THE INFLUENCE OF DEFICIENCY OF MICROELEMENTS IN CHILDREN WITH BRONCHIAL HYPERREACTIVITY

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Abstract: *the study shows pathogenetic mechanisms of formation of bronchial hyperreactivity associated with microelementosis. The study group consisted of 58 children with a combination of atopic dermatitis and bronchial asthma. Methods: inhalation-provocation tests with histamine and metacholine, atomic absorption spectrometry, x-ray fluorescence method. The state of hyperreactivity of the bronchi was accompanied by a deficit of essential microelements (69.6 %) with high sensitivity of the bronchi (PK20 metacholine, histamine-0.125-0.5 mg/ml), against the background of selenium and zinc deficiency (plasma content below 0.2 and 0.35 mg/l, respectively), reducing the speed parameters of the external respiratory function.*

Keywords: *hyperreactivity of the bronchi, microelementoses, atopic dermatitis, bronchial asthma.*

ВЛИЯНИЕ ЗАЩИТЫ МИКРОЭЛЕМЕНТОВ У ДЕТЕЙ С БРОНХИАЛЬНОЙ ГИПЕРРЕАКТИВНОСТЬЮ

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Аннотация: *в исследовании показаны патогенетические механизмы формирования гиперреактивности бронхов, ассоциированной с микроэлементозом. Группу исследования составили 58 детей с сочетанием атопического дерматита и бронхиальной астмы. Методы: ингаляционно-провокационные пробы с гистамином и метахолином, атомно-абсорбционная спектрометрия, рентгенофлуоресцентный метод. Состояние гиперреактивности бронхов сопровождалось дефицитом эссенциальных микроэлементов (69,6%) с высокой чувствительностью бронхов (метахолин РК20, гистамин-0,125-0,5 мг/мл) на фоне дефицита селена и цинка (содержание в плазме крови) ниже 0,2 и 0,35 мг/л соответственно), снижая скоростные параметры функции внешнего дыхания.*

Ключевые слова: *гиперреактивность бронхов, микроэлементозы, атопический дерматит, бронхиальная астма.*

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Introduction. Reactivity of the respiratory tract is the most important characteristic of the functional state of the bronchopulmonary apparatus. Bronchial hyperreactivity syndrome (BHS) occurs not only in bronchial asthma [5, 14, 16, 19], but also in other bronchopulmonary diseases: chronic and recurrent obstructive lung diseases, pollinosis [1, 8, 15], allergic rhinitis, atopic dermatitis [3, 10, 12, 18]. Violation of metal-ligand homeostasis can indirectly affect the reactivity of the bronchial tree [2, 9, 13, 17].

The leading role in the pathogenesis of BHS development it belongs to calcium and magnesium ions, which are directly involved in the reduction of the bronchi; such microelements (ME) as selenium, zinc, copper have influence on the processes of lipid peroxidation and the formation of an allergic inflammatory process of the tracheobronchial tree-the morphological basis for the development of hyperreactivity [4, 6, 9, 11]. In experimental and clinical conditions, the important role of ME in the regulation of bronchial patency, respiratory muscle contractility, sensitization processes, and the intensity of pathochemical and pathophysiological phases of allergic reactions [2, 7, 16, 20].

The purpose of the study: to study possible pathogenetic mechanisms of formation of hyperreactivity of the bronchial tree associated with microelement disorders in children, which live in high climate risk area.

Materials and methods of research. The study group included 58 children (49 patients with combined forms of Allergy and 9 children with atopic dermatitis) with persistent changes in bronchial tone (no dynamics of observation. for 3 to 5 years). The average age of children was 9.1 ± 0.6 years. Exclusion criteria: age less than 4 years, no atopy. The control group consisted of 68 children with no history of atopic or chronic bronchopulmonary diseases and having the last acute respiratory illness more than 1 month before the study.

The vast majority of children (n = 49; 85 %) had initial manifestations of atopic dermatitis in the first year of life. Severe dermatitis was registered in 10 (17 %) patients, moderate-in 22 (38 %) people, and mild - in 26 (44.9%) children. A limited version of skin lesions was found in 38 (65.2 %), diffuse-in 20 (34.8 %) cases. Children's form of atopic dermatitis was registered in 43 (74.1 %), adolescent-in 15 (25.9 %) children. The frequency of exacerbations of the disease averaged 2.0 ± 0.27 episodes per year. Bronchial asthma of mild severity was registered in 18 (40.7 %),of these, intermittent-in 15 (77.3 %), persistent - in 3 (22.7 %), moderate-in 21 (48.2%), severe asthma - in 3 (11.1 %) cases. When allergological examination was most prevalent food sensitization - in 48 (82,6 %) patients, in second place household at 42 (72,4 %), the third pollen - 35 (56.5 percent).

The sensitivity of the receptor apparatus of the bronchial tree was studied by means of an inhalation-provocation test with histamine and metacholine by the dose method [13]. Standard histamine solutions were prepared from histamine phosphate powder and buffer phosphate salt solution in concentrations 0,125; 0,25; 0,5; 1; 2; 4; 8; 16 mg / ml. The methacholine solutions prepared from a powder of methacholine chloride and saline solution in the same concentrations. Measurements of forced exhalation volume (FEV1), forced expiratory vital capacity (FVC), forced expiratory flow at 25,50.75% (FEF25, 50,75) were performed 30 and 60 seconds after each inhalation. The test was stopped when FEV1 decreased by 20 % or more and/or when clinical symptoms of bronchospasm appeared - when the threshold concentration (PK20) was reached. Threshold sensitivity was assessed as high at PK20 to 0.125–0.5 mg/ml, from 1 to 2 mg/ml - moderate, from 4 to 8 mg/ml - low, over 8 mg/ml - normal. The me content was determined by atomic absorption spectrometry (the substrate under study is blood serum) and x - ray fluorescence (the substrate under study is hair). All hair samples were subjected to the sample preparation according to the International Atomic Energy Agency requirements and guidelines "Screening methods to identify high-risk groups among workers in contact with toxic chemicals" approved by the Ministry of Health of the Uzbekistan (1998), No. 41 "Detection and correction of violations of the exchange of macro-and microelements", approved by the Ministry of Health of Uzbekistan 15.09.2009. Energy-dispersive x-ray fluorescence elemental analysis was performed at the SR VEPP-3 elemental analysis station (Institute of nuclear physics in Uzbekistan). We determined the content of essential - Fe, I, Cu, Zn, Co, Cr, Mo, Se, Mn and toxic - As, Br, Ni, Rb, Sr, Zr, Nb, Au, Pb, Hg, Bi me, as well as the macronutrient Ca.

The "external standard" method was used for processing the measurement results. The external standard was a certified sample of human hair NIES-5 (National Institute for Environment Studies, Japan, 2006). Determination of the ME content in blood serum (Se, Zn) was performed by atomic absorption spectrophotometry. Mathematical calculations were performed using the statistical analysis package Microsoft Excel. When working with the database, the arithmetic mean values and standard errors of the arithmetic mean (M ± m) were determined. The significance of differences in the average arithmetic ranked criteria under normal distribution was evaluated using the t - Student criteria. The results were considered reliable at the significance level $p < 0.05$.

The results of the study and their discussion. According to the results of bronchoprovocation tests, all children were found to have combined violations of bronchial reactivity (hypersensitivity of the bronchial receptor apparatus to histamine and metacholine).

Bronchospasm in response to high PK20 (0.125–0.5 mg/ml) of histamine and metacholine was registered in 39 cases, in the rest (n = 23)-there were various gradations of bronchial sensitivity indicators.

The defiency of microelement discovered in all children. There were mainly deficiencies of calcium, selenium, iodine, manganese, and zinc (54 (93,2 %), 48 (82,8 %), 46 (79,7 %), 44 (75,8 %), 35 (60.2 %) respectively). Less frequently, there was a deficiency of molybdenum (20 (34.8 %)), chromium (17 (30.4 %)), copper (15 (26.1 %)), Nickel (13 (24.6 %)), iron (12 (21,7 %)). Insufficiency of more than four ME was noted in 28 (47.8 %), four-in 17 (30.4 %), three - in 12 (21.7 %) cases, no child was found to have a deficit of one or two ME. Hypermicroelementoses were observed in the majority of patients with BHS (n = 55; 95.7 %), more often there was an increased content of several ME: five-seven (n = 24; 40.9%), four (n = 12; 21.7%), three (n = 11; 18.2%), and two (n = 11; 18.2%). The predominant variants were bromine intoxication (n = 48; 69.6 %) and lead (n = 30; 52.2 %), less frequently registered hypermicroelementosis rubidium (n = 19; 31.9 %), zirconium (n = 16; 27.5 %), arsenic (n = 12; 21.7 %), Nickel (n = 13; 20.3 %)

Taking into account that there is a high frequency of microelement disorders in BHS, the analysis of the sensitivity indicators of the bronchial tree was performed depending on the concentration of essential and toxic me. The degree of severity of microelement disorders differed among children - "hyperreactors" with high sensitivity of the bronchi to histamine and metacholine and various gradations of sensitivity (table 1).

Table 1. Concentrations of macro-and microelements in the hair tissue of the examined children (mcg/g)

Element	High sensitivity of the bronchi, n = 36	Different degrees of bronchial sensitivity, n = 22	Average group values, n = 58	Control group, n = 68	"External standard" National Institute for Environment

					Studies, Japan, 1996
As	0,03 ± 0,008	0,028 ± 0,006	0,03 ± 0,001	0,18 ± 0,02	-
Ca	380,94±140,9	460,81±160,4	457,32±138,4	651,33± 277,85	280–900
Cr	2,42 ± 0,18	2,58 ± 0,25	2,45 ± 0,16	1,2 ± 0,15	0,7–1,9
Cu	10,0 ± 2,41*	13,8 ± 3,42	13,52 ± 1,95	13,33 ± 4,20	6,1–12,2
Fe	160,22 ± 68,12	168,36 ± 50,27	165,12 ± 58,20	164,53 ± 48,51	24–54
Hg	0,76 ± 0,24	0,78 ± 0,18	0,77 ± 0,21	0,89 ± 0,33	0–1,7
Mn	2,65 ± 0,38	2,802 ± 0,66	2,82 ± 0,89	3,82 ± 0,46	0,6–2,4
Ni	1,50 ± 0,42	1,41 ± 0,68	1,43 ± 0,59#	4,17 ± 1,35	0,6–2,1
Pb	4,2 ± 0,84*	1,89 ± 0,89	2,59 ± 1,01	3,56 ± 1,19	0–2,1
Se	0,26 ± 0,12*	0,48 ± 0,14	0,42 ± 0,14#	0,68 ± 0,12	0,4–1,2
Ti	16,28 ± 3,42	16,0 ± 3,96	16,14 ± 4,06	17,67 ± 5,14	0,9–4,2
Zn	96,82 ± 25,81*	180,94± 41,32	163,33±40,28	188,67 ± 26,48	110–170
Ga	0,21 ± 0,08	0,19 ± 0,06	0,19 ± 0,09	0,22 ± 0,02	-
Br	50,14±21,20	56,28 ± 18,91	52,78 ± 20,61	34,83 ± 18,63	2–6,4
Rb	0,57 ± 0,21	0,59 ± 0,18	0,58 ± 0,17	0,21 ± 0,04	0,03–0,1
Sr	1,50 ± 0,68	1,44 ± 0,55	1,48 ± 0,72	1,96 ± 0,27	0,7–1,9
Y	0,51 ± 0,11	0,52 ± 0,16	0,52 ± 0,18	0,58 ± 0,25	-
Zr	0,47 ± 0,15	0,57 ± 0,18	0,56 ± 0,12	1,15 ± 0,18	-
Nb	2,51 ± 0,92	2,42 ± 0,78	2,3 ± 0,80#	0,64 ± 0,27	-
Mo	0,26 ± 0,01	0,20 ± 0,008	0,22 ± 0,01	1,10 ± 0,02	-
Au	0,34 ± 0,16	0,39 ± 0,18	0,36 ± 0,22	0,78 ± 0,23	-
Bi	46,84±18,41	56,9 ± 28,64	56,0 ±28,23	42,86 ±20,54	-

Note: * - at $p < 0.05$ (reliability of differences in me concentrations among patients with high sensitivity of the bronchi and different gradations of sensitivity);

- at $p < 0.05$ (reliability of differences in me concentrations among patients with high sensitivity of the bronchi and the control group).

In most children with PK20 histamine and metacholine 0.125–0.5 mg/ml, polymicroelement disorders prevailed. in the case of registration of a deficit of individual ME (selenium, zinc, copper), their average concentrations were significantly lower than the average group indicators. In addition, children with high bronchial sensitivity have the highest lead values-4.2 ± 0.84 mcg/g, compared to with a group of children with moderate and low sensitivity-1.89 ± 0.89 mcg/g, $p < 0.01$.

When studying the correlation interactions of essential and toxic ME contained in the hair tissue, it was found that in the control group, where the indicators as both essential and toxic me did not differ from the values of the "external standard", a moderate negative correlation was determined between zinc and selenium (r = -0.41), indicating the strength of compensatory reactions. A moderate inverse correlation was observed between zinc and lead (r =-0.51), confirming the competing relationships between the ME data, and a direct relationship was observed between selenium and lead (r = 0.65), indicating the controlling role of selenium. In the group of patients with bronchial tree hyperreactivity syndrome, a direct correlation between selenium and zinc was maintained (r = 0.34), indicating a violation of compensatory reactions; a negative correlation was maintained between zinc and lead (r = -0.57), and the relationship between selenium and lead acquired a direct orientation (r = 0.42). Such relationships may reflect a weakening of selenium's controlling role in protecting against toxic ME. So, a close relationship was found between the studied ME, the features of which are manifested depending on the ratio of essential and toxic ME. In parallel, the determination of the content of zinc and selenium in the blood serum was carried out. The choice of these ME was due, first, to the high frequency of occurrence their deficiency in the hair tissue of children with BHS, and secondly, their participation in the processes of lipid peroxidation and maintenance of the chronic inflammatory process and, as a result, hyperreactivity of the respiratory tract.

Among children with "hyperreactors", the average content of selenium in the blood serum was 0.228 ± 0.024 mg / l, zinc-0.561 ± 0.049 mg/l, in the control group-0.889 ± 0.11 and 0.888± 0.13 mg / l, respectively, $p < 0.05$.

Various relationships were revealed when analyzing the concentrations of selenium and zinc in blood serum and indicators that characterize functional changes in the tracheobronchial tree (table 2).

Table 2. Indicators of respiratory function and sensitivity of the bronchial tree in children with different levels of selenium and zinc in the blood serum

Indicators, % of due	**Bronchial hyperreactivity**			
	Se 0,04–0,2 mg/l, n = 29	**Zn 0,08–0,35 mg/l, n = 25**	**Se 0,21–0,75 mg/l, n = 31**	**Zn 0,36–0,62 mg/l, n = 36**
FVC	80,1 ± 4,1	80,9 ± 3,5	92,5 ± 3,2	90,5 ± 2,8

FEV1		78,2 ± 4,6*	80,0 ± 3,6	90,2 ± 2,8	90,6 ± 2,7
FEV1/FVC		82,0 ± 1,5	84,2 ± 1,1	91,4 ± 0,9	93,8 ± 0,8
FEF_{25}		78,8 ± 4,0*	80,1 ± 3,4	92,1 ± 3,9	101,6 ± 2,4
FEF_{50}		76,2 ± 3,6*	78,5 ± 3,7	90,8 ± 4,1	104,4 ± 3,0
FEF_{75}		76,4 ± 4,8*	79,1 ± 4,0	92,4 ± 3,7	100,8 ± 3,9
PC20 histamine, mg / ml, n (%)	0,125–0,5	28 (82,4)*	22 (75,9)	22 (62,9)	25 (62,5)
	1–2	5 (14,7)	6 (20,7)	9 (25,7)	10 (25,0)
	4–8	1 (2,9)	1 (3,4)	4 (11,4)	5 (12,5)
PC20 metacholine, mg / ml, n (%)	0,125–0,5	31 (91,2)*	23 (79,3)	25 (71,4)	26 (65,0)
	1–2	3 (8,8)	5 (17,2)	7 (20,0)	10 (25,0)
	4–8	0	1 (3,5)	3 (8,6)	4 (10,0)

In patients with a decrease in selenium concentration below 0.2 mg / ml, there was a significant decrease in the parameters of external respiration function, reflecting the patency of the bronchi, namely a moderate decrease in volume indicators (FVC, FEV1), their ratio (FEV1/FVC), as well as a decrease in the flow rate at the beginning, middle and end of exhalation (FEF 25,50,75). The distribution OF PC20 histamine and metacholine also had significant differences in the groups under consideration. Sensitivity analysis of the bronchial receptor apparatus showed the prevalence of high threshold concentrations of metacholine and histamine among children with zinc and, especially, selenium content below the physiological values (table 2). Positive correlations ($r = 0.38$) were observed between the PC20 of metacholine and histamine and the concentration of zinc in the blood, the relationship was enhanced in patients with selenium deficiency ($r = 0.46$), $p < 0.01$.

In the future, the comparison of selenium and zinc concentrations in blood serum (as indicators of microelementosis at the organ level) was carried out in children with "hyperreactors", for a short time, under dynamic conditions) and hair tissue (as an assessment of long-term microelementosis, "chronic" deficiency). A parallel decrease in the concentration of selenium in blood serum and hair was observed the overwhelming majority of "hyperreactors" - in 48 (84.1 %) cases, zinc-in 41 (71.0 %), selenium and zinc-in 40 (69.6 %), i.e. this contingent of children there was a tendency to a long-term deficit of me. In other cases, there were various variations in the ME content, but the level of serum selenium in all children was lower than the values of the control group.

The severity of the course of the atopic process and the length of illness were accompanied by the severity of microelement disorders. Thus, among children with a parallel deficiency of selenium and zinc in blood serum and hair ($n = 34$), the experience of atopic dermatitis was 11.2 ± 2.4 years, bronchial asthma-7.6 ± 1.7 years, the SCORAD index-42.4 ± 10.2 points, in most cases severe ($n= 6$; 26.7 %) and moderate ($n = 18$, 60.0%) course of bronchial asthma ($n = 30$), whereas with various combinations of selenium and zinc concentrations ($n = 31$) - 8.2 ± 1.6 years; 5.1 ± 1.2 years; 30.8 ± 4.2 points; $n = 2$; 8.3 %; $n = 8$; 36.4 % ($n = 24$), respectively, $p < 0.05$.

Conclusions. The state of hyperresponsiveness of the bronchial tree in children with combined forms of Allergy is accompanied by politicalamity disorders (deficiency of essential ME identified at 69.6 %), which is especially pronounced at high sensitivity of the bronchi (PK20 of methacholine, histamine is 0.125–0.5 mg/ml), and the lack of selenium and zinc (the plasma below 0.2 and 0.35 mg/l, respectively) and is characterized by decrease in velocity parameters of external respiration function.

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