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ASSESSMENT OF VITAMIN D LEVEL AS A FACTOR OF BRONCHIAL ASTHMA CONTROL IN CHILDREN OF THE AMUR REGION

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Nowadays, control of bronchial asthma (BA) can be achieved only in 2/3 of cases, even in a controlled population with direct daily supervision of a doctor ensuring full compliance with standard treatment regimens. In this regard, factors that can affect the course of asthma, but those which are not taken into account in standard treatment regimens, are of particular importance. Interest in vitamin D as a modifier of atopic inflammation in BA is due to its noncalcemic effects realized through the VDR receptors of immune cells. 78 patients suffering from asthma were examined. The diagnosis of the disease and the degree of control over it were established based on the GINA 2020 criteria. The levels of vitamin D and interleukins in the blood serum were determined by ELISA. The level of immunocompetent cells was determined by flow cytometry. The presence of persistent infection was determined by PCR method. It was found that children with uncontrolled AD have more than two times (29.8 vs 64.5 ng/ml) lower level of vitamin D than patients who control the disease. Children with vitamin D deficiency have three times higher levels of one of the inducers of atopic inflammation – IL5 (0.62 vs 0.22 pg/ml) and require a higher dose of topical glucocorticosteroids (TGC) (347.3 vs 285.5 mcg) to control the disease. Thus, vitamin D has a significant impact on the level of asthma control in children, the immune status and the likelihood of persistence of the herpes virus type 6. Determination and correction of vitamin D deficiency should be recommended, since it influences on pathogenetically significant parameters of atopic inflammation in uncontrolled bronchial asthma in children.

Keywords: bronchial asthma, children, vitamin D, herpes virus type 6.

Introduction. In recent decades, there has been an increase in the prevalence of BA and its incidence has reached 15% among the child population of the Earth [14]. Russia as a whole [6] and the Khabarovsk Territory [8] in particular are not an exception. Twofold increase in the prevalence of BA among children in the Khabarovsk Territory was detected in the period from 2005 to 2020 (teenagers – from 12% to 25%, children under 14 years – from 11% to 20%). At the same time, the relatively lower official rates of the disease (about 2% in Russia and 7-15% in industrialized countries) are due to the method of record keeping of medical aid appealability. According to ISAAC studies asthma like symptoms are detected in 4-15% of children in various regions of our country, which corresponds to the indicators of other industrialized countries [4]. Such BA extension

is due to, first of all, a change in the total genotype of the population of these countries, caused by a radical change in lifestyle in the last century, which leads to an ever wider spread of atopy in general, and BA in particular, thus making the disease practically not treatable. Therefore, the efforts of the medical community are aimed at improving the effectiveness of BA therapy, but not at its primary prevention. However, the proportion of patients who have managed to control BA does not exceed 30%, and complete control is achieved only in 5% of cases. Even when basic therapy is carried out under the direct supervision of a specialist according to accepted treatment regimens, with free provision of drugs and among patients without significant comorbidity of BA, complete control can be achieved only in 34% of cases, good results show 38% of patients and 28% of patients remain with uncontrolled course of the pathological process [18]. In Russia, there are similar ratios of the degrees of disease control [3]. Bronchial asthma is a multifactorial disease, so the causes of an uncontrolled course are very diverse, but in children it is almost always based on atopic inflammation, which is primarily due to congenital factors, but the likelihood and duration of their implementation, as well as the course of the disease, can be significantly modified under the influence of various exogenous factors [11, 13, 16], including regional ones. One of them is the level of insolation and the ability to perceive it by a person in con-

nection with other climatic features. The Amur region is one of the leaders among the regions of Russia in terms of formal indicators of insolation, the number of sunny days for our region exceeds 300 per year. However, a rather harsh climate with large temperature fluctuations, up to extreme ones, does not allow to take full advantage of this benefit, so the level of vitamin D in the population is quite low. According to studies conducted in 2020, vitamin D deficiency was detected in almost half of the child population of our region [2, 7]. Meanwhile, the role of this vitamin in the pathogenesis of BA is known. Recent Iranian studies have shown that asthma patients have lower levels of vitamin D which decrease even more with disease aggravation [21]. Similar results were obtained in the same year by Indian researchers [19]. Several earlier epidemiological and in vivo studies have also found a connection between low vitamin D levels in serum and increased inflammation, decreased lung function, increased exacerbations, and general deterioration in patients with AD [12, 15, 20]. Later, a meta-analysis confirmed a significant reduction in objective indicators of obstruction, such as FEV1, with low vitamin D levels in both children and adults with BA [17]. In addition, a number of scientific works using meta-analysis methods show the effectiveness of vitamin D in the complex therapy of bronchial asthma. Vitamin D contributes to positive changes in the cytokine network during treatment, which is associated with its

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ability to regulate Th2 functions and, as a result, reduce the synthesis of interleukins -13 and -17, which are involved in the allergy pathogenesis [1]. Thus, the detection of vitamin D levels in children with bronchial asthma in our region and confirmation of its effect on the course of asthma is of great scientific interest and may be of high clinical significance.

Aim: To evaluate the effect of vitamin D on the controllability of the course of AD in children of the Amur region and its role in the pathogenesis of atopic inflammation.

Materials and methods. We examined 167 patients with asthma. The diagnosis of BA, the severity and degree of control over the disease were established according to the criteria of the current editions of GINA [14], the National Program "Bronchial asthma in children: a strategy for treatment and prevention" [6], and Clinical guidelines for the diagnosis and treatment of BA [5]. The study of lymphoid populations was carried out on a FACSCalibur Becton Dickinson cytometer. The panel of monoclonal antibodies ("BD") consisted of 7 parameters: CD3+/CD45+ (mature T-lymphocytes), CD19+/CD45+ (mature B-lymphocytes), CD3+/CD4+/CD45+ (T-helpers/inducers), CD3+/CD8+/CD45+ (T-killers/cytotoxic), CD3+/CD25+ (lymphocytic activation marker), CD(16+56)/CD45+ (natural killers). Neutrophil activity indicators were studied in spontaneous and stimulated tests of phagocytic activity with latex particles and in tests of NBT reduction to formazan ("FAN-test", "NBT-test", "Reacomplex", Chita city). To determine the levels of IgA, IgM, IgG, IgE and interleukins 4, 5, 6, 7, 8, 9, 10, 18 and TNF α , as well as the level of vitamin D in blood serum, an immunoenzyme method with the "Vector-Best" test systems was used. The determination was carried out by an automatic spectrophotometer Lazurite "Vector-Best". DNA of viral infections pathogens in swabs from the oropharynx was determined by PCR using the test system of OOO InterLabService (Moscow) AmpSens@EBN/CMV/HHV6 – screen-FI. Detection was performed in real time using a C 1000 Touch CFX96 thermal cycler (BIO-RAD the USA). The DNA of Human herpes virus 4 type (EBN) - Epstein-Bar virus, and Human herpes virus 6 type (HHV6) - herpes 6 type, were detected. The research data were entered into the Excel-2013 electronic database. The statistical analysis of the results of the study used standard methods of variant statistics using the statistical software package: "STATISTICA" for "Windows" (version 10.0). In this paper, all param-

eters are presented as $\bar{M} \pm m$ – mean $\pm$ "standard error of the mean" (SD/sqrt(n) = SEM (Standard Error Means), - where n is the sample size). The statistical hypothesis of equality of group means was tested using Student's t-test (two-sample t-test). When describing the reliability of the results of statistical analysis, the formula " $p < 0.05$ " was used. In addition, a significant difference in the proportions in the groups was assessed. The studies were carried out in accordance with the principles of the ongoing revision of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October, 2013). All data were collected with the personal consent of the subjects and their legal representatives. In all tables showing statistical processing, except for the primary one, the interviewees are presented under serial numbers. The Excel spreadsheet was password-protected and was only accessible to study participants. The study design was approved by the institution's ethics committee.

Results. The studies revealed that children with controlled BA have significantly ($p = 0.006$) higher level of vitamin D (64.5 ± 12.8 ng/ml) than patients with uncontrolled disease (29.8 ± 5.4 ng/ml) (Figure 1).

Immunological parameters of patients with BA depending on the level of vitamin D

Indicator	Level of vitamin D		Reliability
	<30,0 ng/ml	$\geq 30,0$ ng/ml	Accuracy
IL4, pg/ml	0.2 ± 0.09	0.94 ± 0.21	0.03
IL5, pg/ml	0.62 ± 0.18	0.22 ± 0.13	0.04
CD19, absolute	366.0 ± 31.7	427.0 ± 24.2	0.05
CD19, %	13.7 ± 1.05	16.1 ± 1.2	0.05

The average levels of vitamin D in patients with a controlled course were within the normal range (more than 30.0 ng/ml), in children with an uncontrolled course, they were below the reference values.

When analyzing the effect of vitamin D on some clinical and pathogenetic parameters in BA, certain results were obtained (Table).

When studying some indicators of the immune status, it was revealed (Figure 6.6) that children suffering from BA with vitamin D deficiency have truly 3 times higher levels of interleukin-5 (0.62 pg/ml versus 0.22 pg/ml), which directly activates atopic inflammation, but at the same time significantly (4.5 times) lower levels of interleukin-4 (0.2 pg/ml versus 0.94 pg/ml). A significantly lower proportion of active B-lymphocytes (13.7% vs 16.1%) and their absolute number (366 vs 427) were also detected.

Patients with vitamin D deficiency required a significantly higher dose of glucocorticosteroids (GCS) to achieve control over the disease (347.3 mg versus 285.5 mg) (Figure 1).

Discussion. The climatic features of the region affect the course of bronchial asthma in various ways. In particular, Khabarovsk has been repeatedly recognized as the sunniest city in Russia (2449 hours of sunshine per year). However, such climatic characteristics as the extreme temperature fluctuations and humidity do not allow us to take full advantage of the sun, since Khabarovsk residents are forced to wear clothing that covers almost entire body and spend a lot of time indoors. In this regard, residents of the Far East are more likely to have vitamin D deficiency rather than its excess. This study confirmed that despite equal insolation, the level of vitamin D in patients with BA is lower than in the comparison group, and decreases with disease aggravation. It was found that children with uncontrolled asthma have significantly lower levels of this vitamin as compared to patients who control the disease. Interest in vitamin D as a modifier of atopic inflammation in BA is due to its noncalcemic effects

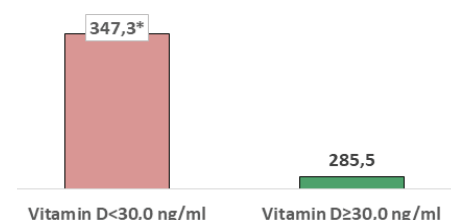


Fig. 1. The dose of TGC required to achieve control over the disease in vitamin D deficiency among children with BA

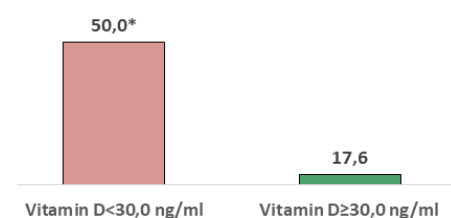


Fig. 2. Proportion of DNA of herpes virus 6 type shed from sputum in vitamin D deficiency in children with BA

realized through the VDR receptors of immune cells. Though insolation is the same for all residents of a given region, it has individual impact in each specific case. The significance of VDR receptor polymorphisms for the pathogenesis of bronchial asthma is known [9, 10]. Therefore, the connection between the level of vitamin D and the controllability of the course of asthma, as well as the mechanisms of its implementation, are of great interest. The study showed that the level of vitamin D affects precisely those immune parameters that play a major role in local atopic inflammation. Interleukin-4, which regulates the differentiation of the second type T-helpers and is more of a cytokine of lymphonodus, is reduced in the patients with vitamin D deficiency. Interleukin-5 directly regulating atopic inflammation is many times higher in situ. Moreover, such patients also have a sharply reduced barrier function of the epithelium, which is signified by more frequent emission of Epstein-Barr virus DNA.

Thus, the content of vitamin D has a significant effect on the level of control of asthma in children, affects the pathogenetically significant indicators of the immune status for atopic inflammation and the likelihood of persistence of the herpes virus type 6. Determination and correction of vitamin D deficiency should be recommended for children with uncontrolled bronchial asthma.

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