolute and relative eosinophilia, hyperimmunoglobulinemia E.

Key words: bronchial asthma, eosinophilia, hyperimmunoglobulinemia E, predictive indices

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ПРОГНОСТИЧНІ КРИТЕРІЇ РИЗИКУ БРОНХІАЛЬНОЇ АСТМИ У ДІТЕЙ З ОБСТРУКТИВНИМ БРОНХІТОМ

Метою дослідження було виявити прогностичні критерії формування бронхіальної астми у дітей із обструктивним бронхітом. Матеріалом для роботи послужили дані ретроспективного обстеження 100 дітей з рецидивним обструктивним бронхітом віком від 1 до 7 років (перша група). До другої групи увійшли 89 дітей із діагнозом бронхіальна астма. Всім дітям було проведено комплексне обстеження, що включає копіювання відомостей із медичних карток, опитування батьків, аналіз факторів ризику, оцінку алергологічного анамнезу та дослідження лабораторних показників. Діагностичний тест на абсолютну кількість еозинофілів показав високу специфічність 84,9±4,9 та чутливість 63,6±14,5. Відносна кількість еозинофілів також мала високу чутливість та специфічність: 81,8±5,2 та 84,1±4,0, відповідно. Дослідження імуноглобуліну Е показало абсолютну чутливість 100,0±0,0, специфічність 72,2±7,5. Таким чином, високу прогностичну ефективність у розвитку бронхіальної астми у дітей з обструктивним бронхітом поряд з алергічними захворюваннями батьків, урогенітальними інфекціями та гестозом матері під час вагітності, родовою травмою та асфіксією в неонатальному періоді мають абсолютну та відносну еозинофілію, гіперімуноглобулінемію Е.

Ключові слова: бронхіальна астма, еозинофілія, гіперімуноглобулінемія Е, прогностичні показники.

The problem of timely diagnosis of bronchial asthma (BA) is one of the most urgent problems in modern pediatrics [5, 9].

Diseases of the lower respiratory tract in children, especially in children of young age are often accompanied by the development of an obstructive syndrome [4, 13]. In some children, we meet a recurrent bronchial obstruction due to repeated episodes of respiratory infections leading to the formation of bronchial hyperactivity and the implementation of bronchial asthma; in other children, the bronchial obstruction syndrome might be transient in nature and disappearing of symptoms occurs at early school

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age. Phenotyping of recurrent bronchial obstruction syndrome in children, taking into account the long-term prognosis of the risk of BA development only based on the clinical pictures is rather difficult [10, 11]. Presently, we have no valid diagnostic criteria for diagnosing asthma in young children, despite the fact namely in this age range the disease makes its debut in 70–80 % of cases. In this connection, the search for ways to predict the risk of BA development in children, revealing informative methods using diagnostic predictor biomarkers does not lose its relevance [2, 7]. This has determined the priority direction of our research work as well.

The purpose of the study was to identify prognostic criteria for the formation of asthma in children with obstructive bronchitis.

Materials and methods. The work was performed on the basis of the Azerbaijan Medical University (Baku, Azerbaijan). The material for the work included the data of a retrospective examination of 100 children with recurrent obstructive bronchitis (ROB) aged from 1 to 7 years. They made up the first group. The second group included 89 children diagnosed with BA; it is to be noted that 27.9 % of patients were diagnosed with mild intermittent BA, 50.0 % with mild persistent BA and 22.1 % with moderate BA. All children underwent a comprehensive examination, including copying of information from medical records, questioning of parents, analysis of risk factors, assessment of allergic history and examination of laboratory parameters.

The statistical processing of the material was carried out on an Excell-2013 SPSS-20 spreadsheet. For the purpose of correct application of statistical procedures, we have calculated the mean values of the obtained samples (M), their standard deviations (σ), standard errors (m), 95 % confidence intervals, minimum (min) and maximum (max) values of the series, and there were determined the frequencies of occurrence of the target indication (p %) in groups. For comparison and probabilistic assessment of differences between the values of the compared groups, we have used the analysis of variance (F-Fisher) and non-parametric rank tests of Wilcoxon U-test (Mann-Whitney) and Kruskal-Wallis test. Pearson's χ^2 method (Pearson Chi-Square) was used to determine the degree of association between qualitative indices. To assess the effectiveness of the diagnostic significance of the test, we have determined first its specificity (Sp) and sensitivity (S). Additionally, for each test, there are determined the predictive utility of positive and negative results, as well as practical application, and the likelihood ratios of positive (LR+) and negative (LR–) results. Based on the values of sensitivity and specificity, a characteristic ROC curve (receiver operating characteristic) was constructed. The quantitative assessment of the ROC curve was determined by the area under the curve. Based on the coordinates of the ROC curve, the cut-off point is defined. Differences and correlation coefficients were considered significant at $p \leq 0.005$.

Results of the study and their discussion. Among the examined patients with both bronchitis and asthma, the majority were boys, accordingly 68 (68.0 %) and 69 (77.5 %). In patients with bronchitis and asthma 32 (32.0 %) and 20 (22.5 %) respectively, were girls ($\chi2=2.144$, $p=0.143$). Despite the fact that there were more boys in the analyzed phenotypes, the gender indication was not defined as a statistically significant risk factor in predicting recurrent bronchial obstruction.

One of the substantial risk factors in the formation of BA is burdened by allergic diseases. In our study, in the group of children with bronchial asthma, fathers in 20.2 % of cases had various allergic diseases, with obstructive bronchitis – in 7.0 % ($\chi2=7.175$, $p=0.07$); mothers – in 24.7 % and 9 %, respectively ($\chi2=8.486$, $p=0.004$). The relatives of the examined patients with bronchitis had allergic diseases in 15.0 % of cases, while those with asthma had 28.1 % ($\chi2=4.836$, $p=0.028$). The hereditary burden of allergic pathologies in bronchial asthma statistically significantly exceeds the indicators of obstructive bronchitis ($p<0.05$) and is a significant predictor (Table 1).

Table 1

Comparative assessment of hereditary burden in children with bronchitis and asthma

		Obstructive bronchitis		BA – mild + moderate		χ2	p
		n	%	n	%		
Gender	Boy	68	68.0 %	69	77.5 %	2.144	0.143
	Girl	32	32.0 %	20	22.5 %		
Allergic diseases of the father		93	93.0 %	71	79.8 %	7.175	0.007
		7	7.0 %	18	20.2 %		
Allergic diseases of the mother		91	91.0 %	67	75.3 %	8.486	0.004
		9	9.0 %	22	24.7 %		
Allergic diseases of the relatives		85	85.0 %	64	71.9 %	4.836	0.028
		15	15.0 %	25	28.1 %		

A comparative characteristic of maternal pathologies during pregnancy was carried out (Table 2).

Table 2

Comparative assessment of maternal diseases during pregnancy among patients with bronchitis and asthma

	Obstructive bronchitis		BA – mild + moderate		$\chi 2$	p
	n	%	n	%		
Acute respiratory viral infection	97	97.0 %	85	95.5 %	0.295	0.587
	3	3.0 %	4	4.5 %		
Urogenital infections	89	89.0 %	88	98.9 %	7.725	0.005
	11	11.0 %	1	1.1 %		
Preeclampsia	84	84.0 %	84	94.4 %	5.139	0.023
	16	16.0 %	5	5.6 %		
Preterm birth	93	93.0 %	84	94.4 %	0.151	0.697
	7	7.0 %	5	5.6 %		
Operational childbirth	94	94.0 %	83	93.3 %	0.044	0.835
	6	6.0 %	6	6.7 %		

The results of a comparative analysis of maternal pathologies during pregnancy showed almost the same ratio of the number of children in both groups born from operative delivery – 6 % and 6.7 % with bronchitis and asthma, respectively, ($\chi 2$=0.044, p=0.835). The premature births were noted in 7 % and 5.6 % of cases in the groups with bronchitis and asthma, respectively ($\chi 2$=0.151, p=0.697). The acute respiratory viral infection during pregnancy in the group of mothers of the children with bronchitis was recorded in 3 % of cases, in the group with asthma – in 4.5 % of cases ($\chi 2$=0.295, p=0.587). Only the frequency of preeclampsia and urogenital infections during pregnancy differed statistically in groups of patients with bronchitis and asthma. The preeclampsia occurred in 16 % in the bronchitis group and in 5.6 % of cases in the asthma group ($\chi 2$=5.139, p=0.023). The urogenital infections in groups with bronchitis and asthma were observed in 11 % and 1.1 % of cases, respectively, ($\chi 2$=7.725, p=0.005).

Pathologies of the neonatal period were noted more often in the group of children with obstructive bronchitis. Thus, birth injuries were recorded in history in children with bronchitis in 15 %, with asthma – in 3.4 % of cases ($\chi 2$=7.391, p=0.007), birth asphyxia in groups with bronchitis and asthma – in 18 % and 4.5 % cases, respectively ($\chi 2$=8.351, p=0.004), perinatal damage of central nervous system – in 12 % and 3.4 % of cases, respectively ($\chi 2$=4.799, p=0.028). The listed pathologies differed statistically significantly between the studied groups, p<0.05. There were no significant differences in the incidence of intrauterine infection, in the group of children with bronchitis – 7 %, with asthma – 6.7 % ($\chi 2$=0.005, p=0.944).

When analyzing the types of nutrition of infancy age in children of the studied groups, it was revealed that the majority of children with bronchial asthma in infancy age were in artificial nutrition (52.8 %), with bronchitis – 13 %. 78 % of children with bronchitis and 31.5 % of children with asthma in infancy age received breast milk, 9 % of children with bronchitis and 15.7 % of children with asthma were on a mixed type of feeding. All these indicators significantly differed between the groups ($\chi 2$=58.865, p=0.000).

We have analyzed the hematological parameters of obstructive bronchitis and bronchial asthma as well. The absolute and relative numbers of eosinophils in bronchitis and asthma were significantly differed from each other (p<0.000). The absolute number of eosinophils in atopic asthma is almost 7 times higher than that in obstructive bronchitis and is equal to 1.72±0.67×109/l (95 % CI: 0.23–3.20) and $0.25\pm0.08\times10^9$/l (95 % CI: 0.1–0.4), respectively. The percentage of eosinophils in asthma is almost 3 times higher than in bronchitis, respectively 6.01±0.43 % (95 % CI: 5.14–6.87) and 1.86±0.23 % (95 % CI: 1.40–2.32). As a result of the laboratory immunological examination it was revealed a significant increase in the level of total IgE in blood serum in children with BA, amounting to 436.1±96.1 (χ^2=8.741, p<0.003) compared with the values of 211.5±53.9 IU/ml (95 % CI: 102.1–321.0) in children with obstructive bronchitis (p<0.056). Comparative analysis of the level of Ig E in children with BA and ROB shows the statistical significance of differences using the Kruskal-Wallis test.

The diagnostic test for the absolute number of eosinophils showed high specificity of 84.9±4.9, sensitivity of 63.6±14.5, and satisfactory results LR+ (4.22) and LR– (0.43). The relative number of eosinophils showed high sensitivity and specificity of 81.8±5.2 and 84.1±4.0, respectively, good LR+ (5.16) and satisfactory results of LR– (0.22). Testing of immunoglobulin E showed absolute sensitivity of 100.0±0.0, specificity 72.2±7.5, satisfactory LR+ 3.60 and excellent LR– 0.22. The presence of eosinophilia in peripheral blood has a greater specificity (Sp=84.1 %) than an increased level of total IgE (Sp=72.2 %) in blood plasma. This fact is explained by the fact that an increased level of reaginic antibody in plasma reflects the potential for the development of allergic diseases, and an increased level of eosinophils is a realized allergic inflammation.

Based on the coordinates of the ROC curve, cut-off-points were determined when the sum of sensitivity and specificity values reached the maximum level. This approach enables us to assess the predictive value of the positive and negative results obtained when using this diagnostic method, evaluated as a marker that can be used to verify and predict the formation of BA.

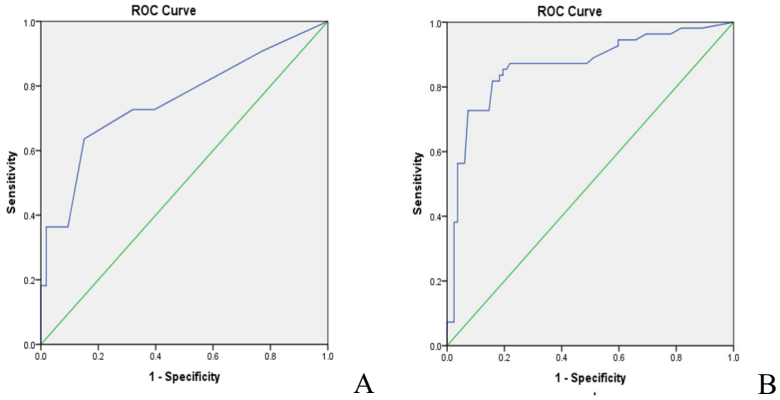
A high cut-off point is noted for immunoglobulin E (135), odds ratios (OR) were 53.0 (95 % CI: 2.8–988.3), p<0 .05. Relative eosinophilia has a development odds ratio of 23.9 (95 % CI: 9.7–59.1), a diagnostic threshold of 3.95, p<0.05. Thus, immunoglobulin E and the relative number of eosinophils have a high prognostic value; they are evaluated as markers that can be used to verify and predict the formation of BA.

We applied one-way ANOVA (analysis of variance) and assessed the weight of factors in predicting asthma. The relative eosinophilia F=403.2, EIF=74.9, 95 % CI 74.2–75.6, EIF=35.5 %, 95 % CI 34.2–36.9, immunoglobulin E F=42 have a high influence weight, EIF=47.7 %, 95 % CI 43.1–52.3, and the absolute eosinophilia F=18.5, EIF=23.0 %, 95 % CI 18.0-28.09 have high influence weight. Moderate weight of influence fell on the following factors: birth asphyxia F=9.1, EIF=4.6 %, 95 % CI 2.6-6.6, birth injury F=7.9, EIF=4.1 %, 95 % CI 2.1-6.1, maternal allergic disease F=9.2, EIF=4.7 %, 95 % CI 2.7–6.7 and paternal allergic disease F=7.7, EIF=3.9 %, 95 % CI 1.9–5.9.

To conduct a comparative analysis of the informative value of risk factors for BA development, we calculated the area under the ROC-curve – AUC (area under the curve). The results for eosinophils are presented in fig. 1.

Analyzing the data obtained for the relative number of eosinophils, it was found that the largest area under the ROC curve was AUC=0.866±0.34 at 95 % CI: 0.799–0.933 (p<0.001), for the absolute number of eosinophils AUC=0.755±0.92 at 95 % CI: 0.574–0.936 (p<0.008).

The results of the AUC for IgE are shown in fig. 2.



A B

Fig. 1. ROC-curve of eosinophils, a – absolute number; b – relative number)

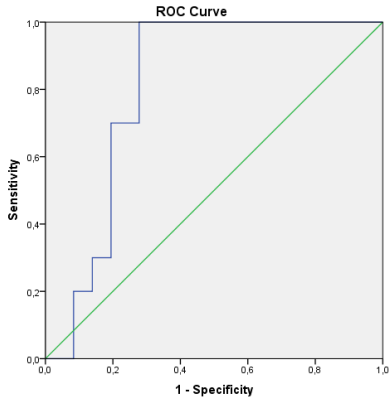


Fig. 2. The ROC-curve of IgE.

Analysis of the internal validation of the model showed predictive value and good informative value for IgE; the area under the ROC curve was AUC=0.808±0.62 at 95 % CI: 0.687–0.930 (p=0.003).

Although some biomarkers specific to different asthma phenotypes have been identified by many researchers, progress in their utility remains slow, because of several disease mechanisms, the variation of biomarkers at different levels of inflammation, changes in relying on one test over time (eg, from sputum eosinophilia to blood eosinophilia), and the degree of invasive tests required to collect biomarkers, which limits their applicability in clinical settings [8, 14]. Our study can help in solving this tasks. So, according results of statistical data high prognostic efficiency in the development of asthma in children with obstructive bronchitis has absolute and relative eosinophilia, and hyperimmunoglobulinemia E.

Zhang XY obtained the similar results analyzing the relationship between some blood parameters in patients with asthma. They revealed that blood eosinophil counts and eosinophil/lymphocyte ratio and eosinophil/neutrophil ratio can accurately predict eosinophilic asthma in patients with persistent uncontrolled asthma despite treatment. In their study ROC curve analysis identified that blood eosinophil percentage (relative number) count was the best predictor for eosinophilic asthma, with an area under the curve (AUC) of 0.907; p<0.001 (AUC=0.866±0.34; p<0.001 in our work). The absolute blood eosinophil count was also highly predictive with an AUC of 0.898; p<0.0001 (AUC=0.755±0.92; p<0.008 in our study). The authors propose that blood counts may be a useful aid in the monitoring of uncontrolled asthma [15].

But opposite to our results Hastie AT, did not find out high predictive value of IgE in patients with a risk of severe asthma. It should be noted that the authors analyzed predictive value for sputum eosinophil and neutrophil percentages, not for the direct risk of asthma development [6].

Several other biomarkers remain useful in recognizing various asthma phenotypes. Thus, some authors indicated that periostin, fractional exhaled nitric oxide, exhaled breath condensate and galectins [3].

Identification of biomarkers is primarily important for improving the effectiveness of treatment. For experimental therapies targeting inflammatory cytokines such as IL-5 and IL-13, the biological activity of therapeutic targets should be considered as they are associated with biomarkers. IL-5 leads to hematopoiesis and mobilization of eosinophils from the bone marrow; IL-13 does not directly induce the production of eosinophils, but induces the expression of chemoattractants in the structural cells of the respiratory tract, which can recruit and retain eosinophils in bronchial tissue [1].

Avramenko Y. studying IL-26 is a potential biomarker of disease severity in asthma revealed the increase of exhaled IL-26 in obese and non-obese moderate-to-severe asthmatic patients. They indicated that exhaled IL-26 might be a perspective biomarker in non-obese and obese asthmatics [2]. But, in our study, we assessed not only laboratory markers but also some maternal and paternal risk factors, diseases of parents, birth injury and asphyxia in the neonatal period etc. Using these predictive markers in children with obstructive bronchitis will be more effective to prevent the development of asthma in comparison with assessment only laboratory tests.

Moreover, we agree with Porpodis K, that the main goal of identifying particularly informative prognostic laboratory and clinical indicators characterizing asthma should be their easy practical use as reliable markers [12]. We emphasize the need to identify different sets of markers to select patients at risk of the development of asthma for prevention and individualized therapeutic approach.

Conclusion

1. The hereditary burden of allergic pathologies in bronchial asthma statistically significantly exceeds the indices of obstructive bronchitis ($p<0.05$) and is a significant predictor.

2. The diagnostic test for the absolute number of eosinophils showed high specificity of 84.9±4.9, sensitivity 63.6±14.5, satisfactory results LR+ (4.22) and LR– (0.43). The relative number of eosinophils showed high sensitivity and specificity of 81.8±5.2 and 84.1±4.0, respectively, good LR+ (5.16) and satisfactory results of LR– (0.22). Testing of immunoglobulin E showed absolute sensitivity of 100.0±0.0, specificity 72.2±7.5, satisfactory LR+ 3.60 and excellent LR– 0.22.

3. The presence of eosinophilia in peripheral blood has a greater specificity (Sp=84.1 %) than an increased level of total IgE (Sp=72.2 %) in blood plasma.

Thus, the calculation of the frequency and variation of each indicator makes it possible to evaluate prognostic criteria, although these indicators occur in many combined cases, and therefore it is impossible to determine which is more important in each case using traditional assessment methods. Mathematical analysis and quantitative evaluation of these indicators make it possible to predict the strength of the influence of the studied indicators on the final result in all possible combined cases. High prognostic efficiency in the development of asthma in children with obstructive bronchitis has parental allergic diseases, urogenital infections and maternal preeclampsia during pregnancy, birth injury and asphyxia in the neonatal period, absolute and relative eosinophilia, hyperimmunoglobulinemia E.

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CORRELATIONS OF TELEROENTGENOGRAPHIC PARAMETERS OF THE JAWS WITH BASAL CRANIAL PARAMETERS IN UKRAINIAN JUVENILE MEN AND JUVENILE WOMEN WITH DIFFERENT FACIAL PROFILES ACCORDING TO SCHWARZ

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Peculiarities of correlations between TRG-indices of the upper and lower jaws, intermaxillary indices that can be corrected during surgical and orthopedic treatment, and TRG-indices of the skull, which usually do not change during such interventions in Ukrainian juvenile men and juvenile women with orthognathic bite with different facial profiles according to Schwarz, were established. In juvenile men with the first face profile (back profile), the revealed reliable connections were mostly direct of medium strength and strong, and in juvenile women, almost the same number of direct and reverse connections of mostly medium strength were established. In juvenile men with the second face profile (straight profile), reliable connections were exclusively strong direct and strong inverse, while in juvenile women direct connections of medium strength prevailed. Both juvenile men and juvenile women with the third face profile (front profile) have mainly direct reliable relationships of medium strength.

Key words: teleradiography, cephalometry, teleradiographic indices, cephalometric analysis according to Schwarz, face profiles, juvenile men and juvenile women, orthognathic occlusion, correlations.

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КОРЕЛЯЦІЇ ТЕЛЕРЕНТГЕНОГРАФІЧНИХ ПОКАЗНИКІВ ЩЕЛЕП ІЗ БАЗАЛЬНИМИ КРАНІАЛЬНИМИ ПОКАЗНИКАМИ В УКРАЇНСЬКИХ ЮНАКІВ І ДІВЧАТ ІЗ РІЗНИМИ ПРОФІЛЯМИ ОБЛИЧЧЯ ЗА SCHWARZ

Встановлені особливості кореляцій між ТРГ-показниками верхньої і нижньої щелеп, міжщелепними показниками, які можуть корегуватися під час хірургічного, ортопедичного лікування та ТРГ-показниками черепа, які зазвичай не змінюються під час таких втручань в українських юнаків і дівчат з ортогнатичним прикусом з різними профілями обличчя за Schwarz. В юнаків з першим профілем обличчя (задній профіль) виявлені достовірні зв'язки були переважно прямими середньої сили та сильними, а у дівчат встановлена майже однакова кількість прямих та зворотних зв'язків переважно середньої сили. В юнаків з другим профілем обличчя (прямий профіль) достовірні зв'язки були виключно сильними прямими та сильними зворотними, а у дівчат переважали прямі зв'язки середньої сили. Як у юнаків, так і в дівчат з третім профілем обличчя (передній профіль) встановлені переважно прямі достовірні зв'язки середньої сили.

Ключові слова: телерентгенографія, кефалометрія, телерентгенографічні показники, цефалометричний аналіз за Schwarz, профілі обличчя, юнаки та дівчата, ортогнатичний прикус, кореляції.

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In modern dental practice, one of the main and most informative methods of research is the teleroentgenographic method, which provides the possibility of intravital determination of the structure of various parts of the skull, features of the location of the jaws, assessment of the symmetry of the maxillofacial structures, establishment of congenital or acquired pathological changes of the dento-jaw apparatus, etc., which is extremely important in planning and evaluating the efficacy of dental treatment [6, 7].

Researchers and practicing doctors use numerous original methods of cephalometric analysis, which were developed mainly in the last century, and normative cephalometric, gnathometric indicators, which are

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