CLINICAL AND IMMUNOLOGICAL CHARACTERISTICS OF BRONCHOBSTRUCTIVE SYNDROME IN CHILDREN

N. O. Turaeva
Samarkand state medical university, Samarkand, Uzbekistan
E-mail: nafisa_turayeva@sammu.uz

Abstract: The pathology of the respiratory organs in young children remains one of the urgent problems of modern pediatrics. This is largely due to the insufficient number of randomized studies conducted to assess the effect of vitamin D on metabolic processes and the course of broncho-obstructive syndrome. The most common broncho-obstructive syndrome occurs in acute obstructive bronchitis, obstructive bronchitis with recurrent course and bronchial asthma.

Keywords: Broncho obstructive, syndrome, children, clinical characteristics, immunological profile, pediatric pulmonology, airway obstruction, asthma in children, immune response, cytokines.

Аннотация: Патология органов дыхания у маленьких детей остаётся одной из актуальных проблем современной педиатрии. Это в значительной степени связано с недостаточным количеством рандомизированных исследований, направленных на оценку влияния витамина D на метаболические процессы и течение бронх обструктивного синдрома. Наиболее часто бронх обструктивный синдром наблюдается при остром обструктивном бронхите, рецидивирующем обструктивном бронхите и бронхиальной астме.

Ключевые слова: Бронх обструктивный, синдром, дети, клинические характеристики, иммунологический профиль, педиатрическая пульмонология, обструкция дыхательных путей, астма у детей, иммунный ответ, цитокины.

Annotatsiya: Yosh bolalarda nafas yo‘llari kasalliklari patologiyasi zamonaviy pediatriyaning dolzarb muammolaridan biri bo‘lib qolmoqda. Bu, asosan, vitamin D ning metabolik jarayonlarga va bronxo-obstruktiv sindrom kechishiga ta’sirini baholash bo‘yicha o‘tkazilgan tasodifiy tadqiqotlar sonining yetarli emasligi bilan bog‘liq. Eng ko‘p uchraydigan bronxo-obstruktiv sindromlar — bu o‘tkir obstruktiv bronxit, qayta-qayta takrorlanuvchi obstruktiv bronxit va bronxial astmadir.

Kalit so‘zlar: Bronxo-obstruktiv, sindrom, bolalar, klinik xususiyatlar, immunologik profil, pediatrik pulmonologiya, nafas yo‘llarining torayishi, bolalarda astma, immun javob, sitokinlar.

Introduction

The purpose of the study was to study the clinical and immunological characteristics of broncho-obstructive syndrome in children. Materials and

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methods. The study involved 86 patients aged 3 to 15 years with acute obstructive bronchitis, recurrent obstructive bronchitis and bronchial asthma. All patients underwent a single set of diagnostic studies: clinical examination, immunological examination. blood, the study of the level of vitamin D in the blood serum.

The results of the study showed that vitamin D deficiency was accompanied by the development of secondary immune deficiency. According to the results of the study of the cytokine status, it was found that in children with acute obstructive bronchitis, the production of IL-4 significantly ($P<0.01$) increased to 18.9±0.3 pg/ml, in patients with obstructive bronchitis of the recurrent course, the production index IL-4 was significantly ($P<0.01$) increased to 21.3±0.3 pg/ml. In patients with bronchial asthma, the rate of IL-4 production was increased to 26.7±1.4 pg/ml, the content of IL-8 was in children of all groups, the level of vitamin D3 in children with bronchial asthma was significantly reduced to 10.9 ±0.6 ng/ml, which is more than 4.2 times lower than the average values in healthy children (46.2±4.2 ng/ml; $P<0.001$) and was significantly lower compared to the indicators of children with acute obstructive pulmonary disease. bronchitis and obstructive bronchitis of recurrent course (18.3±3.2 ng/ml and 12.8±1.2 ng/ml, respectively, $P<0.01$).

Thus, in broncho-obstructive syndrome, depending on the underlying disease, the level of blood serum cytokines changes, which is characterized by a significant increase in such cytokines as IL-4, IL-8, TNFα and a decrease in IFNγ. The increase in the severity of broncho-obstructive syndrome is directly proportional to the decrease in the level of vitamin D metabolites in the blood serum, which is clearly manifested in children with bronchial asthma.

Most often, broncho-obstructive syndrome occurs in acute obstructive bronchitis, obstructive bronchitis with recurrent course and bronchial asthma. Among the known risk factors for repeated episodes of broncho-obstructive syndrome, such as family allergy history, manifestations of atopy, eosinophilia, the role of vitamin D and the significance of its deficiency in the tendency to frequent episodes of bronchial obstruction are currently being actively studied [1-9]. The potential effect of vitamin D on the course of broncho-obstructive syndrome is due to its ability to affect cellular and humoral immunity, thereby reducing the inflammatory process [10-12]. This mechanism is due to gene expression and cytokine synthesis. The point of application here are vitamin D receptors. The molecular mechanism of action of the highly active metabolite of VD - 1,25-dihydroxyvitamin D (1,25 (OH) 2D), the so-called D-hormone (calcitriol) is the interaction with specific receptors in tissues - vitamin D receptors, which are widely represented in the body and are found in many tissues: T- and B-

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lymphocytes, macrophages, including pulmonary alveolocytes and bronchial smooth muscle cells [13-16]. It is worth noting that the molecular mechanism of the non-classical action of vitamin D has not yet been studied. This is largely due to the insufficient number of randomized studies conducted to assess the effect of vitamin D on metabolic processes and the course of broncho-obstructive syndrome. The purpose of this study was to study the effect of vitamin D levels on the course of broncho-obstructive syndrome in children and determine its relationship with cytokine status.

Materials and methods. The study involved 86 patients aged 3 to 15 years. Of these, 38 children with acute obstructive bronchitis (group I), 15 children with recurrent obstructive bronchitis (group II) and 33 children with bronchial asthma (group III). As a control group, 20 practically healthy children of the same age were examined. The study was conducted in the pulmonology department of the Republican Specialized Scientific and Practical Medical Center of Pediatrics. All patients underwent a single set of diagnostic tests: clinical examination, immunological blood test, and serum vitamin D test. The clinical examination included collection of anamnestic data, including past illnesses, allergy history, premorbid background of the child, and assessment of the general condition at the time of examination. The immunological study included determination of the cytokine content: IL-4, IL-8, TNF-α, IFNγ. They were determined by the enzyme immunoassay method using reagent kits manufactured by Cytokine LLC (St. Petersburg Research Institute of Highly Pure Biopreparations). The level of vitamin D (25-(OH) D) in the blood serum was analyzed using enzyme immunoassay. According to the recommendations of the Institute of Medicine of the United States of America, the level of vitamin D ≥ 20 ng/ml was assessed by us as sufficient intake of vitamin D, 11-20 ng/ml – insufficient intake, ≤10 ng/ml – deficiency. The obtained results were processed in the Statistics 10 program, after checking the normality of distribution by the method of variation statistics using the Student's t-test, differences were considered statistically significant at $P<0.05$.

Results and discussion. After the clinical examination, it was revealed that the severity of the examined patients. In all three observation groups, the most common background conditions were anemia, rickets and allergic diathesis. In the group of patients with acute obstructive bronchitis, the above conditions were more significant. Delayed physical development was observed in 24.6% of patients with bronchial asthma.

On admission to the hospital, the main complaints of children with acute obstructive bronchitis and recurrent obstructive bronchitis were cough 53 (100%), shortness of breath 53 (100%), fever in 32 (61.4%) children, decreased appetite 47

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(90.3%), weakness 40 (76.3%), sleep disturbance 41 (91.8%). All children with bronchial asthma complained of cough with mucous sputum - 33 (100.0%) shortness of breath - 33 (100.0%), decreased appetite - 30 (90.8%), lethargy - 31 (95.4%), asthma attacks - 26 (80.0%), sweating - 16 (49.2%), headache - 14 (44.6%). Upon admission to hospital, in patients with acute obstructive bronchitis, the leading clinical manifestation of the disease was respiratory failure, weakness was noted in 21 (56.0%) patients, and appetite was reduced in 30 (81.3%) patients. Sleep disturbance, pale skin and dyspnea were observed in 38 (100.0%) cases. Cyanosis of the nasolabial triangle was observed in 12 (32.0%) children. Body temperature was febrile in 7 (18.7%), subfebrile - in 11 (30.6%). The cough was dry in 30 (81.3%) patients, wet - in 7 (18.7%) patients. During auscultation of the lungs against the background of harsh breathing, dry wheezing was heard in 29 (77.3%) patients, wet wheezing was heard in 8 (22.7%). During percussion of the chest, a box shade of percussion sound was determined in 30 (88.0%). In children with recurrent obstructive bronchitis, the disease was characterized by an acute (subacute) onset, cough, initially dry - in 90.0%, wet - in 10.0% of patients. Cough on admission was paroxysmal in nature, more at night, on the 5-6th day of treatment it transformed into wet. Cyanosis of the nasolabial triangle was observed in 25.0%, and dry skin was observed in 70.0% of patients. Auscultatory signs were varied and mainly depended on the level of damage to the bronchial mucosa. Dry rales were detected in 15.0% of children, and wet conductive rales were detected in 85.0% of children.

The results of the cytokine status study revealed that in children with acute obstructive bronchitis, IL-4 production significantly ($P<0.01$) increased to 18.9±0.3 pg/ml compared to healthy children (Table 1). In patients with recurrent obstructive bronchitis, the IL-4 production rate was significantly ($P<0.01$) increased to 21.3±0.3 pg/ml, which was 4.6 times higher than the norm. In patients with bronchial asthma, the IL-4 production rate was increased to 26.7±1.4 pg/ml, which was 5.8 times higher than the norm. When analyzing the IL-8 content, its reliable increase was revealed in children of all three groups: in acute obstructive bronchitis up to 32.5±2.8 pg/ml, in obstructive bronchitis with recurrent course up to 89.5±3.9 pg/ml, in bronchial asthma up to 100.9±7.7 pg/ml, ($P<0.01$), which exceeded the norm by 5.2 times. Our studies on the level of IFNγ in the examined patients showed a profound deficiency in their content. Thus, in children with acute obstructive bronchitis, the serum IFNγ level averaged - 27.4±1.5 pg/ml ($P<0.05$), in recurrent obstructive bronchitis - 21.4±1.7 pg/ml and in bronchial asthma - 14.3±1.9 pg/ml, respectively, which is 1.2-1.6-1.4 times lower than the values in practically healthy children (P in all cases from <0.05 to <0.001), and the most

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significant changes were determined in children with bronchial asthma. Impaired production of IFNγ, which plays an important role in maintaining homeostasis, is characteristic of the examined patients.

It is known that TNFα is mainly produced by monocytes and macrophages and performs many important functions. During the inflammation initiation period, it activates the endothelium, increases the expression of adhesion molecules on endothelial cells and promotes the adhesion of leukocytes to the endothelium, activates leukocytes (granulocytes, monocytes, lymphocytes), induces the production of other proinflammatory cytokines that have a synergistic effect with TNFα. In our studies, the level of TNFα was 3.5 times higher in children with bronchial asthma, compared with children in the control group (P<0.001), in children with acute obstructive bronchitis it was 48.7±3.5 pg/ml, recurrent obstructive bronchitis - 62.7±3.2 pg/ml versus 28.4±1.5 pg/ml in the control (P<0.001), which reflects the increased activity of macrophages involved in maintaining the inflammatory process.

Table 1.

The content of cytokines in children in the studied groups (M±m)

Indicators	Practically healthy children n=20 (I)	Acute obstructive bronchitis n=38 (II)	Recurrent obstructive bronchitisn =15 (III)	Bronchial asthma n=33 (IV)	P	P_1	P_2
TNFα (пг/мл)	28,4±1,5	48,7±3,5	62,7±3,2	98,4±4,5	<0,01	<0,001	<0,01
IL – 4 (пг/мл)	4,6±0,6	18,9±0,31	21,3±0,34	26,7±1,4	<0,05	<0,001	<0,01
IFNγ (пг/мл)	34,3±2,7	27,4±1,5	21,4±1,7	14,3±1,9	<0,05	<0,001	<0,01
ИЛ – 8 (пг/мл)	19,2±2,4	32,5±2,8	89,55±3,87	100,98±7,67	<0,05	<0,001	<0,01

Note:

P - reliability of differences in indicators between groups I and II of patients;

P1 - reliability of differences in indicators between groups II and III of patients;

P2 - reliability of differences in indicators between groups III and IV of patients.

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According to the results of vitamin D3 content in the blood serum, in group I of patients with acute obstructive bronchitis, 18.5% (12) of patients had vitamin D deficiency, 40.3% (10) had vitamin D insufficiency, and 42% (16) of cases had sufficient vitamin D content. In group II of patients with recurrent obstructive bronchitis, 26.6% (4) of patients had vitamin D deficiency, 40% (6) had vitamin D insufficiency, and 33.3% (5) of cases had sufficient vitamin D content. In group III of patients with bronchitis, 45.4% (15) of patients had vitamin D deficiency, 36.3% (12) had vitamin D insufficiency, and 18.2% (6) of cases had sufficient vitamin D content (Table 2).

Table 2.

Vitamin D levels in study groups

Groups	Vitamin D level ≥ 20 ng/ml		Vitamin D11 level - 20 ng/ml		Vitamin D level ≤10 ng/ml	
	abs	%	абс	%	абс	%
Group I (acute obstructive bronchitis)	16	42	10	40,3	12	18,5
Group II (recurrent obstructive bronchitis)	5	33,3	6	40	4	26,6
III группа (бронхиальная астма)	6	18,2	12	36,3	15	45,4
Control group	10	55	6	30	4	20

The average content of vitamin D (25(OH)-D) in the blood serum of the examined children is shown in Figure 1.

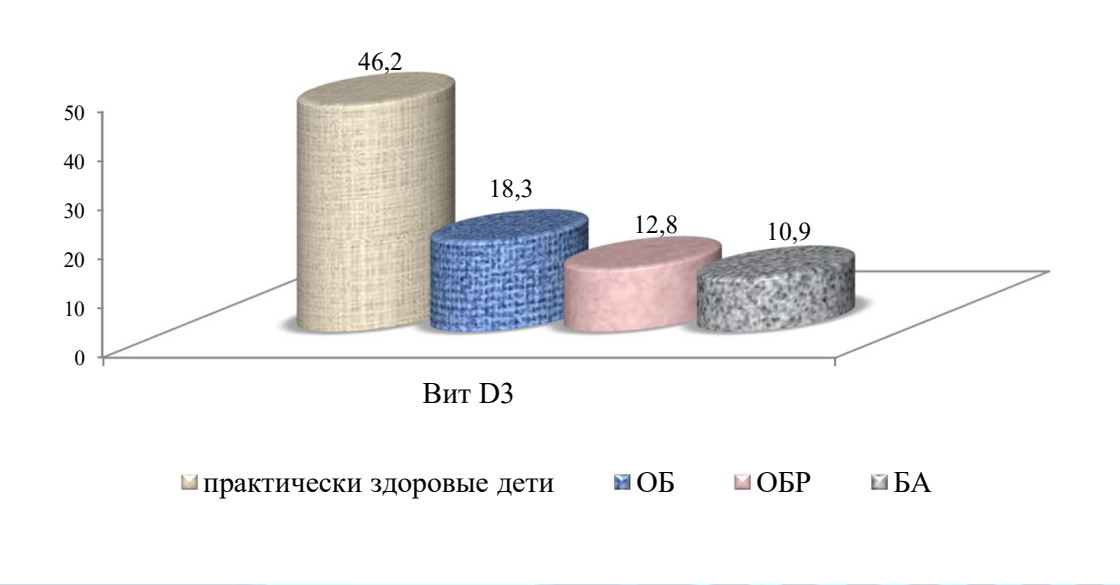


Figure 1. Average values of Vitamin D in the examined children, ng/ml

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As can be seen from Figure 1, the level of vitamin D3 in children with bronchial asthma was significantly reduced to 10.9±0.6 ng/ml, which is more than 4.2 times lower than the average values in healthy children (46.2±4.2 ng/ml; P<0.001) and was significantly lower compared to the values in children with acute obstructive bronchitis and recurrent obstructive bronchitis (18.3±3.2 ng/ml and 12.8±1.2 ng/ml, respectively, P<0.01).

Thus, based on the data obtained, the following can be made

Conclusions:

1. The severity of the course of broncho-obstructive syndrome is associated with an aggravated premorbid background, concomitant and past diseases, which significantly aggravate the course of the underlying pathology. In broncho-obstructive syndrome, depending on the underlying disease, the level of serum cytokines changes, which is characterized by a significant increase in such cytokines as IL-4, IL-8, TNFα and a decrease in IFNγ. Vitamin D deficiency is accompanied by the development of secondary immune deficiency, which is manifested by a decrease in the phagocytic activity of cells, a decrease in interferon production. The greatest changes in the immune status are noted in patients with bronchial asthma, which is characterized by an increase in IL-4, IL-8, TNFα and a decrease in IFNγ.

2. The increase in the severity of broncho-obstructive syndrome is directly proportional to the decrease in the level of vitamin D metabolites in the blood serum, which is clearly evident in children with bronchial asthma.

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